

Supplemental Reading for Chapter 1

Basic Principles of Clinical Pharmacology Relevant to Cardiology

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- Bourne HR, von Zastrow M: Drug receptors and pharmacodynamics. In: Katzung BG, ed. *Basic and Clinical Pharmacology*, 10th ed. New York: McGraw Hill 2007: 11–33.
- Cardiac surgery patients may have clinically relevant changes in the pharmacokinetics of frequently used drugs. *Drugs Therap Perspect* 2009; 25: 23–26.
- Cheng JWM, Frishman WH, Aronow WS: Updates on cytochrome P450-mediated cardiovascular drug interactions. *Disease-a-Month* 2010; 56: 163–179.
- Correia MA: Drug biotransformation. In: Katzung BG, ed. *Basic and Clinical Pharmacology*, 10th ed. New York: McGraw Hill 2007: 50–63.
- Fleg JL, Aronow WS, Frishman WH: Cardiovascular drug therapy in the elderly: benefits and challenges. *Nat Rev Cardiol* epub October 26, 2010.
- Fleming WW: Mechanisms of drug action. In: Craig CR, Stitzel RE, eds. *Modern Pharmacology*, 6th ed. Philadelphia: Lippincott Williams & Wilkins 2004: 10–19.
- Frishman WH: Fifty years of beta-adrenergic blockade: a golden era of clinical medicine and molecular pharmacology (commentary). *Am J Med* 2008; 121: 933–34.
- Godin DV: Pharmacokinetics: disposition and metabolism of drugs. In: Munson PL, Mueller RA, Breese GR, eds. *Principles of Pharmacology: Basic Concepts and Clinical Applications*. New York: Chapman & Hall, 1995:39–84.
- Holford NHG: Pharmacokinetics and pharmacodynamics: Rational dosing and time course of drug action. In: Katzung BG, ed. *Basic and Clinical Pharmacology*, 10th ed. New York: McGraw Hill 2007: 34–49.
- Hollenberg MD, Severson DL: Pharmacodynamics: drug receptors and receptors/mechanisms. In: Munson PL, Mueller RA, Breese GR, eds. *Principles of Pharmacology: Basic Concepts and Clinical Applications*. New York: Chapman & Hall, 1995:7–37.
- Nierenberg DW, Melmon KL: Introduction to clinical pharmacology and rational therapeutics. In: Caruthers SG, Hoffman BB, Melmon KL, Nierenberg DW, eds. *Melmon & Morrelli's Clinical Pharmacology*, 4th ed. New York: McGraw Hill, 2000:3.
- Opie LH, Frishman WH: Drug interactions. In: Fuster V, Alexander RW, O'Rourke RA, et al., eds. *Hurst's The Heart*, 10th ed. New York: McGraw Hill, 2000:2251.
- Pea F, Pavan F, Furlanut M: Clinical relevance of pharmacokinetics and pharmacokinetics in cardiac critical care patients. *Clin Pharmacokinet* 2008; 47: 449–62.
- Rang HP, Dale MM, Ritter HM, Gardner P: *Pharmacology*. New York, Churchill Livingstone, 1995.
- Sokol SI, Cheng-Lai A, Frishman WH, Kaza CS: Cardiovascular drug therapy in patients with hepatic diseases and patients with congestive heart failure. *J Clin Pharmacol* 40:11, 2000.
- Roden DM: Drug-induced prolongation of the QT interval. *NEJM* 2004; 350: 1013–22.
- Schwartz SL, Wellstein A, Woosley RL: Significance of pharmacokinetic principles. In Singh BN, Dzau VJ, Vanhoutte PM, Woosley RL (eds): *Cardiovascular Pharmacology and Therapeutics*. New York: Churchill Livingstone 1994; 15–29.
- Sokol SI, Cheng A, Frishman WH, Kaza CS. Cardiovascular drug therapy in patients with hepatic diseases and patients with congestive heart failure. *J Clin Pharmacol* 2000; 40: 11–30.
- Tracy TS: Drug absorption and distribution. In Craig CR, Stitzel RE (eds): *Modern Pharmacology 6th ed*. New York: Lippincott Williams & Wilkins 2004; 20–33.

Tracy TS: Metabolism and excretion of drugs. In Craig CR, Stizel RE (eds): *Modern Pharmacology 6th ed.* New York: Lippincott Williams & Wilkins 2004; 34-47.

Tracy TS: Pharmacokinetics. In Craig CR, Stizel RE (eds): *Modern Pharmacology 6th ed.* New York: Lippincott Williams & Wilkins 2004; 48-55.

References for Chapter 5

Alpha- and Beta-Adrenergic Blocking Drugs

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1. Ahlquist RP: Study of the adrenotropic receptors. *Am J Physiol* 153:486, 1948.
2. Lands AM, Luduena FP, Buzzo HJ: Differentiation of receptor systems responsive to isoproterenol. *Life Sci* 6:2241, 1967.
3. Emorine LJ, Marullo S, Briend-Sutren M-M, et al: Molecular characterization of the human β_3 -adrenergic receptor. *Science* 245:1118, 1989.
4. Berthelsen S, Pettinger WA: A functional basis for classification of alpha-adrenergic receptors. *Life Sci* 21:596, 1977.
5. Berecek KH, Carey RM: Adrenergic and dopaminergic receptors and actions. In Izzo JL Jr, Sica DA, Black HR: *Hypertension Primer 4th ed.* Dallas: American Heart Assn 2008: 39.
6. Sutherland EW, Robinson GA, Butcher RW: Some aspects of the biological role of adenosine 3'5'-monophosphate (cyclic AMP). *Circulation* 37:279–306, 1968.
7. Insel PA: Adrenergic receptors: evolving concepts and clinical implications. *N Engl J Med* 334:580, 1996.
8. Lefkowitz RJ, Caron MG: Adrenergic receptors: models for the study of receptors coupled to guanine nucleotide regulatory proteins. *J Biol Chem* 263:4993–4996, 1988.
9. Benovic JL, Bouvier M, Caron MG, Lefkowitz RJ: Regulation of adenylyl cyclase-coupled beta-adrenergic receptors. *Annu Rev Cell Biol* 4:405–428, 1988.
10. Lefkowitz RJ: Seven transmembrane receptors: something old, something new. *Acta Physiol* 190: 9-19, 2007.
11. Watanabe AM: Recent advances in knowledge about beta-adrenergic receptors: application to clinical cardiology. *J Am Coll Cardiol* 1:82–89, 1983.
12. Frishman WH, Charlap S: α -Adrenergic blockers. *Med Clin North Am* 72:427, 1988.
13. Pool JL: α -Adrenoceptor antagonists. In Izzo JL Jr, Sica DA, Black HR: *Hypertension Primer 4th ed.* Dallas: American Heart Assn 2008: 450.
14. Katz AM, Hager WD, Mesineo FC, et al: Cellular actions and pharmacology of the calcium channel blocking drugs. *Am J Med* 77:2, 1984.
15. Ribner HS, Bresnahan D, Hsieh AM: Acute hemodynamic responses to vasodilation therapy in congestive heart failure. *Prog Cardiovasc Dis* 25:1, 1982.
16. Neaton JD, Grimm RH, Prineas RI, et al for the Treatment of Mild Hypertension Study Research Group: treatment of mild hypertension study: final results. *JAMA* 270:713, 1993.
17. Materson BJ, Reda DJ, Cushman WC, et al: Single-drug therapy for hypertension in men. A comparison of six antihypertensives with placebo. *N Engl J Med* 328:914, 1994.
18. Davis BR, Cutler JA, Gordon DJ, et al, for the ALLHAT Research Group: Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens* 9:342, 1996.
19. The ALLHAT Offshoots Investigators and Coordinators for the ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 283:1967, 2000.
20. Frishman WH: Update in cardiology. *Ann Intern Med* 135:439, 2001.
21. Davis BR, Cutler JA, Furberg CD, et al: Relationship of antihypertensive treatment regimens and change

- in blood pressure to risk for heart failure in hypertensive patients randomly assigned to doxazosin or chlorthalidone: Further analyses from the antihypertensive and lipid-lowering treatment to prevent Heart Attack Trial. *Ann Intern Med* 137:313, 2002.
22. Frishman WH, Patel K: Lipid-lowering drugs. In: Frishman WH, Sonnenblick EH, eds. *Cardiovascular Pharmacotherapeutics*. New York: McGraw-Hill, 1997:399.
 23. Hachamovitch R, Strom JA, Sonnenblick EH, Frishman WH: Left ventricular hypertrophy in hypertension and the effects of anti-hypertensive drug therapy. *Curr Probl Cardiol* 13:371, 1988.
 24. Black HR, Keck M, Meredith P, et al: Controlled-release doxazosin as combination therapy in hypertension: the GATES study. *J Clin Hypertens* 8: 159-66, 2006.
 25. Gould L, Reddy CVR: Phentolamine. *Am Heart J* 92:392, 1976.
 26. Majid PA, Sharma B, Taylor SH: Phentolamine for vasodilator treatment of severe heart failure. *Lancet* 2:719, 1971.
 27. Gregorini L, Marco J, Palombo C, et al: Postischemic left ventricular dysfunction is abolished by alpha-adrenergic blocking agents. *J Am Coll Cardiol* 31:992, 1998.
 28. Packer M: Vasodilator and inotropic therapy for severe chronic heart failure: passion and skepticism. *J Am Coll Cardiol* 2:841, 1983.
 29. Cohn JN, Archibald DG, Ziesche S, et al: Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study (V-Heft). *N Engl J Med* 314:1547, 1986.
 30. Elkayam U, Bitar F: Effects of nitrates and hydralazine in heart failure: clinical evidence before the African American Heart Failure Trial. *Am J Cardiol* 96(7B): 37i, 2005.
 31. Kukin ML, Kalman J, Mannino M, et al: Combined alpha-beta blockade (doxazosin plus metoprolol) compared with beta blockade alone in chronic congestive heart failure. *Am J Cardiol* 77:486, 1996.
 32. Kern MJ: Appreciating α adrenergic receptors and their role in ischemic left ventricular dysfunction. *Circulation* 99:468, 1999.
 33. Baumgart D, Haude M, Gorge G, et al: Augmented α adrenergic constriction of atherosclerotic human coronary arteries. *Circulation* 99:2090, 1999.
 34. Heusch G: Emerging importance of alpha-adrenergic coronary vasoconstriction in acute coronary syndromes and its genetic background (editorial comment). *J Am Coll Cardiol* 41:195,2003
 35. Orlick AE, Ricci DR, Cipriano PR, et al: The contribution of alpha-adrenergic tone to resting coronary vascular resistance in man. *J Clin Invest* 62:459, 1978.
 36. Winniford MD, Flipchuk N, Hillis DL: Alpha-adrenergic blockade for variant angina: a long-term double-blind randomized trial. *Circulation* 67:1185, 1983.
 37. Corr PB, Shayman JA, Kramer JB, et al: Increased α -adrenergic receptors in ischemic cat myocardium: a potential mediator of electrophysiologic derangements. *J Clin Invest* 67:1232, 1981.
 38. Young WF, Sheps SG: Management of pheochromocytoma. In Izzo JL Jr, Sica DA, Black HR (eds): *Hypertension Primer 4th ed*. Dallas: American Heart Assn 2008; 571.
 39. Honston MC, Thompson WL, Robertson D: Shock. *Arch Intern Med* 144:1433, 1984.
 40. Fein SA, Frishman WH: The pathophysiology and management of pulmonary hypertension. *Cardiol Clin* 5:563, 1987.
 41. Cohen ML, Kronzon I: Adverse hemodynamic effects of phentolamine in primary pulmonary hypertension. *Ann Intern Med* 95:591, 1981.
 42. Henderson WR, Shelhamer JH, Reingold DB, et al: Alpha-adrenergic hyperresponsiveness in asthma. *N Engl J Med* 300:642, 1979.
 43. Barnes PJ, Wilson NM, Vickers H: Prazosin, an α_1 -adrenoceptor antagonist, partially inhibits exercise-induced asthma. *J Allergy Clin Immunol* 68:411,1981.
 44. Hedlund H, Andersson KE, Ek A: Effects of prazosin in patients with benign prostatic obstruction. *J Urol* 130:275, 1983.
 45. Narayan P, Lowe FC: The effects of tamsulosin on vital signs in two multicenter, placebo-controlled studies. *Cardiovasc Rev Rep* 21:494, 2000.
 46. Alfuzosin (Uroxatral) – another α_1 -blocker for benign prostatic hyperplasia. *The Medical Letter* 46 (Issue 1173): 1, 2004.
 47. Frishman WH: β -Adrenoceptor antagonists: new drugs and new indications. *N Engl J Med* 305:500–506, 1981.
 48. Frishman WH: *Clinical Pharmacology of the β -Adrenoceptor Blocking Drugs*, 2nd ed. Norwalk, CT: Appleton-Century-Crofts, 1984.
 49. Frishman WH: β -Adrenergic blockers. *Med Clin North Am* 72:37–81, 1988.
 50. Frishman WH: β -Adrenergic blockers: 50-year historical perspective. *Am J Therap* 15: 565,2008.
 51. Frishman WH: Fifty years of beta-adrenergic blockade: a golden era in clinical medicine and molecular pharmacology (commentary). *Am J Med* 121:933,2008.
 52. Frishman WH, Furberg CD, Friedewald WT: β -Adrenergic blockade for survivors of acute myo-

- cardial infarction. *N Engl J Med* 310:30–837, 1984.
53. TIMI Study Group: Comparison of invasive and conservative strategies after treatment with intravenous tissue-type plasminogen activator in acute myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI) trial phase II. *N Engl J Med* 320: 618–627, 1989.
 54. Frishman WH: Carvedilol. *N Engl J Med* 339:1759, 1998.
 55. MERIT-HF Study Group: Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 353:2001, 1999.
 56. Lefkowitz RJ: A magnificent time with the “magnificent seven” transmembrane spanning receptors. *Circ Res* 92: 342,2003.
 57. Frielle T, Daniel KW, Caron MG, Lefkowitz RJ: Structural basis of β -adrenergic receptor subtype specificity studied with chimeric β 1/ β 2-adrenergic receptors. *Proc Natl Acad Sci USA* 85: 9494,1988.
 58. Dixon RA, Kobilka BK, Strader DJ, et al: Cloning of the gene and cDNA for mammalian β -adrenergic receptor and homology with rhodopsin. *Nature* 321: 75,1986.
 59. Rasmussen SGF, Choi H-J, Rosenbaum DM, et al: Crystal structure of the human β_2 adrenergic G-protein-coupled receptor. *Nature* 450: 383,2007.
 60. Lefkowitz RJ: The superfamily of heptahelical receptors. *Nature Cell Biol* 2: E133,2000.
 61. Lefkowitz RJ, Rajagopal K, Whalen EJ. New roles for β -arrestins in cell signaling: not just for seven-transmembrane receptors. *Molec Cell* 24: 643,2006.
 62. Cruickshank JM, Prichard BNC: Beta-Blockers in Clinical Practice, 2nd ed. Edinburgh: Churchill Livingstone, 1994:1055.
 63. Koch-Weser J: Metoprolol. *N Engl J Med* 301:698, 1979.
 64. Frishman WH: Atenolol and timolol, two new systemic adrenoceptor antagonists. *N Engl J Med* 306:1456, 1982.
 65. Frishman WH: Nadolol: A new β -adrenoceptor antagonist. *N Engl J Med* 305:678, 1981.
 66. Frishman WH: Pindolol: A new β -adrenoceptor antagonist with partial agonist activity. *N Engl J Med* 308:940, 1983.
 67. Frishman WH, Covey S: Penbutolol and carteolol: two new beta-adrenergic blockers with partial agonism. *J Clin Pharmacol* 30:412, 1990.
 68. Frishman WH, Tepper D, Lazar E, Behrmann D: Betaxolol: a new long-acting β_1 -selective adrenergic blocker. *J Clin Pharmacol* 30:699, 1990.
 69. Frishman WH, Cheng-Lai A, Chen J, eds. *Current Cardiovascular Drugs*, 3rd ed. Philadelphia: Current Medicine, 2000:120.
 - 69a. Sule SS, Frishman WH: Nebivolol. New therapy update. *Cardiol in Rev* 14: 259, 2006.
 - 69b. Somberg JC, Preston RA, Ranade V, Molnar J: Developing a safe intravenous sotalol dosing regimen. *Am J Therap* 17: 365, 2010.
 - 69c. Kamp O, Metra M, Bugatti S, et al: Nebivolol. Haemodynamic effects and clinical significance of combined β -blockade and nitric oxide release. *Drugs* 70: 41, 2010
 70. Frishman W: Clinical pharmacology of the new beta-adrenergic blocking drugs. Part I: Pharmacokinetic and pharmacodynamic properties. *Am Heart J* 97:663, 1979.
 71. Conolly ME, Kersting F, Dollery CT: The clinical pharmacology of beta-adrenoceptor blocking drugs. *Prog Cardiovasc Dis* 19:203, 1976.
 72. Singh BN, Deedwania P, Nademanee K, et al: Sotalol: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 34:311, 1987.
 73. Morgan T: Clinical pharmacokinetics and pharmacodynamics of carvedilol. *Clin Pharmacokinet* 26:335, 1994.
 74. Opie LH, Yusuf S: Beta-blocking agents. In: Opie LH, Gersh BJ, eds. *Drugs for the Heart*, 5th ed. Philadelphia:Saunders, 2001:1.
 75. Frishman W, Jacob H, Eisenberg E, Ribner H: Clinical pharmacology of the new beta-adrenergic blocking drugs. Part VIII: Self-poisoning with beta-adrenoceptor blocking drugs: recognition and management. *Am Heart J* 98:798, 1979.
 76. Lands AM, Arnold A, McAuliff JP, et al: Differentiation of receptor systems activated by sympathomimetic amine. *Nature* 214: 597,1967.
 77. Frishman WH: Alpha- and beta-adrenergic blocking drugs. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed.* New York : McGraw Hill 2003: 67.
 78. Wright P: Untoward effect associated with practolol administration: oculomucocutaneous syndrome. *Br Med J* 1: 595,1975.
 79. Frishman WH: α - and β -adrenergic blocking drugs. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics Manual 2nd ed.* New York: McGraw Hill 2005; 19.
 80. Frishman WH Clinical differences between beta-adrenergic blocking agents: implications for therapeutic substitution. *Am Heart J* 113: 1190,1987.
 81. Xamoterol in Severe Heart Failure Study Group: Xamoterol in severe heart failure. *Lancet* 336: 1,1990.
 82. Frishman W, Halprin S. Clinical pharmacology of the new beta-adrenergic blocking drugs. Part VII: new horizons in beta-adrenoceptor blocking thera-

- py: labetalol. *Am Heart J* 1979; 98: 660.
83. Frishman WH, Sica DA: β -Adrenergic blockers. In, Izzo JL, Jr., Sica D, Black HR, Eds.: *Hypertension Primer, 4th ed.: The Essentials of High Blood Pressure*. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2008: p 446-450.
 84. Wisler JW, DeWire SM, Whalen EJ, et al: A unique mechanism of β -blocker action: carvedilol stimulates β -arrestin signaling. *Proc Natl Acad Sci* 104: 16657, 2007.
 85. Waal Manning HJ: Hypertension: which beta-blocker? *Drugs* 12: 412, 1976.
 86. Frishman WH, Lazar EJ, Gorodokin G: Pharmacokinetic optimization of therapy with beta-adrenergic blocking agents. *Clin Pharmacokinet* 20:311, 1991.
 87. Frishman WH, Alwarshetty M: Beta-adrenergic blockers in systemic hypertension: pharmacokinetic considerations related to the JNC-VI and WHO-ISH current guidelines. *Clin Pharmacokinet* 42:505,2002.
 88. Frishman WH, Teicher M: Long-acting propranolol. *Cardiovasc Rev Rep* 4:100, 1983.
 89. Halkin H, Vered I, Saginer A, Rabinowitz B: Once-daily administration of sustained release propranolol capsules in the treatment of angina pectoris. *Eur J Clin Pharmacol* 16:387, 1979.
 90. Abrahamsson B, Lucker P, Olofsson, et al: The relationship between metoprolol plasma concentration and β_1 -blockade in healthy subjects: a study on conventional metoprolol and metoprolol CR/ZOK formulations. *J Clin Pharmacol* 30:S46, 1990.
 91. Sandberg A, Blomqvist I, Jonsson UE, Lundborg P: Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol: a comparison with conventional tablets. *Eur J Clin Pharmacol* 33(Suppl):S9, 1988.
 92. Frishman WH, Murthy VS, Strom JA: Ultra-short acting β -adrenergic blockers. *Med Clin North Am* 72:359, 1988.
 93. Murthy VF, Frishman WH: Controlled beta-receptor blockade with esmolol and flestolol. *Pharmacotherapy* 8:168, 1988.
 94. Parker JO, Porter A, Parker JD: Propranolol in angina pectoris: comparison of long-acting and standard formulation propranolol. *Circulation* 65:1351, 1982.
 95. Matier WL, Patil G: Esprolol hydrochloride. A new beta adrenergic antagonist with a rapid onset of effect. *Heart Dis* 2:146, 2000.
 96. Reid JL: Nebivolol: the role of nitric oxide in hypertension—concluding remarks. *J Cardiovasc Pharmacol* 38(Suppl 3):S37, 2001.
 97. Tzemos N, Lim PO, MacDonald TM: Nebivolol reverses endothelial dysfunction in essential hypertension. A randomized, double-blind, crossover study. *Circulation* 104:511, 2001.
 98. Frishman WH: Acebutolol. *Cardiovasc Rev Rep* 6:979, 1985.
 99. Wurzelmann J, Frishman W, Aronson M, et al: Neuropsychiatric effects of antihypertensive drugs in the old old. *Cardiol Clin* 5:689, 1987.
 100. Carney RM, Rich MW, te Velde AJE, et al: Prevalence of major depressive disorders in patients receiving β -blocker therapy versus other medications. *Am J Med* 83:223, 1987.
 101. Kostis JB, Rosen RC: Central nervous system effects of β -adrenergic blocking drugs: the role of ancillary properties. *Circulation* 75:204, 1987.
 102. Cruickshank JM, Prichard BNC: *Beta-blockers in Clinical Practice*, 2nd ed. Edinburgh: Churchill Livingstone, 1994:277.
 103. Ward SA, Walle T, Walle UK, et al: Propranolol's metabolism is determined by both mephenytoin and debrisoquin hydroxylase activities. *Clin Pharmacol Ther* 45:72, 1989.
 104. Fujimaki M: Oxidation of the R(+) and S(-) carvedilol by rat liver microsome. Evidence for stereoselective oxidation and characterization of the cytochrome P450 isozymes involved. *Drug Metab Dispos* 22:700, 1994.
 105. Panton LB, Guillen GJ, Williams L, et al: The lack of effect of aerobic exercise training on propranolol pharmacokinetics in young and elderly adults. *J Clin Pharmacol* 35:885, 1995.
 106. McAlister FA, Wiebe N, Ezekowitz JA, et al: Meta-analysis: β -Blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 150: 784, 2009.
 107. Cohn JN: Nitroprusside and dissecting aneurysm of aorta (correspondence). *N Engl J Med* 295:567, 1976.
 108. Cohen LS, Braunwald E: Amelioration of angina pectoris in idiopathic hypertrophic subaortic stenosis with beta-adrenergic blockade. *Circulation* 35:847-851, 1967.
 109. Turner JRB: Propranolol in the treatment of digitalis-induced and digitalis-resistant tachycardia. *Am J Cardiol* 18:450, 1966.
 110. Winkle RA, Lopes MG, Goodman DS, et al: Propranolol for patients with mitral valve prolapse. *Am Heart J* 93:422, 1970.
 111. Krahn AD, Yee R, Chauhan V, et al: Beta blockers normalize QT hysteresis in long QT syndrome. *Am Heart J* 143:528, 2002.
 112. Kornbluth A, Frishman WH, Ackerman M: Beta-adrenergic blockade in children. *Cardiol Clin* 5:629, 1987.

113. Meister SG, Engel TR, Feitosa GS, et al: Propranolol in mitral stenosis during sinus rhythm. *Am Heart J* 94:685, 1977.
114. Svedberg K, Hjalmarson A, Waagstein F, Wallentin I: Beneficial effects of long-term beta-blockade in congestive cardiomyopathy. *Br Heart J* 44:117, 1980.
115. Sullebarger JT, Liang C-s: Beta-adrenergic receptor stimulation and inhibition in chronic congestive heart failure. *Heart Failure* 7:154, 1991.
116. Kraus ML, Gottlieb LD, Horwitz RI, Anscher M: Randomized clinical trial of atenolol in patients with alcohol withdrawal. *N Engl J Med* 313:905, 1985.
117. Weber RB, Reinmuth OM: The treatment of migraine with propranolol. *Neurology (NY)* 22:366, 1972.
118. Young RR, Growdon JH, Shahani BT: Beta-adrenergic mechanisms in action tremor. *N Engl J Med* 293:950, 1975.
119. Frishman WH, Razin A, Swencionis C, Sonnenblick EH: Beta-adrenoceptor blockade in anxiety states: a new approach to therapy. Update. *Cardiovasc Rev Rep (Classics of the Decade Series)* 13(2):8, 1992.
120. Ingbar SH: The role of antiadrenergic agents in the management of thyrotoxicosis. *Cardiovasc Rev Rep* 2:683, 1981.
121. Caro JF, Castro JH, Glennon JA: Effect of long-term propranolol administration on parathyroid hormone and calcium concentration in primary hyperparathyroidism. *Ann Intern Med* 91:740, 1979.
122. Lebrech D, Poynard T, Hillon P, Benhamou J-P: Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis. *N Engl J Med* 305:1371, 1981.
123. Herndon DN, Hart DW, Wolf SE, et al: Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 345:1223, 2001.
124. SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 265:3255, 1991.
125. Kostis JB, Berge KG, Davis BR, et al: Effect of atenolol and reserpine on selected events in the Systolic Hypertension in the Elderly Program (SHEP). *Am J Hypertens* 8:1147, 1995.
126. Dahlof B, Lindholm LH, Hansson L, et al: Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP Hypertension). *JAMA* 289: 2560,2003.
127. The Seventh Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC 7 report). *Arch Intern Med* 153:154, 1993.
128. Messerli FH, Grossman E, Goldbourt U: Are β blockers efficacious as first-line therapy for hypertension in the elderly? *JAMA* 279:1903, 1998.
129. Cutler JA, Davis BR: Should β blockers and diuretics remain as first-line therapy for hypertension? *Circulation* 117: 2691,2008.
130. Lindholm LH, Carlberg B, Samuelsson O: Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 366: 1545, 2005.
131. Lindholm LH, Ibsen H, Devereux RB, et al: Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE), a randomised trial against atenolol. *Lancet* 359:1004, 2002.
132. Gress TW, Nieto J, Shahar E, et al for the Atherosclerosis Risk in Communities Study: Hypertension and anti-hypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 342: 905,2000.
133. Sowers JR, Bakris GL: Antihypertensive therapy and the risk of type 2 diabetes mellitus (editorial). *N Engl J Med* 342: 969,2000.
134. Sarafidis P, Bogojevic Z, Basta E, et al: Comparative efficacy of two different β blockers on 24-hour blood pressure control. *J Clin Hypertens* 10: 112,2008.
135. Bakris GL, Fonseca V, Katholi RE, et al for the GEMINI Investigators: Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 292: 2227,2004.
136. Ram CVS: β blockers in hypertension: truths and half-truths (editorial). *J Clin Hypertens* 10: 516,2008.
137. Weber MA, Bakris GL, Giles TD, Messerli FH: β blockers in the treatment of hypertension: new data, new directions. *J Clin Hypertens* 10: 234,2008.
138. Chrysant SG, Chrysant GS, Dimas B: Current and future status of beta blockers in the treatment of hypertension. *Clin Cardiol* 31: 249,2008.
139. Saunders E, Weir MR, Kong BW, et al: A comparison of the efficacy and safety of a β -blocker, a calcium channel blocker, and a converting enzyme inhibitor in hypertensive blacks. *Arch Intern Med* 150:1707, 1990.
- 139a. Frohlich ED: Hyperdynamic *Circulation* and hypertension. *Postgrad Med* 52:68-74, 1972.
140. Blumenfeld ID, Sealey JE, Manner SJ, et al: β -

- Adrenergic receptor blockade as a therapeutic approach for suppressing the renin-angiotensin-aldosterone system in normotensive and hypertensive subjects. *Am J Hypertens* 12:451, 1999.
141. Myers MG, Lewis PJ, Reid JL, Dollery CT: Brain concentration of propranolol in relation to hypotension effects in the rabbit with observations on brain propranolol levels in man. *J Pharmacol Exp Ther* 192:327, 1975.
 142. Prichard BNC: Propranolol as an antihypertensive agent. *Am Heart J* 79:128-133, 1979.
 143. Imhof PR: Characterization of beta-blockers as antihypertensive agents in the light of human pharmacology studies, In: Schweizer W, ed. *Beta-Blockers—Present Status and Future Prospects*. Bern: Huber, 1974:40-50.
 144. Langer SZ: Presynaptic receptors and their role in the regulation of transmitter release. *Br J Pharmacol* 60:481, 1977.
 145. Berthelsen S, Pettinger WA: A functional basis for classification of β -adrenergic receptors. *Life Sci* 21:595, 1977.
 146. Yamaguchi N, de Champlain J, Nadeau RL: Regulation of norepinephrine release from cardiac sympathetic fibers in the dog by presynaptic α - and β -receptors. *Circ Res* 41:108, 1976.
 147. Stjarne L, Brundin J: β -Adrenoceptors facilitate noradrenaline secretion from human vasoconstrictor nerves. *Acta Physiol Scand* 97:88, 1976.
 148. Majewski HJ, McCulloch MW, Rand MJ, Story DF: Adrenaline activation of prejunctional β -adrenoceptors in guinea pig atria. *Br J Pharmacol* 71:435, 1980.
 149. Savolainen A, Keto P, Poutanen V-P, et al: Effects of angiotensin converting enzyme inhibition versus β -adrenergic blockade on aortic stiffness in essential hypertension. *J Cardiovasc Pharmacol* 27:99, 1996.
 150. Waal HJ: Hypotensive action of propranolol. *Clin Pharmacol Ther* 7:588-598, 1966.
 151. Rahn KH, Hawlina A, Kersting F, Peanz G: Studies on the antihypertensive action of the optical isomers of propranolol in man. *Naunyn Schmiedeberg's Arch Pharmacol* 286:319-, 1974.
 152. Pickering TG, Gribbin B, Petersen ES, et al: Effects of autonomic blockade on the baroreflex in man at rest and during exercise. *Circ Res* 30:177, 1972.
 153. Kato N, Sugiyama T, Morita H, et al: Association analysis of β_2 -adrenergic receptor polymorphisms with hypertension in Japanese. *Hypertension* 37:286, 2001.
 154. Bray MS, Krushkal J, Li L, et al: Positional genomic analysis identifies the β_2 -adrenergic receptor gene as a susceptibility locus for human hypertension. *Circulation* 101:2877, 2000.
 155. Bengtsson K, Melander O, Orho-Melander M, et al: Polymorphism in the β_1 -adrenergic receptor gene and hypertension. *Circulation* 104:187, 2001.
 156. Jia H, Hingorani AD, Sharma P, et al: Association of the $G_s\alpha$ gene with essential hypertension and response to β blockade. *Hypertension* 34:8, 1999.
 157. Sonnenblick EH, Ross J Jr, Braunwald E: Oxygen consumption of the heart: newer concepts of its multifactorial determination. *Am J Cardiol* 22:328-336, 1968.
 158. Sonnenblick EH, Skelton CL: Myocardial energetics: basic principles and clinical implications. *N Engl J Med* 285:668-675, 1971.
 159. Black JW, Stephenson JS: Pharmacology of a new adrenergic beta-receptor blocking compound (Nethalide). *Lancet* 2:311-314, 1962.
 160. Frishman WH: Beta-adrenergic blockade in the treatment of coronary artery disease. In: Hurst JW, ed. *Clinical Essays on the Heart*, Vol 2. New York: McGraw-Hill, 1983:25.
 161. Billinger M, Seiler C, Fleisch M, et al: Do beta-adrenergic blocking agents increase coronary flow reserve? *J Am Coll Cardiol* 38:1866, 2001.
 162. Frishman WH, Gabor R, Pepine C, Cavusoglu E: Heart rate reduction in the treatment of chronic stable angina pectoris: experience with a sinus node inhibitor. *Am Heart J* 131:204, 1996.
 163. Brouwer J, Viersma JW, van Veldhuisen DJ, et al: Usefulness of heart rate variability in predicting drug efficacy (metoprolol vs diltiazem) in patients with stable angina pectoris. *Am J Cardiol* 76:759, 1995.
 164. Ardissino D, Savonitto S, Egstrup K, et al: Selection of medical treatment in stable angina pectoris: results of the International Multicenter Angina Exercise (IMAGE) study. *J Am Coll Cardiol* 25:1516, 1995.
 165. Frishman W, Pepine CJ, Weiss R, Baiker WM for the Zatebradine Study Group: Addition of zatebradine, a direct sinus node inhibitor, provides no greater exercise tolerance benefit in patients with angina pectoris taking extended-release nifedipine: results of a multicenter, randomized, double-blind, placebo-controlled, parallel group study. *J Am Coll Cardiol* 26:305, 1995.
 166. Parratt JR, Grayson J: Myocardial vascular reactivity after β -adrenergic blockade. *Lancet* 1:338-340, 1966.
 167. Becker LC, Fortuin NJ, Pitt B: Effects of ischemia and anti-anginal drugs on the distribution of radioactive microspheres in the canine left ventricle. *Circ Res* 28:263-269, 1971.
 168. Wolfson S, Gorlin R: Cardiovascular pharmacolo-

- gy of propranolol in man. *Circulation* 40:501, 1969.
169. Barrett AM: A comparison of the effect of (+) propranolol and (+) propranolol in anesthetized dogs: β -receptor blocking and hemodynamic action. *J Pharm Pharmacol* 21:241, 1969.
 170. Bjorntorp P: Treatment of angina pectoris with beta-adrenergic blockade: mode of action. *Acta Med Scand* 184:259, 1968.
 171. Fihn SD, Williams SV, Daley J, Gibbons RJ: Guidelines for the management of patients with chronic stable angina: treatment. *Ann Intern Med* 135:616, 2001.
 172. Haim M, Shotan A, Boyko V, et al for the Bezafibrate Infarction Prevention (BIP) Study Group: effect of beta blocker therapy in patients with coronary artery disease in New York Heart Association classes II and III. *Am J Cardiol* 81:1455, 1998.
 173. Heidenreich PA, McDonald KM, Hastie T, et al: Meta-analysis of trials comparing β blockers, calcium antagonists, and nitrates for stable angina. *JAMA* 281:1927, 1999.
 174. Marie PY, Danchin N, Branly F, et al: Effects of medical therapy on outcome assessment using exercise thallium-201 single photon emission computer tomography imaging. Evidence from a protective effect of beta-blocking antianginal medications. *J Am Coll Cardiol* 34:113, 1999.
 175. Task Force of the European Society of Cardiology: management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 18:394, 1997.
 176. Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: Executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). *Circulation* 99:2829, 1999.
 177. Frishman WH, Smithen C, Befler B, et al: Non-invasive assessment of clinical response to oral propranolol. *Am J Cardiol* 35:635, 1975.
 178. Gauri AJ, Raxwal VK, Roux L, et al: Effects of chronotropic incompetence and β blocker use on the exercise treadmill test in men. *Am Heart J* 142:136, 2001.
 179. Robinson BF: The mode of action of beta-antagonists in angina pectoris. *Postgrad Med J* 47:41, 1971.
 180. Packer M: Combined beta-adrenergic and calcium-entry blockade in angina pectoris. *N Engl J Med* 320:709, 1989.
 181. Weiner DA, Klein MD: Calcium antagonists for the treatment of angina pectoris. In: Weiner DA, Frishman WH, eds. *Therapy of Angina Pectoris*. New York: Marcel Dekker, 1986:45-204.
 182. Weiner DA: Calcium channel blockers. *Med Clin North Am* 72:83, 1988.
 183. Frishman WH, Charlap S, Farham J, et al: Combination propranolol and bepridil therapy in stable angina pectoris. *Am J Cardiol* 55:43C, 1985.
 184. Schwarz ER, Klues HG, vom Dahl J, et al: Functional, angiographic and intracoronary Doppler flow characteristics in symptomatic patients with myocardial bridging: effect of short-term intravenous beta-blocker medication. *J Am Coll Cardiol* 27:1637, 1996.
 185. ACC/AHA 2002 Guidelines Update for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction. www.acc.org/clinical/guidelines/unstable.pdf 2002.
 186. Doo Y-C, Kim D-M, Oh D-J, et al: Effect of beta blockers on expression of interleukin-6 and C-reactive protein in patients with unstable angina pectoris. *Am J Cardiol* 88:422, 2001.
 - 186a. Rangel C, Shu RG, Lazar LD, et al: β -Blockers for Chest pain associated with recent cocaine use. *Arch Intern Med* 170: 874, 2010.
 187. Jenkins NP, Keevil BG, Hutchinson IV, Brooks NH: Beta-blockers are associated with lower C-reactive protein concentrations in patients with coronary artery disease. *Am J Med* 112:269, 2002.
 188. Miura D, Frishman WH, Dangman KH: Class II drugs. In: Dangman KH, Miura D, eds. *Basic and Clinical Electrophysiology and Pharmacology of the Heart*. New York: Marcel Dekker, 1991:665-676.
 189. Nademanee K, Taylor R, Bailey WE, et al: Treating electrical storm. Sympathetic blockade versus advanced cardiac life support-guided therapy. *Circulation* 102:742, 2000.
 190. Xu X, Zhang M, Kyker K, et al: Ischemic inactivation of G protein-coupled receptor kinase and altered desensitization of canine cardiac β -adrenergic receptors. *Circulation* 102:2535, 2000.
 191. Tisdale JE, Sun H, Zhao H, et al: Antifibrillatory effect of esmolol alone and in combination with lidocaine. *J Cardiovasc Pharmacol* 27:376, 1996.
 192. Cavusoglu E, Frishman WH: Sotalol: a new β -adrenergic blocker for ventricular arrhythmias. *Prog Cardiovasc Dis* 37:423, 1995.
 193. Anderson JL, Prystowsky EN: Sotalol: an important new antiarrhythmic. *Am Heart J* 137:388, 1999.
 194. Kühlkamp V, Mewis C, Mermi J, et al: Suppression of sustained ventricular tachyarrhythmias: a comparison of d,l-sotalol with no antiarrhythmic drug treatment. *J Am Coll Cardiol* 33:46, 1999.
 195. Pacifico A, Hohnloser SH, Williams JH, et al for the d,l-Sotalol Implantable Cardioverter-Defibrillator

- Study Group: prevention of implantable defibrillator shocks by treatment with sotalol. *N Engl J Med* 340:1855, 1999.
196. Mewis C, Kùhlkamp V, Mermi J, et al: Long-term reproducibility of electrophysiologically guided therapy with sotalol in patients with ventricular tachyarrhythmias. *J Am Coll Cardiol* 33:1989, 1999.
 197. Lai L-P, Lin J-L, Lien W-P, et al: Intravenous sotalol decreases transthoracic cardioversion energy requirement for chronic atrial fibrillation in humans: assessment of the electrophysiological effects by biatrial basket electrodes. *J Am Coll Cardiol* 35:1434, 2000.
 198. Southworth MR, Zarembski D, Viana M, Bauman J: Comparison of sotalol versus quinidine for maintenance of normal sinus rhythm in patients with chronic atrial fibrillation. *Am J Cardiol* 83:1629, 1999.
 199. Tse H-F, Lau C-P, Ayers GM: Incidence and modes of onset of early reinitiation of atrial fibrillation after successful internal cardioversion, and its prevention by intravenous sotalol. *Heart* 82:319, 1999.
 200. Gomes JA, Ip J, Santoni-Rugiu F, et al: Oral d,l sotalol reduces the incidence of postoperative atrial fibrillation in coronary artery bypass surgery patients: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 34:334, 1999.
 201. Benditt DG, Williams JH, Deering TF, et al for the d,l Sotalol Atrial Fibrillation/Flutter Study Group: Maintenance of sinus rhythm with oral d,l sotalol therapy in patients with symptomatic atrial fibrillation and/or atrial flutter. *Am J Cardiol* 84:270, 1999.
 202. Bellandi F, Simonetti I, Leoncini M, et al: Long-term efficacy and safety of propafenone and sotalol for the maintenance of sinus rhythm after conversion of recurrent symptomatic atrial fibrillation. *Am J Cardiol* 88:640, 2001.
 203. Amato Vincenzo de Paola A, Horta Veloso H, for the SOCESP Investigators: efficacy and safety of sotalol versus quinidine for the maintenance of sinus rhythm after conversion of atrial fibrillation. *Am J Cardiol* 84:1033, 1999.
 204. Kochiadakis GE, Igoumenidis NE, Marketous ME, et al: Low dose amiodarone and sotalol in the treatment of recurrent, symptomatic atrial fibrillation: a comparative, placebo controlled study. *Heart* 84:251, 2000.
 205. Waldo AL, Camm AJ, deRuyter H, et al for the SWORD Investigators: effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 348:7, 1996.
 206. Pratt CM, Camm AJ, Cooper W, et al for the SWORD Investigators: mortality in the Survival with Oral D-Sotalol (SWORD) Trial: Why did patients die? *Am J Cardiol* 81:869, 1998.
 207. Lehmann MH, Hardy S, Archibald D, MacNeil DJ: JTc prolongation with d,l sotalol in women versus men. *Am J Cardiol* 83:354, 1999.
 208. Chung MK, Schweikert RA, Wilkoff BL, et al: Is hospital admission for initiation of anti-arrhythmic therapy with sotalol for atrial arrhythmias required? Yield of in-hospital monitoring and prediction of risk for significant arrhythmia complications. *J Am Coll Cardiol* 32:169, 1998.
 209. Barbey JT, Sale ME, Woosley RL, et al: Pharmacokinetic, pharmacodynamic, and safety evaluation of an accelerated dose titration regimen of sotalol in healthy middle-aged subjects. *Clin Pharmacol Ther* 66:91, 1999.
 210. Kùhlkamp V, Schirdewan A, Stangl K, et al: Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 36:139, 2000.
 211. Page RL: Beta blockers for atrial fibrillation: must we consider asymptomatic arrhythmias? *J Am Coll Cardiol* 36:147, 2000.
 212. Farshi R, Kistner D, Sarma JSM, et al: Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol* 33:304, 1999.
 213. Sager PT: Modulation of antiarrhythmic drug effects by beta-adrenergic sympathetic stimulation. *Am J Cardiol* 82:201, 1998.
 214. Boutitie F, Boissel J-P, Connolly SJ, et al and the EMIAT and CAMIAT Investigators: Amiodarone interaction with β blockers. Analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. *Circulation* 99:2268, 1999.
 215. Antz M, Cappato R, Kuck K-H: Metoprolol versus sotalol in the treatment of sustained ventricular tachycardia. *J Cardiovasc Pharmacol* 26:627, 1995.
 216. Pitzalia MV, Mastropasqua F, Massari F, et al: Holter-guided identification of premature ventricular contractions susceptible to suppression by β blockers. *Am Heart J* 131:508, 1996.
 217. Reiter MJ, Reiffel JA: Importance of beta blockade in the therapy of serious ventricular arrhythmias. *Am J Cardiol* 82:9I, 1998.
 218. Exner DV, Reiffel JA, Epstein AE, et al and the AVID Investigators: beta blocker use and survival in patients with ventricular fibrillation or symptomatic ventricular tachycardia: the Antiarrhythmics versus Implantable Defibrillators (AVID)

- trial. *J Am Coll Cardiol* 34:325, 1999.
219. Frishman WH, Cavusoglu E: β -Adrenergic blockers and their role in the therapy of arrhythmias. In: Podrid PJ, Kowey PR, eds. *Cardiac Arrhythmias: Mechanisms, Diagnosis and Management*. Baltimore: Williams & Wilkins, 1995:421-433.
 220. Ryden L, Ariniego R, Arnman K, et al: A double-blind trial of metoprolol in acute myocardial infarction: effects on ventricular tachyarrhythmias. *N Engl J Med* 308:614-618, 1983.
 221. Lichstein E, Morganroth J, Harrist R, et al for the BHAT Study Group: Effect of propranolol on ventricular arrhythmia—the Beta Blocker Heart Attack Trial Experience. *Circulation* 67:15, 1983.
 222. Szabo BM, Crijin HJGM, Wiesfeld ACP, et al: Predictors of mortality in patients with sustained ventricular tachycardias or ventricular fibrillation and depressed left ventricular function: importance of β blockade. *Am Heart J* 130:281, 1995.
 223. Mason JW for the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM): a comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. *N Engl J Med* 329:452, 1993.
 224. Kennedy HL, Brooks MM, Barker AH, et al: Beta blocker therapy in the Cardiac Arrhythmia Suppression Trial. *Am J Cardiol* 74:674, 1994.
 225. Steinbeck G, Andresen D, Bach P, et al: A comparison of electrophysiologically guided antiarrhythmic drug therapy with beta blocker therapy in patients with symptomatic, sustained ventricular tachyarrhythmias. *N Engl J Med* 327:987, 1992.
 226. Chiale PA, Rosenbaum MB, Elizari MV, et al: High prevalence of antibodies against β_1 - and β_2 -adrenoceptors in patients with primary electrical cardiac abnormalities. *J Am Coll Cardiol* 26:864, 1995.
 227. Iwata M, Yoshikawa T, Baba A, et al: Autoantibodies against the second extracellular loop of β_1 -adrenergic receptors predict ventricular tachycardia and sudden death in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 37:418, 2001.
 228. Braunwald E, Muller JE, Kloner RA, Maroko P: Role of beta-adrenergic blockade in the therapy of patients with myocardial infarction. *Am J Med* 74:113-123, 1983.
 229. Abrams J, Frishman W, Weitz J, Opie L: Pharmacologic options for treatment of ischemic disease. In: Antman E, ed. *Cardiovascular Therapeutics. A Companion to Braunwald's Heart Disease*, 2nd ed. Philadelphia: Saunders, 2002:97.
 230. Boissel-J-P, Leizorovicz A, Picolet H, et al for the APSI Investigators: secondary prevention after high risk myocardial infarction with low-dose acebutolol. *Am J Cardiol* 66:251, 1990.
 231. Parks KC, Forman DE, Wei JY: Utility of beta-blockade treatment for older postinfarction patients. *J Am Geriatr Soc* 43:751, 1995.
 232. Freemantle N, Cleland J, Young P, et al: β blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 318:1730, 1999.
 233. Furberg CD, Hawkins CM, Lichstein E: Effect of propranolol in post-infarction patients with mechanical or electrical complications. *Circulation* 69:761, 1984.
 234. Frishman WH: Role of β -adrenergic blockade. In: Fuster V, Ross R, Topol EJ, eds. *Atherosclerosis and Coronary Artery Disease*. New York: Lippincott, 1996:1205.
 235. Frishman WH: Secondary prevention of myocardial infarction: the roles of β -adrenergic blockers, calcium-channel blockers, angiotensin converting enzyme inhibitors, and aspirin. In: Willich SN, Muller JE, eds. *Triggering of Acute Coronary Syndromes*. The Netherlands: Kluwer, 1996:367.
 236. Frishman WH, Skolnick AE, Miller KP: Secondary prevention post infarction: The role of beta-adrenergic blockers, calcium-channel blockers, and aspirin. In: Gersh B, Rahimtoola S, eds. *Acute Myocardial Infarction*, 2nd ed. New York: Chapman & Hall, 1996: 766.
 237. Kendall MJ, Lynch KP, Hjalmarson A, Kjekshus J: β -Blockers and sudden cardiac death. *Ann Intern Med* 123:358, 1995.
 238. Tuininga YS, Crijns HJGM, Brouwer J, et al: Evaluation of importance of central effects of atenolol and metoprolol measured by heart rate variability during mental performance tasks, physical exercise, and daily life in stable postinfarct patients. *Circulation* 92:3415, 1995.
 239. Gottlieb SS, McCarter RJ: Comparative effects of three beta blockers (atenolol, metoprolol, and propranolol) on survival after acute myocardial infarction. *Am J Cardiol* 87:823, 2001.
 240. β Blockers are best antiarrhythmics for reducing post-MI mortality. *Drugs Ther Perspect* 17:5, 2001.
 241. Frishman WH, Lazar EJ: Reduction of mortality, sudden death and non-fatal reinfarction with beta-adrenergic blockers in survivors of acute myocardial infarction: a new hypothesis regarding the cardioprotective action of beta-adrenergic blockade. *Am J Cardiol* 66:66G, 1990.
 242. Williams MJA, Low CJS, Wilkins GT, Stewart RAH: Randomised comparison of the effects of nicardipine and esmolol on coronary artery wall stress: implications for the risk of plaque rupture. *Heart* 84:377, 2000.

243. Dargie HJ: Effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction: the CAPRICORN randomized trial. *Lancet* 357: 1385,2001.
244. Coreg CR (carvedilol phosphate) extended release capsules (package insert). Research Triangle Park, NC: GlaxoSmithKlein, 2007.
245. International Collaborative Study Group: Reduction of infarct size with the early use of timolol in acute myocardial infarction. *N Engl J Med* 310:9-15, 1984.
246. Hjalmarson A, Elmfeldt D, Herlitz J, et al: Effect of mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet* 2:823-827, 1981.
247. MIAMI Trial Research Group: Metoprolol in acute myocardial infarction (MIAMI): a randomized placebo-controlled international trial. *Eur Heart J* 6:199-226, 1985.
248. ISIS-I collaborative Group: Randomized trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-I. *Lancet* 2: 57, 1986.
249. Muller J, Roberts R, Stone P, et al: Failure of propranolol administration to limit infarct size in patients with acute myocardial infarction (abstr). *Circulation* 68 (Suppl. III):III294, 1983.
250. Barron HV, Rundle AC, Gore JM, et al for the Participants in the National Registry of Myocardial Infarction-2. Intracranial hemorrhage rates and effect of immediate beta-blocker use in patients with acute myocardial infarction treated with tissue plasminogen activators. *Am J Cardiol* 85:294, 2000.
251. Pfisterer M, Cox JL, Granger CB, et al for the GUSTO-I Investigators: atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction: the GUSTO-I experience. *J Am Coll Cardiol* 32:634, 1998.
252. Phillips BG, Yim JM, Brown EJ Jr, et al: Pharmacologic profile of survivors of acute myocardial infarction at United States academic hospitals. *Am Heart J* 131:872, 1996.
253. Ayanian JZ, Hauptman PJ, Guadagnoli E, et al: Knowledge and practices of generalist and specialist physicians regarding drug therapy for acute myocardial infarction. *N Engl J Med* 331:1136, 1994.
254. Soumerai SB, McLaughlin TJ, Spiegelman D, et al: Adverse outcomes of underuse of beta blockers in elderly survivors of acute myocardial infarction. *JAMA* 277:115, 1997.
255. Grand DA, Newcomer LN, Frieburger A, Tian H: Cardiologist's practice compared with practice guidelines: use of beta blockade after acute myocardial infarction. *J Am Coll Cardiol* 26:1432, 1995.
256. Phillips KA, Shlipak MG, Coxson P, et al: Health and economic benefits of increased β blocker use following myocardial infarction. *JAMA* 284:2748, 2000.
257. Chen J, Radford MJ, Wang Y, et al: Effectiveness of beta blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol* 37:1950, 2001.
258. Aronow WS, Ahn C: Effect of beta blockers on incidence of new coronary events in older persons with prior myocardial infarction and diabetes mellitus. *Am J Cardiol* 87:780, 2001.
259. Rochon PA, Tu JV, Anderson GM, et al: Rate of heart failure and 1-year survival for older people receiving low-dose β blocker therapy after myocardial infarction. *Lancet* 356:639, 2000.
260. Barron HV, Viskin S: Dispelling the myths surrounding the use of beta blockers in patients after acute myocardial infarction. *Prev Cardiol* 3:13, 1998.
261. Krumholz HM, Radford MJ, Wang Y, et al: National use and effectiveness of β blockers for the treatment of elderly patients after acute myocardial infarction. National Cooperative Cardiovascular Project. *JAMA* 280:623, 1998.
262. Krumholz HM, Radford MJ, Wang Y, et al: Early β blocker therapy for acute myocardial infarction in elderly patients. *Ann Intern Med* 131:648, 1999.
263. Chen J, Marciniak TA, Radford MJ, et al: Beta blocker therapy for secondary prevention of myocardial infarction in elderly diabetic patients. *J Am Coll Cardiol* 34:1388, 1999.
264. Gottlieb SS, McCarter RJ, Vogel RA: Effect of beta blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 339:489, 1998.
265. Heller DA, Ahern FM, Kozak M: Changes in rates of β blocker use between 1994 and 1997 among elderly survivors of acute myocardial infarction. *Am Heart J* 140:663, 2000.
266. Chen J, Radford MJ, Wang Y, et al: Are β blockers effective in elderly patients who undergo coronary revascularization after acute myocardial infarction? *Arch Intern Med* 160:947, 2000.
267. The CAPRICORN Investigators: Effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 357:1385, 2001.
268. Bradley EH, Holmboe ES, Matterna JA, et al: A qualitative study of increasing β blocker use after myocardial infarction. Why do some hospitals suc-

- ceed? *JAMA* 285:2604, 2001.
269. Soumerai SB, McLaughlin TJ, Gurwitz JH, et al: Effect of local medical opinion leaders on quality of care for acute myocardial infarction: a randomized controlled trial. *JAMA* 279:1358, 1998.
 270. Sarasin FP, Maschiangelo M-L, Schaller M-D, et al: Successful implementation of guidelines for encouraging the use of beta blockers in patients after acute myocardial infarction. *Am J Med* 106:499, 1999.
 271. Barron HV, Viskin S, Lumdstrom RJ, et al: β Blocker dosages and mortality after myocardial infarction. Data from a large health maintenance organization. *Arch Intern Med* 158:449, 1998.
 272. Gardtman M, Dellborg M, Brunnhage C, et al: Effect of intravenous metoprolol before hospital admission on *Chest* pain in suspected acute myocardial infarction. *Am Heart J* 137:821, 1999.
 273. Frishman WH, Teicher M: Antianginal drug therapy for silent myocardial ischemia. *Med Clin North Am* 72:185-196, 1988.
 274. Andrews TC, Fenton T, Toyosaki N, et al for the Angina and Silent Ischemia Study Group (ASIS): subsets of ambulatory myocardial ischemia based on heart rate activity. Circadian distribution and response to anti-ischemic medication. *Circulation* 88:92, 1993.
 275. Rogers WJ, Bourassa MG, Andrews TC, et al: Asymptomatic Cardiac Ischemia Pilot (ACIP) Study: Outcome at 1 year for patients with asymptomatic cardiac ischemia randomized to medical therapy or revascularization. *J Am Coll Cardiol* 26:594, 1995
 276. Pepine CJ, Cohn PF, Deedwania PC, et al for the ASIST (Atenolol/ Silent Ischemia Study) Study Group: effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. *Circulation* 90:762, 1994.
 277. Portegies MCM, Sijbring P, Gobel EJA, et al: Efficacy of metoprolol and diltiazem in treating silent myocardial ischemia. *Am J Cardiol* 74:1095, 1994.
 278. von Arnim T for the TIBBS Investigators: prognostic significance of transient ischemic episodes: response to treatment shows improves prognosis. *J Am Coll Cardiol* 28:20, 1996.
 279. Madjlessi-Simon T, Mary-Krause M, Fillette F, et al: Persistent transient myocardial ischemia despite beta-adrenergic blockade predicts a higher risk of adverse cardiac events in patients with coronary artery disease. *J Am Coll Cardiol* 27:1586, 1996.
 280. Engelhardt S, Bohm M, Erdmann E, Lohse MJ: Analysis of beta-adrenergic receptor mRNA levels in human ventricular biopsy specimens by quantitative polymerase chain reactions: progressive reduction of beta₁-adrenergic receptor mRNA in heart failure. *J Am Coll Cardiol* 27:146, 1996.
 281. De Mello WC: Impaired regulation of cell communication by β -adrenergic receptor activation in the failing heart. *Hypertension* 27:265, 1996.
 282. Wu J-R, Chang H-R, Huang T-Y, et al: Reduction in lymphocyte β -adrenergic density in infants and children with heart failure secondary to congenital heart failure. *Am J Cardiol* 22:120, 1996.
 283. Akhter SA, Eckhart AD, Rockman HA, et al: In vivo inhibition of elevated myocardial β -adrenergic receptor kinase activity in hybrid transgenic mice restores normal β -adrenergic signaling and function. *Circulation* 100:648, 1999.
 284. Cho M-C, Rao M, Koch WJ, et al: Enhanced contractility and decreased β -adrenergic receptor kinase-1 in mice lacking endogenous norepinephrine and epinephrine. *Circulation* 99:2702, 1999.
 285. Moniotte S, Kobzik L, Feron O, et al: Upregulation of beta₃ adrenoceptors and altered contractile response to inotropic amines in human failing myocardium. *Circulation* 103:1649, 2001.
 286. Sackner-Bernstein JD, Mancini DM: Rationale for treatment of patients with chronic heart failure with adrenergic blockade. *JAMA* 274:1462, 1995.
 287. LeJemtel TH, Sonnenblick EH, Frishman WH: Diagnosis and management of heart failure. In: Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's The Heart*, 10th ed. New York: McGraw-Hill, 2000:687.
 288. White DC, Hata JA, Shah AS, et al: Preservation of myocardial β -adrenergic receptor signaling delays the development of heart failure after myocardial infarction. *Proc Natl Acad Sci USA* 97:5428, 2000.
 289. Manning BS, Shotwell K, Mao L, et al: Physiological induction of a β -adrenergic receptor kinase inhibitor transgene preserves β -adrenergic responsiveness in pressure-overload cardiac hypertrophy. *Circulation* 102:2751, 2000.
 290. Shad AS, White DC, Emani S, et al: In vivo ventricular gene delivery of a β -adrenergic receptor kinase inhibitor to the failing heart reverses cardiac dysfunction. *Circulation* 103:1311, 2001.
 291. Podlowski S, Luther HP, Morwinski R, et al: Agonistic anti-beta₁-adrenergic receptor autoantibodies from cardiomyopathy patients reduces the beta₁-adrenergic receptor expression in neonatal rat cardiomyocytes. *Circulation* 98:2470, 1998.
 292. Francis GS, Goldsmith SR, Cohn JN: Relationship of exercise capacity to resting left ventricular performance and basal plasma norepinephrine levels in patients with congestive heart failure. *Am Heart J* 104:725, 1982.
 293. Viquerat CE, Daly P, Swedberg K, et al: Endogenous catecholamine levels in congestive heart failure: relation to severity of hemodynamic abnor-

- mality. *Am J Med* 78:455, 1985.
294. Stanek B, Frey B, Hulsmann M, et al: Prognostic evaluation of neurohumoral plasma levels before and during beta blocker therapy in advanced left ventricular dysfunction. *J Am Coll Cardiol* 38:436, 2001.
295. Frishman WH: Multifactorial actions of β -adrenergic blocking drugs in ischemic heart disease. *Circulation* 67(Suppl I):I-11, 1983.
296. Daley PA, Sole MJ: Myocardial catecholamines and the pathophysiology of heart failure. *Circulation* 82(Suppl I):I-35, 1990.
297. Henderson EB, Kahn JK, Corbett JR, et al: Abnormal I123 metaiodobenzylguanidine myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive heart failure. *Circulation* 78:1192, 1988.
298. Cruikshank JM, Neil-Dwyer G, Degaute JP, et al: Reduction of stress/catecholamine induced cardiac necrosis by beta I-selective blockade. *Lancet* 2:585, 1987.
299. Pauletto P, Vescove G, Scannapieco G, et al: Cardioprotection by beta blockers: molecular and structural aspects in experimental hypertension. *Drugs Exp Clin Res* 16(3):1055, 1990.
300. Shizukuda Y, Buttrick PM, Geenen DL, et al: β -Adrenergic stimulation causes cardiocyte apoptosis: influence of tachycardia and hypertrophy. *Am J Physiol* 275:H961, 1998.
301. Iwai-Kanai E, Hasegawa K, Araki M, et al: α - and β -adrenergic pathways differentially regulate cell type-specific apoptosis in rat cardiac myocytes. *Circulation* 100:305, 1999.
302. Podrid PJ, Fuchs T, Candinas R: Role of the sympathetic nervous system in the genesis of ventricular arrhythmias. *Circulation* 82 (Suppl I):I-103, 1990.
303. Wit AL, Cranefield PF: Triggered and automatic activity in the canine coronary sinus. *Circ Res* 41:433, 1977.
304. Engelmeier RS, O'Connell JB, Walsh R, et al: Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial. *Circulation* 72:536, 1985.
305. Waagstein F, Bristow MR, Swedberg K, et al: Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 342:1441, 1993.
306. Olsen SL, Gilbert EM, Renlund DG, et al: Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. *J Am Coll Cardiol* 25:1225, 1995.
307. Metra M, Nardi M, Giubbini R, Dei Cas L: Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity, and clinical conditions in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 24:1678, 1994.
308. Krum H, Sackner-Bernstein J, Goldsmith RL, et al: Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation* 92:1499, 1995.
309. Australia-New Zealand Heart Failure Research Collaborative Group: Effects of carvedilol, a vasodilator- β blocker, in patients with congestive heart failure due to ischemic heart disease. *Circulation* 92:212, 1995.
310. Eichhorn EJ, McGhie AA, Bendotto JB, et al: Effects of bucindolol on neurohormonal activation in congestive heart failure. *Am J Cardiol* 67:67, 1991.
311. Leizorovicz A, Lechat P, Cucherat M, Bugnard F: Bisoprolol for the treatment of chronic heart failure: a meta analysis on individual data of two placebo-controlled studies—CIBIS and CIBIS II. *Am Heart J* 143:301, 2002.
312. Goldstein S: Benefits of β -blocker therapy for heart failure. Weighing the evidence. *Arch Intern Med* 162: 641, 2002.
313. Farrell MH, Foody JM, Krumholz HM: β -blockers in heart failure: clinical applications. *JAMA* 287: 890, 2002.
314. Packer M, Coats AJS, Fowler MB, et al for the Carvedilol Prospective Randomized Cumulative Survival Study Group: Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 344: 1651, 2001.
315. Packer M, Bristow MR, Cohn N, et al: Effect of carvedilol on morbidity and mortality in chronic heart failure. *N Engl J Med* 334:1349-1355, 1996.
316. Joglar JA, Acosta AP, Shusterman NH, et al: Effect of carvedilol on survival and hemodynamics in patients with atrial fibrillation and left ventricular dysfunction: retrospective analysis of the U.S. Carvedilol Heart Failure Trials Program. *Am Heart J* 142:498, 2001.
317. Fowler MB, Vera-Llonch M, Oster G, et al for the U.S. Carvedilol Heart Failure Study Group: influence of carvedilol on hospitalizations in heart failure: incidence, resource utilization and costs. *J Am Coll Cardiol* 37:1692, 2001.
318. Yancy CW, Fowler MB, Colucci WS, et al for the U.S. Carvedilol Heart Failure Study Group: Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N Engl J Med* 344:1358, 2001.
319. Kumar A, Choudhary G, Antonio C, et al: Carvedilol titration in patients with congestive heart

- failure receiving inotropic therapy. *Am Heart J* 142:512, 2001.
320. CIBIS-II Investigators and Committee: The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomized trial. *Lancet* 353: 9, 1999.
 321. Hjalmarson A, Goldstein S, Fagerberg B, et al: for the MERIT-HF Study Group: Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *JAMA* 283:1295, 2000.
 322. Prakash A, Markham A: Metoprolol. A review of its use in chronic heart failure. *Drugs* 60:647, 2000.
 323. Ghali JK, Piña IL, Gottlieb SS, et al: Metoprolol CR/XL in female patients with heart failure. Analysis of the experience in Metoprolol Extended-release Randomized Intervention Trial in Heart Failure (MERIT-HF). *Circulation* 105:1585, 2002.
 324. Gottlieb SS, Fisher ML, Kjekshus J, et al: Tolerability of β -blocker initiation and titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *Circulation* 105:1182, 2002.
 325. The Beta Blocker Evaluation of Survival Trial Investigators: a trial of the beta blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 344: 1659, 2001.
 326. Remme WJ, Torp-Pedersen C, Cleland JG, et al: Carvedilol protects better against vascular events than metoprolol in heart failure results from COMET. *J Am Coll Cardiol* 49: 963, 2007.
 327. Flather MD, Shibata MC, Coats AJ, et al: Randomized trial to determine the effects of nebivolol on mortality and cardiovascular hospital admissions in elderly patients with heart failure (SENIORS). *Eur Heart J* 26:215, 2005.
 328. van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al on behalf of the SENIORS Investigators: Beta blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction. Data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure). *J Am Coll Cardiol* 53: 2150, 2009.
 329. Hernandez AF, Hammill BG, O'Connor CM, et al: Clinical effectiveness of beta blockers in heart failure. Findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry. *J Am Coll Cardiol* 53: 184, 2009.
 330. Gilbert EM, Sandoval A, Larrabee P, et al: Lisinopril lowers cardiac adrenergic drive and increases beta-receptor density in the failing human heart. *Circulation* 88:472, 1993.
 331. Whyte K, Jones CR, Howie CA, et al: Haemodynamic, metabolic, and lymphocyte beta 2-adrenoceptor changes following chronic beta-adrenoceptor antagonism. *Eur Heart J* 32:237, 1987.
 332. Lowes BD, Gilbert EM, Abraham MT, et al: Myocardial gene expression in dilated cardiomyopathy treated with beta blocking agents. *N Engl J Med* 346:1357, 2002.
 333. Luchner A, Burnett JC Jr, Jougasaki M, et al: Augmentation of the cardiac natriuretic peptides by beta-receptor antagonism: evidence from a population-based study. *J Am Coll Cardiol* 32:1839, 1998.
 334. Floras J, Jones J, Hassan O, Sleight P: Effects of acute and chronic beta-adrenergic blockade on baroreflex sensitivity (abstr). *J Am Coll Cardiol* 11:148A, 1988.
 335. Shimoyama H, Sabbah HN, Rosman H, et al: Effect of β blockade on left atrial contribution to ventricular flow. Iptilling in dogs with moderate heart failure. *Am Heart J* 131:772, 1996.
 336. Kubo H, Margulies KB, Piacentino V, et al: Patients with end-stage congestive heart failure treated with β -adrenergic receptor antagonists have improved ventricular myocyte calcium regulatory protein abundance. *Circulation* 104:1012, 2001.
 337. Reiken S, Gaburjakova M, Gaburjakova J, et al. β -Adrenergic receptor blockers restore cardiac calcium release channel (ryanodine receptor) structure and function in heart failure. *Circulation* 104:2843, 2001.
 338. Doi M, Yano M, Kabayashi S, et al: Propranolol prevents the development of heart failure by restoring FKBP 12.6-mediated stabilization by ryanodine receptor. *Circulation* 105:1374, 2002.
 339. Jonas M, Reicher-Reiss H, Boyko V, et al: Usefulness of beta blocker therapy in patients with non-insulin dependent diabetes mellitus and coronary artery disease. *Am J Cardiol* 27:1233, 1996.
 340. Swan DA, Bell B, Oakley CM, Goodwin J: Analysis of symptomatic course and prognosis and treatment of hypertrophic obstructive cardiomyopathy. *Br Heart J* 33:671, 1971.
 341. Hubner PJB, Ziady GM, Lane GK, et al: Double-blind trial of propranolol and practolol in hypertrophic cardiomyopathy. *Br Heart J* 35:116, 1973.
 342. Epstein SE, Henry WL, Clark CE, et al: Asymmetric septal hypertrophy. *Ann Intern Med* 81:650, 1974.
 343. Jeresaty RM: Mitral valve prolapse syndrome. *Prog Cardiovasc Dis* 15:623, 1973.
 344. Slater EE, DeSanctis RW: Dissection of the aorta. *Med Clin North Am* 63:141, 1979.
 345. Rios AS, Silber EN, Bavishi N, et al: Effect of long-

- term β blockade on aortic root compliance in patients with Marfan syndrome. *Am Heart J* 137:1057, 1999.
346. Rossi-Foulkes R, Roman MJ, Rosen SE, et al: Phenotypic features and impact of beta blocker or calcium antagonist therapy on aortic lumen size in the Marfan Syndrome. *Am J Cardiol* 83:1364, 1999.
 - 346a. Ong K-T, Perdu J, DeBacker J, et al: Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial. *Lancet* 376: 1476, 2010.
 347. Shimizu W, Antzelevitch C: Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J Am Coll Cardiol* 35:778, 2000.
 348. Moss AJ, Zareba W, Hall WJ, et al: Effectiveness and limitations of β blocker therapy in congenital long QT syndrome. *Circulation* 101:616, 2000.
 349. Dorostkar PC, Eldar M, Belhassen B, Scheinman MM: Long-term follow-up of patients with long QT syndrome treated with β blockers and continuous pacing. *Circulation* 100:2431, 1999.
 350. Hedblad B, Wikstrand J, Janson L, et al: Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness. Main results from the β Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation* 103:1721, 2001.
 351. Sipahi I, Tuzcu EM, Wolski KE, et al: β Blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. *Ann Intern Med* 147: 10,2007.
 352. Magsino CH Jr, Hamouda W, Bapna V, et al: Nadolol inhibits reactive oxygen species generation by leukocytes and linoleic acid oxidation. *Am J Cardiol* 86:443, 2000.
 353. The Propranolol Aneurysm Trial Investigators: propranolol for small abdominal aortic aneurysms: results of a randomized trial. *J Vasc Surg* 35:72, 2002.
 354. Mahanonda N, Bhuripanyo K, Kangkagate C, et al: Randomized, double-blind, placebo-controlled trial of oral atenolol in patients with unexplained syncope and positive upright tilt table test results. *Am Heart J* 130:1250, 1995.
 355. Cox MM, Perlman BA, Mayor MR, et al: Acute and long-term beta-adrenergic blockade for patients with neurocardiogenic syncope. *J Am Coll Cardiol* 26:1293, 1995.
 356. Iskors D, Dutton J, Scheinman MM, Lurie KG: Usefulness of pindolol in neurocardiogenic syncope. *Am J Cardiol* 82:1121, 1998.
 357. Madrid AH, Ortego J, Rebollo JG, et al: Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a highly symptomatic population: a prospective, double-blind, randomized and placebo-controlled study. *J Am Coll Cardiol* 37:554, 2001.
 358. Harte B, Jaffer AK: Perioperative beta-blockers in noncardiac surgery: evolution of the evidence. *Cleveland Clinic J Med* 75: 513,2008.
 359. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter study of perioperative ischemia research group. *N Engl J Med* 335:1713, 1996.
 360. Poldermans D, Boersma E, Bax JJ, et al for the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group: the effect of bisoprolol on peri-operative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *N Engl J Med* 341:1789, 1999.
 361. Shojania KG, Duncan BW, McDonald KM, et al: Making health care safer: A critical analysis of patient safety practices. *Evid Rep Technol Assess (Summ)* 43: 1,2003.
 362. National Quality Forum: *Safe practices for better healthcare – 2006 update*. Washington, DC: National Quality Forum, 2006.
 363. POISE Study Group: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE Trial): a randomized, controlled trial. *Lancet* 371; 1839,2008.
 364. Fleisher LA, Poldermans D: Perioperative β blockade: where do we go from here? (commentary). *Lancet* 371: 1813,2008.
 - 364a. Chopra V, Eagle KA: Perioperative β -blockers for cardiac risk reduction. Time for clarity (commentary). *JAMA* 303: 551, 2010.
 365. Fleisher LA, Beckman JA, Buller CE, et al: 2009 ACCF/AHA focused update on perioperative beta blockade. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 54: e13, 2009.
 366. Poldermans D, Bax JJ, Boersma E, et al: Guidelines for pre-operative cardiac risk assessment and peri-operative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur J Anaesthesiol* 27: 92, 2010.
 367. Han JA, Frishman WH, Sun SW, et al: Cardiovascular and respiratory considerations with pharma-

- cotherapy of glaucoma and ocular hypertension. *Cardiol in Rev* 16: 95,2008.
368. Gluud LL, Klingenberg S, Nikolova D, Gluud C: Banding ligation versus beta blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. *Am J Gastroenterol* 102: 2842,2007.
369. Groszmann RJ, Garcia-Tsao G, Bosch J, et al for the Portal Hypertension Collaborative Group: Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 353: 2254, 2005.
370. Provencher S, Herve P, Jais X, et al: Deleterious effects of β -blockers on exercise capacity and hemodynamics in patients with portopulmonary hypertension. *Gastroenterol* 130:120,2006.
- 370a. Rutten FH, Zuithoff NPA, Hak E, et al: β -blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. *Arch Intern Med* 170: 880, 2010.
371. Kornbluth A, Frishman WH, Ackerman B. Beta-adrenergic blockade in children. *Cardiol Clin* 5:629,1987.
372. Schlienger RG, Kraenzlin ME, Jick SS, Meier CR: Use of β blockers and risk of fractures. *JAMA* 292: 1326, 2004.
- 372a. Ackland GL, Yao ST, Rudiger A, et al: Cardioprotection, attenuated systemic inflammation, and survival benefit of β_1 -adrenoceptor blockade in severe sepsis in rats. *Crit Care Med* 38: 388, 2010.
373. Friedman LM: How do the various beta-blockers compare in type, frequency and severity of their adverse effects? *Circulation* 67(Suppl 1):89, 1983.
374. Frishman W, Silverman R, Strom J, et al: Clinical pharmacology of the new beta-adrenoceptor blocking drugs. Part IV. Adverse effects: choosing a β -adrenoceptor blocker. *Am Heart J* 98:256, 1979.
375. Frishman WH: Beta-adrenergic receptor blockers: adverse effects and drug interactions. *Hypertension* 11(Suppl II):1121, 1988.
376. Frishman WH, Kostis J: The significance of intrinsic sympathomimetic activity in beta-adrenoceptor blocking drugs: update. *Cardiovasc Rev Rep (Classics of the Decade Series)* 12(12):46, 1991.
377. Jondeau G, Neuder Y, Eicher JC, et al for the B-CONVINCED Investigators: B-CONVINCED: Beta blocker Continuation vs interruption in patients with congestive heart failure hospitalized for a decompensation episode. *Eur Heart J* 30: 2186, 2009.
378. Frishman W, Kostis J, Strom J, et al: Clinical pharmacology of the new beta-adrenergic blocking drugs. Part VI. A comparison of pindolol and propranolol in treatment of patients with angina pectoris: the role of intrinsic sympathomimetic activity. *Am Heart J* 98:526, 1979.
379. Giudicelli JF, Lhoste F: β -Adrenoceptor blockade and atrioventricular conduction in dogs: role of intrinsic sympathomimetic activity. *Br J Clin Pharmacol* 13(Suppl 2):167, 1982.
380. Frishman WH: Beta-adrenergic blocker withdrawal. *Am J Cardiol* 59: 26F,1987.
381. Frishman WH, Klein N, Strom J, et al: Comparative effects of abrupt propranolol and verapamil withdrawal in angina pectoris. *Am J Cardiol* 50:1191, 1982.
382. Morimoto S-i, Shimizu K, Yamada K, et al: Can β blocker therapy be withdrawn from patients with dilated cardiomyopathy? *Am Heart J* 137:456, 1999.
383. George RB, Manocha K, Burford JG, et al: Effects of labetalol in hypertensive patients with chronic obstructive pulmonary disease. *Chest* 83:457, 1983.
384. Olenchock BA, Fonarow GG, Pan W, et al: Current use of beta blockers in patients with reactive airway disease who are hospitalized with acute coronary syndromes. *Am J Cardiol* 103: 295, 2009.
385. Benson MK, Berrill WT, Cruickshank JM, et al: A comparison of four adrenoceptor antagonists in patients with asthma. *Br J Clin Pharmacol* 5:415, 1978.
386. Frohlich ED, Tarazi RC, Dustan HP: Peripheral arterial insufficiency: a complication of beta-adrenergic blocking therapy. *JAMA* 208:2471, 1969.
387. Lundvall J, Jarhult J: Beta-adrenergic dilator component of the sympathetic vascular response in skeletal muscle. *Acta Physiol Scand* 96: 180, 1976.
388. Simpson FO: β -Adrenergic receptor blocking drugs in hypertension. *Drugs* 7:85, 1974.
389. Radack K, Deck C: β -Adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. *Arch Intern Med* 151:1769, 1991.
390. Thadani U, Whitsett TL: Beta-adrenergic blockers and intermittent claudication. *Arch Intern Med* 151:1705, 1991.
391. Hiatt WR, Stoll S, Nies A: Effect of beta-adrenergic blockers on the peripheral *Circulation* in patients with peripheral vascular disease. *Circulation* 72:1226, 1985.
392. Reveno WS, Rosenbaum H: Propranolol and hypoglycaemia. (letter to editor). *Lancet* 1:920, 1968.
393. Allison SP, Chamberlain MI, Miller JE: Effects of propranolol on blood sugar, insulin and free fatty acids. *Diabetologia* 5:339, 1969.
394. Sharma AM, Pischon T, Hardt S, et al: β -Adrenergic receptor blockers and weight gain. A systematic analysis. *Hypertension* 37:250, 2001.
395. Deacon SP, Barnett D: Comparison of atenolol and propranolol during insulin-induced hypoglycaemia.

- mia *BMJ* 2:272, 1976.
396. Lloyd-Mostyn RH, Oram S: Modification by propranolol of cardiovascular effects of induced hypoglycaemia. *Lancet* 1:1213, 1975.
 397. Fogari R, Zoppi A, Corradi L, et al: β Blocker effects on plasma lipids during prolonged treatment of hypertensive patients with hypercholesterolemia. *J Cardiovasc Pharmacol* 33:534, 1999.
 398. Dimmitt SB, Williams PD, Croft KD, Beilin LJ: Effects of β -blockers on the concentration and oxidizability of plasma lipids. *Clin Sci* 94:573, 1998.
 399. Perez-Stable EJ, Halliday R, Gardiner PS, et al: The effects of propranolol on cognitive function and quality of life: a randomized trial among patients with diastolic hypertension. *Am J Med* 108:359, 2000.
 400. Jacob H, Brandt LJ, Farkas P, Frishman WH: Beta-adrenergic blockade and the gastrointestinal system. *Am J Med* 74:1042, 1983.
 401. Stephen SA: Unwanted effects of propranolol. *Am J Cardiol* 18:463, 1966.
 402. Lydakis C, Lip GYH, Beevers M, Beevers DG: Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens* 12:541, 1999.
 403. Bailey R, Neale TJ: Rapid clonidine withdrawal with blood pressure overshoot exaggerated by beta-blockade. *BMJ* 1:942, 1976.
 404. Agabiti-Rosei E, Brown JJ, Lever AF, et al: Treatment of phaeochromocytoma and clonidine withdrawal hypertension with labetalol. *Br J Clin Pharmacol* 3(Suppl 3):809, 1976.
 405. Wright P: Untoward effect associated with practolol administration: oculomucocutaneous syndrome. *BMJ* 1:595, 1975.
 406. Blaufarb I, Pfeifer TM, Frishman WH: β Blockers: drug interactions of clinical significance. *Drug Safety* 13(6):359, 1995.
 407. Opie LH, Frishman WH: Adverse cardiovascular drug interactions and complications. In: Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's The Heart*, 10th ed. New York: McGraw-Hill, 2001:2251.

References for Chapter 6

Central and Peripheral Sympatholytics

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1. Hoffman BB: Therapy of Hypertension. In Brunton LL, Lazo JS, Parker KL (eds): *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th ed. NY: McGraw-Hill, 2006: 845.
2. Drugs for hypertension. *Med Lett* 43:17, 2001.
3. Materson BJ: Central and peripheral sympatholytics. In: Izzo JL, Sica DA, Black HR, eds. *Hypertension Primer*, 4th ed. Dallas: American Heart Association 2008: 453.
4. Frishman WH, Sinatra ST, Moizuddin M: Herbal approach to cardiac disease. In Frishman WH, Weintraub MI, Micozzi MS (ed): *Complementary and Integrative Therapies for Cardiovascular Disease*. St. Louis: Elsevier/Mosby 2005: 86.
5. Chobanian AV: Shattuck Lecture. The hypertension paradox – more uncontrolled disease despite improved therapy. *N Engl J Med* 361: 878, 2009.
6. Grossman E, Messerli FH, Goldbourt U: Carcinogenicity of antihypertensive therapy. *Curr Hypertens Rep* 4:195, 2002.
7. Kronig B, Pittrow DB, Kirch W, et al: Different concepts in first-line treatment of essential hypertension. Comparison of a low-dose reserpine-thiazide combination with nitrendipine monotherapy. German Reserpine in Hypertension Study Group. *Hypertension* 29:651, 2001.
8. SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: Final results of the Systolic Hypertension in the Elderly Program SHEP. *JAMA* 265:3255, 1991.
9. Eland IA, van Puijenbroek EP, Sturkenboom MJ, et al: Drug-associated acute pancreatitis: 21 years of spontaneous reporting in The Netherlands. *Am J Gastroenterol* 94:2417, 1999.
10. Frishman WH, Schlocke SJ, Awad K, Tejani N: Pathophysiology and medical management of systemic hypertension in pregnancy. *Cardiol in Rev* 13: 274, 2005.
11. Hypertension Detection and Follow-up Program: Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA* 242:2562, 1979.
12. Mitchell A, Bührmann S, Opazo Saez A, et al: Clonidine lowers blood pressure by reducing vascular resistance and cardiac output in young, healthy males. *Cardiovasc Drugs Ther* 19: 5, 2005.
13. Brahmabhatt R, Baggaley P, Hockings B: Normalization of blood pressure in a patient with severe orthostatic hypotension and supine hypertension using clonidine. *Hypertension* 37:E24, 2001.
14. Frye CB, Vance MA: Hypertensive crisis and myocardial infarction following massive clonidine overdose. *Ann Pharmacother* 34:611, 2000.
15. Bravo EL, Tarazi RC, Fouad FM, et al: Clonidine-suppression test: A useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 305:623, 1981.
16. Hui TP, Krakoff LR, Felton K, Yeager K: Diuretic treatment alters clonidine suppression of plasma norepinephrine. *Hypertension* 8:272, 1986.
17. Bravo EL, Gifford RW Jr: Pheochromocytoma: Diagnosis, localization and management. *N Engl J Med* 311:1298, 1984.
18. Grossman E, Goldstein DS, Hoffman A, Keiser HR: Glucocagon and clonidine testing in the diagnosis of pheochromocytoma. *Hypertension* 17:733, 1991.
19. Manelli M, Ianni L, Cilotti A, Conti A: Pheochromocytoma in Italy: A multicentric retrospective study. *Eur J Endocrinol* 141:619, 2001.
20. Makino Y, Kawano Y, Okuda N, et al: Autonomic

- function in hypertensive patients with neurovascular compression of the ventrolateral medulla oblongata. *J Hypertens* 17:1257, 2001.
21. Roche WJ, Nwofia C, Gittler M, et al: Catecholamine-induced hypertension in lumbosacral paraplegia: Five case reports. *Arch Phys Med Rehabil* 81:222, 2000.
 - 21a. Guanfacine extended-release (*Intuniv*) for ADHD. *Med Ltr* 52: 82, 2010.
 22. Materson BJ, Reda DJ, Cushman WC, et al: Single-drug therapy for hypertension in men: A comparison of six antihypertensive agents with placebo. *N Engl J Med* 328:914, 1993.
 23. Materson BJ, Reda DJ, Cushman WC, Henderson WG: Results of combination anti-hypertensive therapy after failure of each of the components. Department of Veterans Affairs Cooperative Study Group on Anti-hypertensive Agents. *J Hum Hypertens* 9:791, 1995.
 24. Mansoor GA, Frishman WH: Comprehensive management of hypertensive emergencies and urgencies. *Heart Dis* 4: 358, 2002.
 25. Dziedzic SW, Elijevich F, Felton K, et al: Effect of guanabenz on blood pressure responses to posture and exercise. *Clin Pharm Ther* 33:151, 1983.
 26. Danchin N, Genton P, Atlas P, et al: Comparative effects of atenolol and clonidine on polygraphically recorded sleep in hypertensive men: A randomized, double-blind, crossover study. *Int J Clin Pharmacol Ther* 33:52, 1995.
 27. Issa FG: Effect of clonidine in obstructive sleep apnea. *Am Rev Respir Dis* 145:435, 1992.
 28. Robege JR, Kimball ET, Warren J: Clonidine and sleep apnea syndrome interaction: Antagonism with yohimbine. *J Emerg Med* 16:727, 2001.
 29. White WB, Gilbert JC: Transdermal clonidine in a patient with resistant hypertension and malabsorption. *N Engl J Med* 313: 1418, 1985.
 30. Murphy M, Carmichael AJ: Transdermal drug delivery systems and skin sensitivity reactions. Incidence and management. *Am J Clin Dermatol* 1:361, 2000.
 31. Manolis AJ, Olympios C, Sifaki M, et al: Combined sympathetic suppression and angiotensin-converting enzyme inhibition in congestive heart failure. *Hypertension* 29:525, 2001.
 32. Manolis AJ, Olympios C, Sifaki M, et al: Suppressing sympathetic activation in congestive heart failure: A new therapeutic strategy. *Hypertension* 26:719, 1995.
 33. Azevedo ER, Newton GE, Parker JD: Cardiac and systemic sympathetic activity in response to clonidine in human heart failure. *J Am Coll Cardiol* 33:186, 1999.
 34. Grassi G, Turri C, Seravalle G, et al: Effects of chronic clonidine administration on sympathetic nerve traffic and baroreflex function in heart failure. *Hypertension* 38:286, 2001.
 35. Gavras I, Manolis AJ, Gavras H: The alpha₂-adrenergic receptors in hypertension and heart failure: Experimental and clinical studies. *J Hypertens* 19:2115, 2001.
 36. Aggarwal A, Esler MD, Socratous F, Kaye DM: Evidence for functional presynaptic alpha-2 adrenoceptors and their down-regulation in human heart failure. *J Am Coll Cardiol* 37:1246, 2001.
 37. Simpson CS, Ghali WA, Sanfilippo AJ, et al: Clinical assessment of clonidine in the treatment of new-onset rapid atrial fibrillation: A prospective, randomized clinical trial. *Am Heart J* 142:300, 2001.
 38. Ernsberger P, Haxhiu MA: The I1-imidazoline-binding site is a functional receptor mediating vasodepression via the ventral medulla. *Am J Physiol* 273: R1572, 1997.
 39. Fenton C, Keating GM, Lyseng-Williamson KA: Moxonidine: a review of its use in essential hypertension. *Drugs* 66: 477, 2006.
 40. Mobini R, Fu M, Jansson PA, et al: Influence of central inhibition of sympathetic nervous activity on myocardial metabolism in chronic heart failure: acute effects of the imidazoline I1-receptor agonist moxonidine. *Clin Sci* 110: 329, 2006.
 41. Pöyhönen-alho MK, Manhem K, Katzman P, et al: Central sympatholytic therapy has anti-inflammatory properties in hypertensive postmenopausal women. *J Hypertens* 26: 2445, 2008.
 42. Krakoff LR, Garbowit D: Adeno-medullary hypertension: a review of syndromes, patho-physiology, diagnosis and treatment. *Clin Chem* 37: 49, 1991.
 43. Pacak K, Linehan WM, Eisenhofer G, et al. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. *Ann Intern Med* 134:315, 2001.
 44. Krakoff LR: History of hypertension. In *Hypertension: Principles and Practice* (ed by EJ Battegay, GL Yip, GL Bakris. New York: Taylor & Francis 2005: 3.
 45. Taler SJ: Treatment of pregnant hypertensive patients. In: Izzo JL Jr, Sica DA, Black HR, eds. *Hypertension Primer*, 4th ed. Dallas: American Heart Association, 2008:536.
 46. Abalos E, Duley L, Steyn DW, Henderson-Smith DJ: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy (Cochrane Review). The Cochrane Library, 2007.
 47. Magee LA, Duley L: Oral beta-blockers for mild to moderate hypertension during pregnancy (Cochrane Review). The Cochrane Library 2003.

48. Fahlke C, Berggren U, Balldin J: Cardiovascular responses to clonidine in alcohol withdrawal: Are they related to psychopathology and mental well-being? *Alcohol* 1:231, 2000.
49. Adinoff B: Double-blind study of alprazolam, diazepam, clonidine, and placebo in the alcohol withdrawal syndrome: Preliminary findings. *Alcohol Clin Exp Res* 18:873, 1994.
50. Frishman W: Smoking cessation pharmacotherapy. *Ther Adv Cardiovasc Dis* 3: 287, 2009.
51. Wijesundera DN, Naik JS, Beattie S: Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. *Am J Med* 114: 742, 2003.

References for Chapter 7

Cholinergic and Anticholinergic Drugs

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1. Hoffman BB, Taylor P: Neurotransmission: The autonomic and somatic motor nervous systems. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York: McGraw-Hill, 2001:115.
2. Dale HH: The action of certain esters and ethers of choline, and their relation to muscarine. *J Pharmacol Exp Ther* 6:147, 1914.
3. Caulfield MP: Muscarinic receptors: Characterization, coupling and function. *Pharmacol Ther* 58:319, 1993.
4. Bonner TI, Buckley NJ, Young AC, Brann MR: Identification of a family of muscarinic receptor genes. *Science* 237:527, 1987.
5. Hammer R, Berrie CP, Birdsall NJ, et al: Pirenzepine distinguishes between different subclasses of muscarinic receptors. *Nature* 283: 90, 1980.
6. Levine RR, Birdsall NJM, eds: Symposium: Subtypes of muscarinic receptors: V. *Life Sci* 52:405, 1993.
7. Levine RR, ed: Symposium: Subtypes of muscarinic receptors: VI. *Life Sci* 56:801, 1995.
8. Oberhauser V, Schwertfeger E, Rutz T, et al: Acetylcholine release in human heart atrium. Influence of muscarinic autoreceptors, diabetes, and age. *Circulation* 103:1638, 2001.
9. Brodde OE, Michel MC: Adrenergic and muscarinic receptors in the human heart. *Pharmacol Rev* 51:651, 1999.
10. Landzberg JS, Parker JD, Gautheir DF, Colucci WS: Effects of intracoronary acetylcholine and atropine on basal and dobutamine stimulated left ventricular contractility. *Circulation* 89:164, 1994.
11. Moncada S, Palmer RMJ, Higgs EA: Nitric oxide: Physiology, pathophysiology, and pharmacology. *Pharmacol Rev* 43:109, 1991.
12. Furchgott RF: The role of endothelium in the responses of vascular smooth muscle to drugs. *Annu Rev Pharmacol Toxicol* 24:175, 1984.
13. Tio RA, Monnink SHJ, Amoroso G, et al: Safety evaluation of routine intracoronary acetylcholine infusion in patients undergoing a first diagnostic coronary angiogram. *J Investig Med* 50:133, 2002.
14. Goyal RK: Identification, localization, and classification of muscarinic receptor subtypes in the gut. *Life Sci* 43:2209, 1988.
15. Wein AJ: Practical uro pharmacology. *Urol Clin North Am* 18:269, 1991.
16. Eglen RM, Choppin A, Dillon MP, Hegde S: Muscarinic receptor ligands and their therapeutic potential. *Curr Opin Chem Biol* 3:426, 1999.
17. Taylor P: Anticholinesterase agents. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York: McGraw-Hill, 2001:175.
18. Morris RB, Cronnelly R, Miller RD, et al: Pharmacokinetics of edrophonium and neostigmine when antagonizing d-tubocurarine neuromuscular blockade in man. *Anaesthesiology* 54:399, 1981.
19. Morris RB, Cronnelly R, Miller RD, et al: Pharmacokinetics of edrophonium in anephric and renal transplant patients. *Br J Anaesth* 53:399, 1981.
20. American Society of Hospital Pharmacists: *AHFS Drug Information 1994*. Bethesda MD: American Hospital Formulary Service, American Society of Hospital Pharmacists, 1994.
21. McCarthy GH, Mirackhur RK, Maddineni VR, McCoy EP: Dose-responses for edrophonium during antagonism of vecuronium block in young and older adult patients. *Anaesthesia* 50:503, 1995.
22. Kiajima T, Ishii K, Ogata H: Edrophonium as an antagonist of vecuronium-induced neuromuscu-

- lar block in the elderly. *Anaesthesia* 50:359, 1995.
23. Lurie KG, Dutton J, Mangat R, et al: Evaluation of edrophonium as a provocative agent for vasovagal syncope during head-up tilt-table testing. *Am J Cardiol* 72:1286, 1993.
 24. Medow MS, Stewart JM, Sanyal S, et al: Pathophysiology, diagnosis and treatment of orthostatic hypotension and vasovagal syncope. *Cardiol in Rev* 16: 4, 2008.
 25. Rokkas T, Anggiansah A, McCullagh M, Owen WJ: Acid perfusion and edrophonium provocation tests in patients with *Chest* pain of undetermined etiology. *Dig Dis Sci* 37:1212, 1992.
 26. Hofer S, Eisenbach C, Lukic IK, et al: Pharmacologic cholinesterase inhibition improves survival in experimental sepsis. *Crit Care Med* 36: 404-408, 2008.
 27. Drachman DB: Myasthenia gravis. *N Engl J Med* 330: 1797, 1994.
 28. Birks J: Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev* 1: CD005593, 2006.
 29. Gill SS, Anderson GM, Fischer HD, et al: Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors. *Arch Intern Med* 169: 867-873, 2009.
 30. Brown JH, Taylor P: Muscarinic receptor agonists and antagonists. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York: McGraw-Hill, 2001:155.
 31. Zhou HH, Adedoyin A, Wood AJ: Differing effect of atropine on heart rate in Chinese and white subjects. *Clin Pharm Ther* 52:120, 1992.
 32. Marine JE, Watanabe MA, Smith TW, Monahan KM: Effects of atropine on heart rate turbulence. *Am J Cardiol* 89:767, 2002.
 33. Wellstein A, Pitschener HF: Complex dose-response curves of atropine in man explained by different functions of M1 and M2 cholinergic receptors. *Naunyn Schmiedeberg Arch Pharmacol* 338:861, 1988.
 34. Pican E, Mathias W, Pingitore A, et al: Safety and tolerability of dobutamine-atropine stress echocardiography: A prospective, multicentre study. *Lancet* 344:1190, 1994.
 35. Poldermans D, Fioretti PM, Boersma E: Safety of dobutamine-atropine stress echocardiography in patients with suspected or proven coronary artery disease. *Am J Cardiol* 73:456, 1994.
 36. McNeill AJ, Fioretti PM, El-Said SM, et al: Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. *Am J Cardiol* 70:41, 1992.
 37. Poldermans D, Fioretti PM, Boersma E: Dobutamine-atropine stress echocardiography in elderly patients unable to perform an exercise test: Hemodynamic characteristics, safety, and prognostic value. *Arch Intern Med* 154:2681, 1994.
 38. Meisner JS, Shirani J, Alaeddini J, et al: Use of pharmaceuticals in noninvasive cardiovascular diagnosis. *Heart Dis* 4:315, 2002.
 39. van Noord JA, Bantje TA, Eland ME, et al: A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. The Dutch Tiotropium Study Group. *Thorax* 55:289, 2000.
 40. Chapman KR: The role of anticholinergic bronchodilators in adult asthma and chronic obstructive pulmonary disease. *Lung* 168(Suppl): 295, 1990.
 41. Gross NJ: Ipratropium bromide. *N Engl J Med* 319:486, 1988.
 42. Ogale SS, Lee TA, Au DH, et al: Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 137: 13, 2010.
 43. Celli B, Decramer M, Leimer I, et al: Cardiovascular safety of tiotropium in patients with COPD. *Chest* 137: 20, 2010.
 44. Salpeter SR: Do inhaled anticholinergics increase or decrease the risk of major cardiovascular events? A synthesis of the available evidence. *Drugs* 69:2025, 2009.
 45. Wilkinson JA: Side effects of transdermal scopolamine. *J Emerg Med* 5:389, 1987.
 46. Ziskind AA: Transdermal scopolamine-induced psychosis. *Postgrad Med* 84:73, 1988.
 47. Hall RCW, Hall RCW, Chapman MJ: Anticholinergic syndrome: presentations, etiological agents, differential diagnosis, and treatment. *Clin Geriatr* 17: 22, 2009.
 48. LaRovere MT, DeFerrari GM: New potential uses for transdermal scopolamine (hyoscine). *Drugs* 50:769, 1995.

References for Chapter 8

Calcium Channel Blockers

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8. Calcium Channel Blockers

1. Keefe D, Frishman WH: Clinical pharmacology of the calcium-channel blocking drugs. In: Packer M, Frishman WH, eds. *Calcium Channel Antagonists in Cardiovascular Disease*. Norwalk, CT: Appleton-Century-Crofts, 1984:3.
2. Braunwald E: Mechanism of action of calcium-channel blocking agents. *N Engl J Med* 307:1618, 1983.
3. Frishman WH, Sonnenblick EH: Beta-adrenergic blocking drugs and calcium channel blockers. In: Alexander RW, Schlant RC, Fuster V, eds. *Hurst's The Heart*, 9th ed. New York: McGraw Hill, 1998: 1583.
4. Weir MR: Calcium antagonists. In Izzo JL Jr, Sica DA, Black HR (eds): *Hypertension Primer 4th ed*. Dallas, American Heart Assn 2008: 465.
5. Frishman WH, Cheng-Lai A, Nawarskas J, eds. *Current Cardiovascular Drugs*, 4th ed. Philadelphia: Current Medicine, 2005.
6. Malhotra HS, Plosker GL: Barnidipine. *Drugs* 61:989, 2001.
7. Tomoda F, Takata M, Kagitani S, et al: Effects of a novel calcium antagonist, benidipine hydrochloride, on platelet responsiveness to mental stress in patients with essential hypertension. *J Cardiovasc Pharmacol* 34:248, 1999.
8. Sakata K, Shirohara M, Yoshida H, et al: Effects of amlodipine and cilnidipine on cardiac sympathetic nervous system and neurohormonal status in essential hypertension. *Hypertension* 33:1447, 1999.
9. Sánchez M, Sobrino J, Ribera L, et al: Long-acting lacidipine versus short-acting nifedipine in the treatment of asymptomatic acute blood pressure increase. *J Cardiovasc Pharmacol* 33:479, 1999.
10. Casiglia E, Mazza A, Tikhonoff V, et al: Therapeutic profile of manidipine and lercanidipine in hypertensive patients. *Adv Therap* 21: 357, 2004.
11. Ohashi N, Mitamura H, Ogawa S: Development of newer calcium channel antagonists. Therapeutic potential of efonidipine in preventing electrical remodeling during atrial fibrillation. *Drugs* 69: 21, 2009.
12. Lindner E: Phenyl-propyl-diphenyl-propyl-amin, a new substance with a dilating action in the coronary vessels. *Arzneim Forsch* 10:569, 1960.
13. Haas H, Hartfelder G: A-Isopropyl-a(N-methyl-N-homoveratryl)-y aminopropyl)-3,4-dimethoxyphenyl-acetonitrol, a substance with vasodilating properties. *Arzneim Forsch* 12:549, 1962.
14. Fleckenstein A, Kammermeier H, Doring H, et al: On the action mechanism of new coronary dilators with oxygen sparing myocardial effects—Prenylamin and Iproveratril. *Z Kreislauf Forsch* 56:716, 839, 1967.
15. Fleckenstein A: Control of myocardial metabolism by verapamil: Sites of action and therapeutic effects. *Arzneim Forsch* 20:1317, 1970.
16. Singh BN, Vaughan-Williams EM: A fourth class of antidysrhythmic action? Effect of verapamil on ouabain toxicity, on atrial and ventricular intracellular potentials, and on other features of cardiac function. *Cardiovasc Res* 6:109, 1972.
17. Vaughan Williams EM: Classification of antiarrhythmic drugs. In: Sande E, Flensted-Jensen E, Olsen KH, eds. *Symposium on Cardiac Arrhythmias*. Elsinor, Denmark: AB Astra, 1979:449.
18. Ge W, Ren J: Combined L-/T-type calcium channel blockers. Ready for prime time. *Hypertension* 53: 592, 2009.
19. de Curzon OP, Ghaleh B, Hittinger L, et al: Beneficial effects of the T- and L-type calcium channel

- antagonist, mibefradil, against exercise-induced myocardial stunning in dogs. *J Cardiovasc Pharmacol* 35:240, 2000.
20. Schwartz A, Matlib A, Balwierczak J, Lathrop DA: Pharmacology of calcium antagonists. *Am J Cardiol* 55:3C, 1985.
 21. Dhein S, Salameh A, Berkels R, Klaus W: Dual mode of action of dihydropyridine calcium antagonists. A role for nitric oxide. *Drugs* 58:397, 1999.
 22. Kitakaze M, Asanuma H, Takashima S, et al: Nifedipine-induced coronary vasodilation in ischemic hearts is attributable to bradykinin- and NO-dependent mechanisms in dogs. *Circulation* 101:311, 2000.
 23. Taddei S, Virdis A, Ghiadoni L, et al: Restoration of nitric oxide availability after calcium antagonist treatment in essential hypertension. *Hypertension* 37:943, 2001.
 24. Wei C, Burnett JC Jr: Inhibition by calcium antagonism of circulating and renal endothelin in experimental congestive heart failure. *Am J Physiol* 278:H263, 2000.
 25. Ikeda U, Hojo Y, Ueno S, et al: Amlodipine inhibits expression of matrix metalloproteinase-1 and its inhibitor in human vascular endothelial cells. *J Cardiovasc Pharmacol* 35:887, 2000.
 26. van Breeman C, Mangel A, Fahim M, et al: Selectivity of calcium antagonistic action in vascular smooth muscle. *Am J Cardiol* 49:507, 1982.
 27. Millard RW, Lathrop DA, Grupp G, et al: Differential cardiovascular effects of calcium channel blocking agents: Potential mechanisms. *Am J Cardiol* 49:499, 1982.
 28. Fleckenstein A: Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. *Annu Rev Pharmacol Toxicol* 17:149, 1977.
 29. Henry PD, Borda L, Schuchleib R: Chronotropic and inotropic effects of vasodilators. In: Lichtlen PR, Kimura E, Taira N, eds. *International Adalat Panel Discussion: New Experimental and Clinical Results*. Amsterdam: Excerpta Medica, 1979:14–21.
 30. Cohn JN, Franciosa JA: Vasodilatory therapy of cardiac failure. *N Engl J Med* 297:27, 1977.
 31. Himori N, Ono H, Taira N: Simultaneous assessment of effects of coronary vasodilators on the coronary blood flow and the myocardial contractility by using the blood perfused canine papillary muscle. *Jpn J Pharmacol* 26:427, 1976.
 32. Singh BN, Hecht HS, Nademanee K, et al: Electrophysiologic and hemodynamic effects of slow channel blocking drugs. *Prog Cardiovasc Dis* 25:103, 1982.
 33. Ellrodt G, Chew CYC, Singh BN: Therapeutic implications of slow channel blockade in cardiocirculatory disorders. *Circulation* 62:669, 1980.
 34. Landau AJ, Gentilucci M, Cavusoglu E, Frishman WH: Calcium antagonists for the treatment of congestive heart failure. *Coron Artery Dis* 5:37, 1994.
 35. Veniant M, Clozel JP, Hess P, et al: Hemodynamic profile of RO 40-5967 in conscious rats: Comparison with diltiazem, verapamil and amlodipine. *J Cardiovasc Pharmacol* 18 (Suppl 10):S55, 1991.
 36. Frishman WH, LeJemtel T: Electropharmacology of the slow channel inhibitors in the management of cardiac arrhythmias: verapamil. *Pace* 5:402, 1982.
 37. Singh BN, Nademanee K, Baky S: Calcium antagonists. *Drugs* 25:125, 1983.
 38. Nayler WG, Poole-Wilson PH: Calcium antagonists: Definition and mode of action. *Basic Res Cardiol* 76:1, 1981.
 39. Yamaguchi I, Obayashi K, Mandel WJ: Electrophysiologic effects of verapamil. *Cardiovasc Res* 12:597, 1978.
 40. Singh BN, Collet J, Chew CYC: New perspectives in the pharmacologic therapy of cardiac arrhythmias. *Prog Cardiovasc Dis* 22:243, 1980.
 41. Wit A, Cranefield P: The effects of verapamil on the sinoatrial and atrioventricular nodes of the rabbit and the mechanisms by which it arrests reentrant AV nodal tachycardia. *Circ Res* 35:413, 1974.
 42. Findling R, Frishman W, Javed MT, et al: Calcium channel blockers and the gastrointestinal tract. *Am J Ther* 3:383, 1996.
 43. Schoen RE, Frishman WH, Shamoon H: Hormonal and metabolic effects of calcium-channel antagonists in man. *Am J Med* 84:492, 1988.
 44. Shamoon H, Baylor P, Kamobosos D, et al: Influence of oral verapamil on glucoregulatory hormones in man. *J Clin Endocrinol Metabol* 60:536, 1985.
 45. Frishman WH, Klein N, Strom J, et al: Comparative effects of abrupt withdrawal of propranolol and verapamil in angina pectoris. *Am J Cardiol* 50:1191, 1982.
 46. Mehta JL: Influence of calcium-channel blockers on platelet function and arachidonic acid metabolism. *Am J Cardiol* 55:158B, 1985.
 47. Sanguigni V, Gallu M, Sciarra L, et al: Effect of amlodipine on exercise-induced platelet activation in patients affected by chronic stable angina. *Clin Cardiol* 22:575, 1999.
 48. Kates R: Calcium antagonists—pharmacokinetic properties. *Drug* 25:113, 1983.
 49. Frishman WH, Stroh JA, Greenberg SM, et al: Calcium-channel blockers in systemic hypertension. *Curr Prob Cardiol* 12:287, 1987.

50. Katz B, Rosenberg A, Frishman WH: Controlled-release drug delivery systems in cardiovascular medicine. *Am Heart J* 129:359, 1995.
51. Plosker GL, Faulds D: Nisoldipine coat-core. *Drugs* 52:232, 1996.
52. White WB: A chronotherapeutic approach to the management of hypertension. *Am J Hypertens* 9:29S, 1996.
53. Frishman WH, Kirstein E, Klein M, et al: Clinical relevance of verapamil plasma levels in stable angina pectoris. *Am J Cardiol* 50:1180, 1982.
54. Frishman WH, Charlap S, Kimmel B, et al: Diltiazem compared to nifedipine and combination treatment in patients with stable angina: Effects on angina, exercise tolerance and the ambulatory ECG. *Circulation* 77:774, 1988.
55. Sica DA, Gehr TWB: Calcium-channel blockers and the cytochrome P450 system. In: Epstein M, ed: *Calcium Antagonists in Clinical Medicine*, 3rd ed. Philadelphia: Hanley and Belfus, 2002:93.
56. Sica DA, Gehr TWB: Calcium-channel blockers and end-stage renal disease. In: Epstein M, ed. *Calcium Antagonists in Clinical Medicine*, 3rd ed. Philadelphia: Hanley and Belfus, 2002:701.
57. Singh BN, Chew CYC, Josephson MA, et al: Hemodynamic mechanisms underlying the antianginal actions of verapamil. *Am J Cardiol* 50:886, 1982.
58. Opie LH: Calcium channel antagonists in the treatment of coronary artery disease: Fundamental pharmacological properties relevant to clinical use. *Prog Cardiovasc Dis* 38(4):273, 1996.
59. Pepine CJ, Lambert CR: Usefulness of nicardipine for angina pectoris. *Am J Cardiol* 59:13J, 1987.
60. Scheidt S, Frishman WH, Packer M, et al: Long-term effectiveness of verapamil in stable and unstable angina pectoris: One year follow-up of patients treated-controlled double-blind randomized clinical trials. *Am J Cardiol* 50:1185, 1982.
61. Opie LH: Calcium channel antagonists in the management of anginal syndromes: Changing concepts in relation to the role of coronary vasospasm. *Prog Cardiovasc Dis* 38:291, 1996.
62. Frishman WH, Klein NA, Strom JA, et al: Superiority of verapamil to propranolol in stable angina pectoris—a double-blind, randomized crossover trial. *Circulation* 65(Suppl I):151, 1982.
63. Frishman WH, Klein N, Klein P, et al: Comparison of oral propranolol and verapamil for combined systemic hypertension and angina pectoris: A placebo-controlled double-blind randomized crossover trial. *Am J Cardiol* 50:1164, 1982.
64. Frishman WH, Charlap S: Calcium-channel blockers for combined systemic hypertension and myocardial ischemia. *Circulation* 75:V154, 1988.
65. Abrams J, Frishman WH, Bates SM, et al: Pharmacologic options for treatment of ischemic disease. In: Antman EM, ed. *Cardiovascular Therapeutics*, 3rd ed. Philadelphia: Saunders, 2007: 77.
66. Kizer JR, Kimmel SE: Epidemiologic review of the calcium channel blocker drugs. An up-to-date perspective on the proposed hazards. *Arch Intern Med* 161:1145, 2001.
67. Stone PH, Gibson RS, Glasser SP, et al: Comparison of propranolol, diltiazem, and nifedipine in the treatment of ambulatory ischemia in patients with stable angina: Differential effects on ambulatory ischemia, exercise performance, and anginal symptoms. *Circulation* 82:1962, 1990.
68. Frishman WH, Glasser S, Stone P, et al: Comparison of controlled-onset extended-release verapamil to amlodipine and amlodipine plus atenolol on exercise performance and ambulatory ischemia in patients with chronic stable angina pectoris. *Am J Cardiol* 83:507, 1999.
69. Johnson SM, Mauritsen DR, Willerson JT, et al: A controlled trial of verapamil for Prinzmetal's variant angina. *N Engl J Med* 304:862, 1981.
70. Antman E, Muller JE, Goldberg S, et al: Nifedipine therapy for coronary artery spasm experience in 127 patients. *N Engl J Med* 302:1269, 1980.
71. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227, 1982.
72. Chahine RA, Feldman RL, Giles TD, et al: Randomized placebo controlled trial of amlodipine in vasospastic angina. *J Am Coll Cardiol* 21:1365, 1993.
73. Parodi O, Simonetti I, LAbbate A, et al: Comparative effectiveness of verapamil and propranolol in angina at rest. *Am J Cardiol* 50:923, 1982.
74. Johnson SM, Mauritsen DR, Willerson JT, et al: Comparison of verapamil and nifedipine in the treatment of variant angina pectoris: preliminary observations in 10 patients. *Am J Cardiol* 47:1295, 1981.
75. Gerstenblith G, Ouyang P, Achuff S, et al: Nifedipine in unstable angina: a double-blind randomized trial. *N Engl J Med* 306:885, 1982.
76. Anderson JL, Adams CD, Antman EM et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction) developed in collaboration with the American

- College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007; 50: 1-157.
77. Pehrsson SK, Ringqvist I, Ekdahl S, et al: Monotherapy with amlodipine or atenolol versus their combination in stable angina pectoris. *Clin Cardiol* 23:763, 2000.
 78. Emanuelsson H, Egstrup K, Nikus K, et al: Anti-anginal efficacy of the combination of felodipine-metoprolol 10/100 mg compared with each drug alone in patients with stable effort-induced angina pectoris: A multicenter parallel group study. *Am Heart J* 137:854, 1999.
 79. Packer M, Leon MB, Bonow RO, et al: Hemodynamic and clinical effects of combined therapy with verapamil and propranolol in ischemic heart disease. *Am J Cardiol* 50:903, 1982.
 80. Packer M, Frishman WH: Calcium channel antagonists in perspective. In: Packer M, Frishman WH, eds. *Calcium Channel Antagonists in Cardiovascular Disease*. Norwalk, CT: Appleton-Century-Crofts, 1984:xvii.
 81. Gabrielli A, Gallagher J, Caruso LJ, et al: Diltiazem to treat sinus tachycardia in critically ill patients. A four-year experience. *Crit Care Med* 29: 1874, 2000.
 82. Hemels MEW, Van Noord T, Crijns HJGM, et al: Verapamil versus digoxin and acute versus routine serial cardioversion for the improvement of rhythm control for persistent atrial fibrillation. *J Am Coll Cardiol* 48: 1001, 2006.
 83. Pandozi C, Bianconi L, Calo L, et al: Postcardioversion atrial electrophysiologic changes induced by oral verapamil in patients with persistent atrial fibrillation. *J Am Coll Cardiol* 36:2234, 2000.
 84. Pritchett ELC: Management of atrial fibrillation. *N Engl J Med* 326:1264, 1992.
 85. Klein HO, Pauzner H, DiSegni E, et al: The beneficial effects of verapamil in chronic atrial fibrillation. *Arch Intern Med* 139:747, 1979.
 86. Klein HO, Kaplinsky E: Comparative effectiveness of verapamil and digoxin in atrial fibrillation. *Am J Cardiol* 50:894, 1982.
 87. De Simone A, Stabile G, Vitale DF, et al: Pretreatment with verapamil in patients with persistent or chronic atrial fibrillation who underwent electrical cardioversion. *J Am Coll Cardiol* 34:810, 1999.
 88. Amar D, Roistacher N, Rusch VW, et al: Effects of diltiazem prophylaxis on the incidence and clinical outcome of atrial arrhythmias after thoracic surgery. *J Thorac Cardiovasc Surg* 120:790, 2000.
 89. Krikler DM, Spurrell RAJ: Verapamil in the treatment of paroxysmal supraventricular tachycardia. *Postgrad Med J* 50:447, 1974.
 90. Singh BN, Nademanee D, Baky S: Calcium antagonists: Uses in the treatment of cardiac arrhythmias. *Drugs* 25:125, 1983.
 91. Hartel G, Hartikainen M: Comparison of verapamil and practolol in paroxysmal supraventricular tachycardia. *Eur J Cardiol* 4:87, 1976.
 92. Mauritson DR, Winniford MD, Walker WS, et al: Oral verapamil for paroxysmal supraventricular tachycardia: A long term, double-blind, randomized trial. *Ann Intern Med* 96:409, 1982.
 93. Matsuyama E, Konishi T, Okazaki H, et al: Effects of verapamil on accessory pathway properties and induction of circus movement tachycardia in patients with the Wolff-Parkinson-White syndrome. *J Cardiovasc Pharmacol* 3:11, 1981.
 94. Gotsman M, Lewis B, Bakst A, et al: Verapamil in life-threatening tachyarrhythmias. *S Afr Med J* 46:2017, 1972.
 95. Aiba T, Shimizu W, Inagaki M, et al: Cellular and ionic mechanism for drug-induced long QT syndrome and effectiveness of verapamil. *J Am Coll Cardiol* 45: 300, 2005.
 96. Carrasco HA, Fuenmayor A, Barboza J, et al: Effect of verapamil on normal sino-atrial node dysfunction and on sick sinus syndrome. *Am Heart J* 96:760, 1978.
 97. Frishman WH, Stroh JA, Greenberg SM, et al: Calcium-channel blockers in systemic hypertension. *Med Clin North Am* 72:449, 1988.
 98. Frishman WH, Zawada ET, Smith LK, et al: A comparative study of diltiazem and hydrochlorothiazide as initial medical therapy for mild to moderate hypertension. *Am J Cardiol* 59:615, 1987.
 99. Materson BJ, Reda DJ, Cushman WC, et al: Single-drug therapy for hypertension in men: A comparison of six antihypertensive agents with placebo. *N Engl J Med* 328:914, 1993.
 100. Frishman WH, Garofalo JL, Rothschild A, et al: Multicenter comparison of the nifedipine gastrointestinal system and long-acting propranolol in patients with mild to moderate systemic hypertension receiving diuretics: A preliminary experience. *Am J Med* 83:15, 1987.
 101. Johnson BF, Frishman WH, Brobyn R, et al: A randomized placebo controlled, double-blind comparison of amlodipine and atenolol in patients with essential hypertension. *Am J Hypertens* 5:727, 1992.
 102. Charlap S, Kimmel B, Laifer L, et al: Twice daily nicardipine in the treatment of patients with mild to moderate hypertension. *J Clin Hypertens* 2:271,

- 1986.
103. Todd PA, Faulds D: Felodipine: A review of the pharmacology and therapeutic use of the extended-release formulation in cardiovascular disorders. *Drugs* 44:251, 1992.
 104. Hamilton BP: Treatment of essential hypertension with PN 200-110 (isradipine). *Am J Cardiol* 59:141, 1987.
 105. Basile JN: Treatment of the elderly hypertensive: systolic hypertension. In Izzo JL Jr., Sica DA, Black HR (eds): *Hypertension Primer 4th ed.* Dallas, American Heart Assn, 2008, 485.
 - 105a. Fleg JL, Aronow WS, Frishman WH: Cardiovascular drug therapy in the elderly: benefits and challenges. *Nat Rev Cardiol* 2010 in press.
 106. Staessen JA, Fagard R, Thijs L, et al: Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 350:757, 1997.
 107. Forette F, Seux M-L, Staessen JA, et al: Prevention of dementia in randomized double-blind, placebo-controlled systolic hypertension in Europe (SYST-EUR). *Lancet* 352:1347, 1998.
 108. The Seventh Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC-VII). *JAMA* 289: 2560, 2003.
 109. Wang JG, Staessen JA, Gong L, et al: Chinese trial on Isolated Systolic Hypertension in the Elderly. Systolic Hypertension in China (SYST-CHINA) Collaborative Group. *Arch Intern Med* 160:211, 2000.
 110. Black HR, Elliott WJ, Weber MA, et al for the Stage I Systolic Hypertension (SISH) Study Group: One-year study of felodipine or placebo for stage 1 isolated systolic hypertension. *Hypertension* 38:1118, 2001.
 111. Grimm RH Jr., Black H, Rowen R, et al: Amlodipine versus chlorthalidone versus placebo in the treatment of stage I isolated systolic hypertension. *Am J Hypertens* 15:31, 2002.
 112. Dahlof B, Lindholm LH, Hansson L, et al: Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 338:1281, 1991.
 113. Hansson L, Lindholm LH, Ekblom I, et al: Randomized trial of old and new antihypertensive drugs in elderly patients: Cardiovascular mortality and morbidity in the Swedish Trial of Old Patients with Hypertension-2 Study. *Lancet* 354:1751, 1999.
 114. Brown MJ, Palmer CR, Castaigne A, et al: Morbidity and mortality in patients randomized to double-blind treatment with long-acting calcium channel blocker or diuretic in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 356:366, 2000.
 115. Hansson L, Hedner T, Lund-Johansen P, et al: Randomized trial of effects of calcium antagonists compared with diuretics and beta blockers on cardiovascular morbidity and mortality in hypertension: The Nordic Diltiazem (NORDIL) Study. *Lancet* 356:359, 2000.
 116. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. National Intervention Cooperative Study in Elderly Hypertensives Study Group. *Hypertension* 34:1129, 1999.
 117. Hansson L, Zanchetti A, Carruthers SG, et al: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results from the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 351:1755, 1998.
 118. ALLHAT Officers and Coordinators: Major outcomes in high-risk hypertensive patients randomized to angiotensin converting enzyme inhibitor therapy or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288: 2981, 2002.
 119. Black HR, Elliott WJ, Neaton JD, et al: Rationale and design for the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE). *Control Clin Trials* 19:370, 1998.
 120. Hachamovitch R, Strom JA, Sonnenblick EH, Frishman WH: Left ventricular hypertrophy in hypertension and the effects of antihypertensive drug therapy. *Curr Probl Cardiol* 13(6):371, 1988.
 121. Sica DA: Combination calcium channel blocker therapy in the treatment of hypertension. *J Clin Hypertens* 3:322, 2001.
 122. Frishman WH, Ram CVS, McMahon FG, et al: Comparison of amlodipine and benazepril monotherapy to combination therapy in patients with systemic hypertension: A randomized, double-blind, placebo-controlled, parallel group study. *J Clin Pharmacol* 35:1060, 1995.
 123. Messerli F, Frishman WH, Elliott W, and the Trandolapril Study Group: Additive effects of verapamil and trandolapril in the treatment of hypertension. *J Hypertens* 11(3 Pt 1):322, 1998.
 124. Plosker GL, Robinson DM: Amlodipine/valsartan. Fixed-dose combination in hypertension. *Drugs* 68: 373, 2008.
 125. Sanford M, Keam SJ: Olmesartan medoxomil/amlodipine. *Drugs* 69: 717, 2009.
 126. Frishman WH, Hainer JW, Sugg J, and M-FACT Study Group: A factorial study of combination

- hypertension treatment with metoprolol succinate extended-release and felodipine extended-release. Results of the metoprolol succinate-felodipine antihypertension combination trial (M-FACT). *Am J Hypertens* 19:388, 2006.
127. Jamerson K, Weber M, Bakris G, et al: Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 359: 2417, 2008.
 128. Chobanian AV: The hypertension paradox – more uncontrolled disease despite improved therapy. *N Engl J Med* 361: 878, 2009.
 129. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al: A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease: the International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 290: 2805, 2003.
 130. Dahlof B, Sever PS, Poulter NR, et al: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised, controlled trial. *Lancet* 36: 895, 2005.
 131. Zing W, Ferguson RK, Vlasses PH: Calcium antagonists in elderly and black hypertensive patients: Therapeutic controversies. *Arch Intern Med* 151:2154, 1991.
 132. Kloner RA, Sowers JR, DiBona GF, et al for the Amlodipine Cardiovascular Community Trial Study Group: Sex- and age-related antihypertensive effects of amlodipine. *Am J Cardiol* 77:713, 1996.
 133. Buhler FR, Hulthen UL, Kiowski W, et al: Greater anti-hypertensive efficacy of the calcium channel inhibitor verapamil in older and low renin patients. *Clin Sci* 63:439S, 1982.
 134. Brozena SC, Johnson MR, Ventura H, et al: Effectiveness and safety of diltiazem or lisinopril in treatment of hypertension after heart transplantation. *J Am Coll Cardiol* 27:1707, 1996.
 135. Tuomilehto J, Rastenyte D, Birkenhager WH, et al: Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 340:677, 1999.
 136. Estacio RO, Jeffers BW, H iatt WR, et al: The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 338:645, 1998.
 137. Tatti P, Pahor M, Byington RP, et al: Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 21:597, 1998.
 138. Opie LH, Schall R: Evidence-based evaluation of calcium channel blockers for hypertension. *J Am Coll Card* 39:315, 2002.
 139. Pahor M, Psaty BM, Alderman MH, et al: Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: A meta-analysis of randomised controlled trials. *Lancet* 356:1949, 2000.
 140. Psaty BM, Heckbert SR, Koepsell TD, et al: The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 274:620, 1995.
 141. Pahor M, Guralnik JM, Corti C, et al: Long-term survival and use of antihypertensive medications in older persons. *J Am Geriatr Soc* 43:1191, 1995.
 142. Furberg CD, Psaty BM: Calcium antagonists: Not appropriate as first-line antihypertensive agents. *Am J Hypertens* 9:122, 1996.
 143. Epstein E: Calcium antagonists should continue to be used for first-line treatment of hypertension (commentary). *Arch Intern Med* 155:2150, 1995.
 144. Grossman E, Messerli FH: Calcium antagonists. *Prog Cardiovasc Dis* 47: 34, 2004.
 145. Sica DA, Douglas JG: The African American Study of Kidney Disease and Hypertension (AASK): New findings. *J Clin Hypertens* 3:244, 2001.
 146. Sica DA, Gehr TW: Pharmacologic treatment of hypertension. In Antman EM (ed): *Cardiovascular Therapeutics, A Companion to Braunwald's Heart Disease 3rd ed.* Philadelphia: Saunders/Elsevier 2007: 578.
 147. Chugh AR, Bakris GL: Treatment of hypertension with chronic renal insufficiency or albuminuria. In Izzo JL Jr., Sica DA, Black HR (eds): *Hypertension Primer 4th ed.* Dallas, American Heart Assn, 2008: 522.
 148. Frishman WH, Weinberg P, Peled H, et al: Calcium-entry blockers for the treatment of severe hypertension and hypertensive emergencies. *Am J Med* 77(2B):35, 1984.
 149. Ellrodt AG, Ault M, Riedinger MS, et al: Efficacy of sublingual nifedipine in hypertensive emergencies. *Am J Med* 79(4A):19, 1985.
 150. Curran MP, Robinson DM, Keating GM: Intravenous nicardipine. Its use in the short-term treatment of hypertension and various other indications. *Drugs* 66: 1755, 2006.
 151. Vidt DG: Treatment of hypertensive urgencies and emergencies. In Izzo JL Jr., Sica DA, Black HR (eds): *Hypertension Primer 4th ed.* Dallas, American Heart Assn 2008: 489.

152. Prlesi L, Cheng-Lai A: Clevidipine: a novel ultra-short acting calcium antagonist. *Cardiol in Rev* 17: 147, 2009.
153. Deedwania PC, Carbajal EV: Silent myocardial ischemia: A clinical perspective. *Arch Intern Med* 151:2373, 1991.
154. Epstein SE, Quyyumi Aa, Bonow RO: Myocardial ischemia—silent or symptomatic. *N Engl J Med* 318:1038, 1988.
155. Stone PH, Gibson RS, Glasser SP, et al: Comparison of propranolol, diltiazem and nifedipine in the treatment of ambulatory ischemia in patients with stable angina. Differential effects on ambulatory ischemia, exercise performance, and anginal symptoms. *Circulation* 82:1962, 1990.
156. Rogers WJ, Bourassa MG, Andrews TC, et al: Asymptomatic Cardiac Ischemia Pilot (ACIP) Study: Outcome at 1 year for patients with asymptomatic cardiac ischemia randomized to medical therapy or revascularization. *J Am Coll Cardiol* 26:594, 1995.
157. Pratt CM, McMahon RP, Goldstein S, et al: Comparison of subgroups assigned to medical regimens used to suppress cardiac ischemia [The Asymptomatic Cardiac Ischemia Pilot (ACIP) Study]. *Am J Cardiol* 77:1302, 1996.
158. Nayler WG: Cardioprotective effects of calcium ion antagonists in myocardial ischemia. *Clin Invest Med* 3:91, 1980.
159. Frishman WH, Skolnick AE: Secondary prevention post-infarction: The role of β -adrenergic blockers, calcium-channel blockers and aspirin. In: Gersh BJ, Rahimtoola SH, eds. *Acute Myocardial Infarction*, 2nd ed. New York: Chapman & Hall, 1997:766–796.
160. Furberg CD, Psaty BM, Meyer JV: Nifedipine: Dose-related increase in mortality in patients with coronary heart disease. *Circulation* 92:1326, 1995.
161. Gibson RS, Boden WE, Theroux P, et al: Diltiazem and reinfarction in patients with non-Q-wave-myocardial infarction. *N Engl J Med* 315:423, 1986.
162. The Multicenter Diltiazem Postinfarction Trial Research Group: The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 319(7):385, 1988.
163. The Danish Study on Verapamil in Myocardial Infarction: The effect of verapamil on mortality and major events after myocardial infarction: The Danish Verapamil Infarction Trial II (DAVIT II). *Am J Cardiol* 66:779, 1990.
164. Boden WE, van Gilst WH, Scheldewaert RG, et al for the Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis (INTERCEPT): Diltiazem in acute myocardial infarction treated with thrombolytic agents: A randomised placebo-controlled trial. *Lancet* 355:1751, 2000.
165. Theroux P, Gregoire J, Chin C, et al: Intravenous diltiazem in acute myocardial infarction. Diltiazem as adjunctive therapy to activase (DATA) trial. *J Am Coll Cardiol* 32: 620, 1998.
166. Sleight P: Calcium antagonists during and after myocardial infarction. *Drugs* 51:216, 1996.
167. Gibson RS, Hansen JE, Messerli F, et al: Long-term effects of diltiazem and verapamil on mortality and cardiac events in non-Q-wave acute myocardial infarction without pulmonary congestion: Post hoc subset analysis of the Multicenter Diltiazem Postinfarction Trial and the Second Danish Verapamil Infarction Trial studies. *Am J Cardiol* 86:275, 2000.
168. Pelliccia F, Cianfrocca C, Romeo F, et al: Hypertrophic cardiomyopathy: Long-term effects of propranolol versus verapamil in preventing sudden death in low-risk patients. *Cardiovasc Drugs Ther* 4:1515, 1990.
169. Cohen LS, Braunwald E: Amelioration of angina pectoris in idiopathic hypertrophic subaortic stenosis with beta-adrenergic blockade. *Circulation* 35:847, 1967.
170. Rosing DR, Bonow RO, Packer M, et al: Verapamil therapy for the management of hypertrophic cardiomyopathy. In: Packer M, Frishman WH, eds. *Calcium Channel Antagonists in Cardiovascular Disease*. Norwalk, CT: Appleton-Century-Crofts, 1984:313–342.
171. Kaitenbach M, Hopf R, Kober G, et al: Treatment of hypertrophic obstructive cardiomyopathy with verapamil. *Br Heart J* 42:35, 1979.
172. Rosing DR, Kent KM, Maron BJ, et al: Verapamil therapy—a new approach for the pharmacologic treatment of hypertrophic cardiomyopathy: II. Effects on exercise capacity and symptomatic status. *Circulation* 60:1208, 1979.
173. Bonow RO, Rosing DR, Bacharach SL, et al: Effects of verapamil on left ventricular systolic function and diastolic filling in patients with hypertrophic cardiomyopathy. *Circulation* 64:787, 1981.
174. Rosing DR, Cannon RO, Watson RM, et al: Comparison of verapamil and nifedipine effects on symptoms and exercise capacity in patients with hypertrophic cardiomyopathy. *Circulation* 66(Suppl II):II-24, 1982.
175. Betocchi S, Piscione F, Losi M-A, et al: Effects of diltiazem on left ventricular systolic and diastolic function in hypertrophic cardiomyopathy. *Am J Cardiol* 78:451, 1996.
176. Packer M: Calcium channel blockers in chronic heart failure. *Circulation* 82:2254, 1990.
177. Charlap S, Frishman WH: Calcium antagonists and

- heart failure. *Med Clin North Am* 73:339, 1989.
178. Elkayam U, Amin J, Mehra A, et al: A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. *Circulation* 82:1954, 1990.
 179. Polese A, Fiorentini C, Olivari MT, Guazzi M: Clinical use of a calcium antagonistic agent (nifedipine) in acute pulmonary edema. *Am J Med* 66:825, 1979.
 180. Fifer MA, Colucci WS, Lorell BH, et al: Comparison of hemodynamic responses to nifedipine in heart failure: Comparison with nitroprusside. *J Am Coll Cardiol* 5:731, 1985.
 181. Packer M, Lee WH, Medina N, et al: Prognostic importance of the immediate hemodynamic response to nifedipine in patients with severe left ventricular dysfunction. *J Am Coll Cardiol* 10:1303, 1987.
 182. Cleophas TJ, van Marum R: Meta-analysis of efficacy and safety of second-generation dihydropyridine calcium channel blockers in heart failure. *Am J Cardiol* 87:487, 2001.
 183. Krombach RS, Clair MJ, Hendrick JW, et al: Amlodipine therapy in congestive heart failure: Hemodynamic and neurohormonal effects at rest and after treadmill exercise. *Am J Cardiol* 84:3L, 1999.
 184. Udelson JE, DeAbate A, Berk M, et al for the Amlodipine Exercise Trial Investigators: Effects of amlodipine on exercise tolerance, quality of life, and left ventricular function in patients with heart failure from left ventricular systolic dysfunction. *Am Heart J* 139:503, 2000.
 185. Figulla HR, Gietzen F, Zeymer U, et al: Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy. *Circulation* 94:346, 1996.
 186. Boden WE, Ziesche S, Carson PE, et al for the V-HeFT III Investigators: Rationale and design of the Third Vasodilator-Heart Failure Trial (V-HeFT III): Felodipine as adjunctive therapy to enalapril and loop diuretics with or without digoxin in chronic congestive heart failure. *Am J Cardiol* 77:1078, 1996.
 187. Smith RF, Germanson T, Judd D, et al: Plasma norepinephrine and atrial natriuretic peptide in heart failure: Influence of felodipine in the Third Vasodilator Heart Failure Trial. V-HeFT III Investigators. *J Card Fail* 6:97, 2000.
 188. O'Connor CM, Belkin RN, Carson PE, et al: Effect of amlodipine on mode of death in severe chronic heart failure: The PRAISE Trial. *Circulation* 92:676, 1996.
 188. Packer M, O'Connor CM, Ghali JK, et al: Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 335:1107, 1996.
 190. Wijeyesundera HC, Hansen MS, Stanton E, et al: Neurohormones and oxidative stress in nonischemic cardiomyopathy: relationship to survival and the effect of treatment with amlodipine. *Am Heart J* 146: 291, 2003.
 191. Kostis JB, Lacy CR, Cosgrove NM, Wilson AC: Association of calcium channel blocker use with the increased rate of myocardial infarction in patients with left ventricular dysfunction. *Am Heart J* 133: 550, 1997.
 192. Scognamiglio R, Rahimtoola S, Fasoli G, et al: Nifedipine in symptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med* 331:689, 1994.
 193. Sotaro JF, Zaret BL, Schulman DS, et al: Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. *Am J Cardiol* 66:981, 1990.
 194. Nishikawa N, Masuyama T, Yamamoto K, et al: Long-term administration of amlodipine prevents decompensation to diastolic heart failure in hypertensive rats. *J Am Coll Cardio* 38:1539, 2001.
 195. Sondergaard L, Aldershvile J, Hildebrandt P, et al: Vasodilatation with felodipine in chronic asymptomatic aortic regurgitation. *Am Heart J* 139:667, 2000.
 196. Fein SA, Frishman WH: The pathophysiology and management of primary pulmonary hypertension. *Cardiol Clin* 5:563, 1987.
 197. Farber HW, Loscalzo J: Pulmonary arterial hypertension. *N Engl J Med* 351:1655, 2004.
 198. Rich S, Kaufman E, Levy PS: The effect of high doses of calcium channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 327:76, 1992.
 199. Packer M: Vasodilator therapy for primary pulmonary hypertension. Limitations and hazards. *Ann Intern Med* 103:258, 1985.
 200. Neely CF, Stein R, Matot I, et al: Calcium blockage in pulmonary hypertension and hypoxic vasoconstriction. *New Horizons* 4:99, 1996.
 201. Allen GS, Ahn HS, Preziosi TJ, et al: Cerebral arterial spasm—A controlled trial of nimodipine in patients with subarachnoid hemorrhage. *N Engl J Med* 308:619, 1983.
 202. Bussey HI, Talbert RL: Promising uses of calcium-channel blocking agents. *Pharmacotherapy* 4:137, 1984.
 203. Allen GS, Bahr AL: Cerebral arterial spasm: X. Reversal of acute and chronic spasm in dogs with orally administered nifedipine. *Neurosurgery* 4:43, 1979.
 204. Wadworth AN, McTavish D: Nimodipine: A re-

- view of its pharmacological properties, and therapeutic efficacy in cerebral disorders. *Drugs Aging* 2:262, 1992.
205. Feigin VL, Rinkel GJ, Algra A, et al: Calcium antagonists in patients with subarachnoid hemorrhage: A systematic review. *Neurology* 50:876, 1998.
 206. Gelmers HJ, Gorter K, DeWeerd CJ, Wiezer HJA: A controlled trial of nimodipine in acute ischemic stroke. *N Engl J Med* 318:203, 1988.
 207. Weinberger J, Terashita D: Drug therapy of neurovascular disease. *Heart Dis* 1:163, 1999.
 208. Steen PA, Gisvold SE, Milde JH, et al: Nimodipine improves outcome when given after complete cerebral ischemia in primates. *Anesthesiology* 62:406, 1985.
 209. Trust Study Group: Randomised, double-blind, placebo-controlled trial of nimodipine in acute stroke. *Lancet* 336:1205, 1990.
 210. The American Nimodipine Study Group: Clinical trial of nimodipine in acute ischemic stroke. *Stroke* 23:3, 1992.
 211. Meyer JS: Calcium channel blockers in the prophylactic treatment of vascular headache. *Ann Intern Med* 102:395, 1985.
 212. Meyer JS, Hardenberg J: Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headaches. *Headache* 23:266, 1983.
 213. Morich FJ, Bieber F, Lewis JM, et al: Nimodipine in the treatment of probable Alzheimers disease. *Clin Drug Invest* 11:185, 1996.
 214. Burger SK, Saul RF, Selhorst JB, et al: Transient monocular blindness caused by vasospasm. *N Engl J Med* 325:870, 1991.
 215. Winterkorn JMS, Kupersmith MJ, Wirtschafter JD, et al: Brief report: treatment of vasospastic amaurosis fugax with calcium-channel blockers. *N Engl J Med* 329:396, 1993.
 216. Bartsch P, Maggiorini M, Ritter M, et al: Prevention of high altitude pulmonary edema by nifedipine. *N Engl J Med* 325:1284, 1991.
 217. Coffman JD: Raynaud's phenomenon. *Hypertension* 17:593, 1991.
 218. Rodeheffer RJ, Rommer JA, Wigley F, et al: Controlled double-blind trial of nifedipine in the treatment of Raynaud's phenomenon. *N Engl J Med* 308:880, 1983.
 219. Raynaud's Treatment Study Investigators: Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon: results from a randomized clinical trial with 1-year follow up. *Arch Intern Med* 160:1101, 2000.
 220. Ram CV: Antiatherosclerotic and vasculoprotective actions of calcium antagonists. *Am J Cardiol* 66:29I, 1990.
 221. Lichtlen PR, Hugenholtz PG, Rafflenbeul W, et al: Retardation of angiographic progression of coronary artery disease by nifedipine. *Lancet* 335:1109, 1990.
 222. Waters D, Lesperance J, Francetich M, et al: A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis. *Circulation* 82:1940, 1990.
 223. Motro M, Shemesh J: Calcium channel blocker nifedipine slows down progression of coronary calcification in hypertensive patients compared with diuretics. *Hypertension* 37:1410, 2001.
 224. Mason RP: Mechanisms of atherosclerotic plaque stabilization for a lipophilic calcium antagonist amlodipine. *Am J Cardiol* 88 (Suppl): 2M, 2001.
 225. Pitt B, Byington RP, Furberg CD, et al: Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation* 102:1503, 2000.
 226. Mason RP: Scientific rationale for combination of a calcium channel antagonist and an HMG-CoA reductase inhibitor. A new approach to risk factor management. *Drugs* 68: 885, 2008.
 227. Schroeder JS, Gao S-Z, Alderman EL, et al: A preliminary study of diltiazem in the prevention of coronary artery disease in heart transplant recipients. *N Engl J Med* 328:164, 1993.
 228. Borhani NO, Mercuri M, Borhani PA, et al: Final outcome results of the multicenter isradipine diuretic atherosclerosis study (MIDAS). *JAMA* 276:785, 1996.
 229. Einecke D: ELSA studies progression of atherosclerosis: Calcium antagonist arrests the process more than a beta blocker. *MMW Fortschr Med* 143:6, 2001.
 230. Schwartz ML, Rotmensch HH, Frishman WH, Vlases P: Potential applications of calcium-channel antagonists in the management of noncardiac disorders. In: Packer M, Frishman WH, eds. *Calcium Channel Antagonists in Cardiovascular Disease*. Norwalk, CT: Appleton-Century-Crofts, 1984:371-382.
 231. Cristakis GT, Fremes SE, Weisel RD, et al: Diltiazem cardioplegia: A balance of risk and benefit. *J Thorac Cardiovasc Surg* 91:647, 1986.
 232. Seitelberger R, Zwolfer W, Huber S, et al: Nifedipine reduces the incidence of myocardial infarction and transient ischemia in patients undergoing coronary bypass grafting. *Circulation* 83:460, 1991.
 233. Piessens J, Brzostek T, Stammen F, et al: Effect of intravenous diltiazem on myocardial ischemia during percutaneous transluminal coronary angioplasty.

- Am J Cardiol* 64:1103, 1989.
234. Hillegass WB, Ohman EM, Leimberger JD, et al: A meta-analysis of randomized trials of calcium antagonists to reduce restenosis after coronary angioplasty. *Am J Cardiol* 23:835, 1994.
 235. Factor SM, Minase T, Cho S, et al: Microvascular spasm in the cardiomyopathic Syrian hamster: A preventable cause of focal myocardial necrosis. *Circulation* 66:342, 1982.
 236. Palmer BF, Dawidson I, Sagalowsky A, et al: Improved outcome of cadaveric renal transplantation due to calcium channel blockers. *Transplantation* 52:640, 1991.
 237. Epstein M: Calcium antagonists and renal protection: Current status and future perspectives. *Arch Intern Med* 152:1573, 1992.
 238. Terry RW: Nifedipine therapy in angina pectoris: Evaluation of safety and side effects. *Am Heart J* 104:681, 1982.
 239. Ellis JS, Seymour RA, Steele JG, et al: Prevalence of gingival overgrowth induced by calcium channel blockers: A community-based study. *J Periodontol* 70:63, 1999.
 240. Croom KF, Wellington K: Modified-release nifedipine. A review of the use of modified-release formulations in the treatment of hypertension and angina pectoris. *Drugs* 66: 497, 2006.
 241. Padrell MD, Navarro M, Faura CC, Horga JF: Verapamil-induced parkinsonism. *Am J Med* 99:436, 1995.
 242. Garcia Rodriguez LA, Cattaruzzi C, Grazia Troncon M, Agostinis L: Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med* 158:33, 1998.
 243. Cohen HJ, Pieper CF, Hanlon JT, et al: Calcium channel blockers and cancer. *Am J Med* 108: 210, 2000.
 244. Lindholm LH, Anderson H, Ekblom T, et al: Relation between drug treatment and cancer in hypertensives in the Swedish Trial in Old Patients with Hypertension 2: A 5-year, prospective, randomised, controlled trial. *Lancet* 358:539, 2001.
 245. Sorensen HT, Olsen JH, Mellemkjaer L, et al: Cancer risk and mortality in users of calcium channel blockers. A cohort study. *Cancer* 89:165, 2000.
 246. Harris NS: Case 24-2006: A 40-year old woman with hypotension after an overdose of amlodipine. *N Engl J Med* 355: 602, 2006.
 247. Boyer EW, Shannon M: Treatment of calcium-channel blocker intoxication with insulin infusion (correspondence). *N Engl J Med* 344:1721, 2001.
 248. Frishman WH, Sica DA: Calcium channel blockers. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed.* New York: McGraw Hill: 2003, 105.
 249. Klein HO, Lang R, Weiss E, et al: The influence of verapamil on serum digoxin concentrations. *Circulation* 65:998, 1982.
 250. Pedersen KE, Dorph-Pedersen A, Hvidt S, et al: Digoxin-verapamil interaction. *Clin Pharmacol Ther* 30:311, 1981.
 251. Belz GG, Aust PE, Munkes R: Digoxin plasma concentrations and nifedipine. *Lancet* 1:844, 1981.
 252. Mitchell LB, Jutzy KR, Lewis SJ, et al: Intracardiac electrophysiologic study of intravenous diltiazem and combined diltiazem-digoxin in patients. *Am Heart J* 103:57, 1982.
 253. Dargie HJJ for the TIBET Study Group: Medical treatment of angina can favourably affect outcome (abstr). *Eur Heart J* 14(Suppl):304, 1993.
 254. Saseen JJ, Carter BL, Brown TER, et al: Comparison of nifedipine alone and with diltiazem or verapamil in hypertension. *Hypertension* 28:109, 1996.

References for Chapter 9

The Renin-Angiotensin Axis

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

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1. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 42:1206, 2003.
2. Brunner HR, Waeber B, Nussberger J: Angiotensin-converting enzyme inhibitors. In: Messerli F, ed. *Cardiovascular Drug Therapy*. 2nd ed. Philadelphia: WB Saunders, 690–711, 1996.
3. Sica DA. Renin-angiotensin system blockade: Therapeutic Agents. In: Singh AJ, William GH (Eds). *Textbook of Nephro-Endocrinology*. (1st edition), New York, New York. Elsevier 189, 2009.
4. Ahimastos AA, Lawler A, Reid CM, et al: Ramipril markedly improves walking ability in patients with peripheral arterial disease. *Ann Intern Med* 144: 660, 2006.
5. Cheng A, Frishman WH: Use of angiotensin-converting enzyme inhibitors as monotherapy and in combination with diuretics and calcium channel blockers. *J Clin Pharmacol* 38:477, 1998.
6. Yusuf S, Sleight P, Pogue J, et al: Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 342:145, 2000.
7. Fox KM, EUROpean trial On reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 362: 782, 2003.
8. Giatras I, Lau J, Levey SS: Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: A meta-analysis of randomized trials. *Ann Intern Med* 127:337, 1997.
9. Jafar TH, Schmid CH, Landa M, et al: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 135:73, 2001.
10. Hoogwerf BJ. Renin-angiotensin system blockade and cardiovascular and renal protection. *Am J Cardiol* 105 (1 Suppl):30A, 2010.
11. Garg R, Yusuf S, for the Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 273:1450, 1995.
12. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 338: B1665, 2009.
13. Kjeldsen SE, Julius S. Hypertension mega-trials with cardiovascular end points: effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. *Am Heart J* 148. 747, 2004.
14. Toto R: Angiotensin II subtype 1-receptor blockers and renal function. *Arch Intern Med* 161:1492, 2001.
15. Al Khalaf MM, Thalib L, Doi SA. Cardiovascular outcomes in high-risk patients without heart failure treated with ARBs: a systematic review and meta-analysis. *Am J Cardiovasc Drugs* 9:29, 2009.
16. JAMAli AH, Tang WH, Khot UN, Fowler MB: The role of angiotensin receptor blockers in the management of chronic heart failure. *Arch Intern Med* 161:667, 2001.
17. Johnston C, Risvanis J: Preclinical pharmacology of angiotensin II receptor antagonists: Update and outstanding issues. *Am J Hypertens* 10:306S, 1997.
18. Burnier M: Angiotensin II type 1-receptor block-

- ers. *Circulation* 103:904, 2001.
19. Carretero OA, Scicli AG: The kallikrein-kinin system as a regulator of cardiovascular and renal function. In: Brenner BM, Laragh JH, eds. *Hypertension: Pathophysiology, Diagnosis, and Management*. 2nd ed. New York: Raven Press, 1995:983–999.
 20. Juillerat L, Nussberger J, Menard J, et al: Determinants of angiotensin II generation during converting enzyme inhibition. *Hypertension* 16:564, 1990.
 21. Bacani C, Frishman WH: Chymase: a new pharmacologic target in cardiovascular disease. *Cardiol in Rev* 14: 187, 2006.
 22. Petrie MC, Padmanabhan N, McDonald JE, et al: Angiotensin-converting enzyme and non-ACE dependent angiotensin II generation in resistance arteries from patients with heart failure and coronary heart disease. *J Am Coll Cardiol* 37:1056, 2001.
 23. Ennezat PV, Berlowitz M, Sonnenblick EH, Le Jemtel TH: Therapeutic implications of escape from angiotensin-converting enzyme inhibition in patients with chronic heart failure. *Curr Cardiol Rep* 2:258, 2000.
 24. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L: Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. *Circulation* 82:1730, 1990.
 25. Mooser V, Nussberger J, Juillerat L, et al: Reactive hyperreninemia is a major determinant of plasma angiotensin II during ACE inhibition. *J Cardiovasc Pharmacol* 15:276, 1990.
 26. Vander AJ, Geelhoed GW: Inhibition of renin secretion by angiotensin II. *Proc Soc Exp Biol Med* 120:399, 1965.
 27. Grima M, Ingert C, Michel B, et al: Renal tissue angiotensins during converting enzyme inhibition in the spontaneously hypertensive rat. *Clin Exp Hypertens* 19:671, 1997.
 28. Nussberger J, Brunner DB, Waeber A, et al: Lack of angiotensin I accumulation after converting enzyme blockade with enalapril or lisinopril in man. *Clin Sci (Lond)* 72:387, 1987.
 29. Staessen J, Fagard R, Lijnen P, et al: The hypotensive effect of propranolol in captopril-treated patients does not involve the plasma renin-angiotensin-aldosterone system. *Clin Sci (Lond)* 61:441S, 1981.
 30. Hodsman GP, Isles CG, Murray GD, et al: Factors related to the first dose hypotensive effect of captopril: Prediction and treatment. *Brit Med J* 286:832, 1983.
 31. Case DB, Atlas SA, Laragh JH, et al: Use of first dose response or plasma renin activity to predict the long-term effect of captopril: Identification of triphasic pattern of blood pressure response. *J Cardiovasc Pharmacol* 2:339, 1980.
 32. Brunner HR, Waeber B, Nussberger J: Does pharmacological profiling of a new drug in normotensive volunteers provide a useful guide to antihypertensive therapy. *Hypertension* 5 (Supple III):101, 1983.
 33. Egan BM, Basile JN, Rehman SU, et al: Plasma Renin test-guided drug treatment algorithm for correcting patients with treated but uncontrolled hypertension: a randomized controlled trial. *Am J Hypertens* 22, 792, 2009.
 34. Gainer JV, Morrow JD, Loveland A, et al: Effect of bradykinin-receptor blockade on the response to angiotensin-converting enzyme inhibitor in normotensive and hypertensive subjects. *N Engl J Med* 339:1285, 1998.
 35. Squire IB, O’Kane KP, Anderson N, Reid JL: Bradykinin B (2) receptor antagonism attenuates blood pressure response to acute angiotensin-converting enzyme inhibition in normal men. *Hypertension* 36:132, 2000.
 36. Su JB, Barbe F, Crozatier B, et al: Increased bradykinin levels accompany the hemodynamic response to acute inhibition of angiotensin-converting enzyme in dogs with heart failure. *J Cardiovasc Pharmacol* 34:700, 1999.
 37. Ogihara T, Maruyama A, Hata T, et al: Hormonal responses to long-term converting enzyme inhibition in hypertensive patients. *Clin Pharmacol Ther* 30:328, 1981.
 38. Gavras I: Bradykinin-mediated effects of ACE inhibition. *Kidney Int* 42:1020, 1992.
 39. Mazzolai L, Maillard M, Rossat J, et al: Angiotensin II receptor blockade in normotensive subjects: A direct comparison of three AT₁ receptor antagonists. *Hypertension* 33:850, 1999.
 40. Abadir PM, Carey RM, Siragy HM: Angiotensin AT₂-receptors directly stimulate renal nitric oxide in bradykinin B₂-receptor null mice. *Hypertension* 42:600, 2004.
 41. Rodriguez-Garcia JL, Villa E, Serrano M, et al: Prostacyclin: Its pathogenic role in essential hypertension and the class effect of ACE inhibitors on prostaglandin metabolism. *Blood Press* 8: 279, 1999.
 42. Waeber B, Nussberger J, Brunner HR: Angiotensin-converting enzyme inhibitors in hypertension. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis, and Management*. 2nd ed. New York: Raven Press, 1995:2861–2875.
 43. Quest DW, Gopalakrishnan V, McNeill JR, Wilson TW: Effect of losartan on angiotensin II-mediated endothelin and prostanoid excretion in humans. *Am J Hypertens* 13:1288, 2000.

44. Salvetti A, Abdel-Hag B, Magagna A, et al: Indomethacin reduces the antihypertensive effect of enalapril. *Clin Exp Hypertens* 9:559, 1987.
45. Wilson SL, Poulter NR. The effect of non-steroidal anti-inflammatory drugs and other commonly used non-narcotic analgesics on blood pressure level in adults. *J Hypertens* 24:1457, 2006.
46. Nawarskas JJ, Townsend RR, Cirigliano MD, Spinler SA: Effect of aspirin on blood pressure in hypertensive patients taking enalapril or losartan. *Am J Hypertens* 12:784, 1999.
47. Nawarskas JJ, Spinler SA: Does aspirin interfere with the therapeutic efficacy of angiotensin-converting enzyme inhibitors in hypertension or congestive heart failure. *Pharmacotherapy* 18:1041, 1998.
48. Guazzi MD, Campodonico J, Celeste F, et al: Antihypertensive efficacy of angiotensin-converting enzyme inhibition and aspirin counteraction. *Clin Pharmacol Ther* 63:79, 1998.
49. Balt JC, Mathy MJ, Pfaffendorf M, van Zwieten PA: Inhibition of angiotensin II-induced facilitation of sympathetic neurotransmission in the pithed rat: A comparison between losartan, irbesartan, telmisartan, and captopril. *J Hypertens* 19:465, 2001.
50. Lang CC, Stein M, He HB, et al: Angiotensin-converting enzyme inhibition and sympathetic activity in healthy subjects. *Clin Pharmacol Ther* 59:668, 1996.
51. Ranadive SA, Chen AX, Serajuddin AT: Relative lipophilicities and structural-pharmacological considerations of various angiotensin-converting enzyme (ACE) inhibitors. *Pharm Res* 9:1480, 1992.
52. Gohlke P, Weiss S, Jansen A, et al: AT1 receptor antagonist telmisartan administered peripherally inhibits central responses to angiotensin II in conscious rats. *J Pharmacol Exp Ther* 298:62, 2001.
53. Culman J, von Heyer C, Piepenburg B, et al: Effects of systemic treatment with irbesartan and losartan on central responses to angiotensin II in conscious, normotensive rats. *Eur J Pharmacol* 367:255, 1999.
54. Krum H: Differentiation in the angiotensin II receptor 1 blocker class on autonomic function. *Curr Hypertens Rep* 3 (Suppl 1):S17, 2001.
55. Fagard R, Amery A, Reybrouck T, et al: Acute and chronic systemic and hemodynamic effects of angiotensin-converting enzyme inhibition with captopril in hypertensive patients. *Am J Cardiol* 46:295, 1980.
56. Yee KM, Struthers AD: Endogenous angiotensin II and baroreceptor dysfunction: A comparative study of losartan and enalapril in man. *Br J Clin Pharmacol* 46:583, 1998.
57. Vanhoutte PM: Endothelial dysfunction and inhibition of converting enzyme. *Eur Heart J* 19 (Suppl J):J7, 1998.
58. Schiffrin EL, Park JB, Pu Q: Effect of crossing over hypertensive patients from a beta-blocker to an angiotensin receptor antagonist on resistance artery structure and on endothelial function. *J Hypertens* 20:71, 2002.
59. Schiffrin EL: Effects of antihypertensive drugs on vascular remodeling: Do they predict outcome in response to antihypertensive therapy. *Curr Opin Nephrol Hypertens* 10:617, 2001.
60. Oparil S, Guthrie R, Lewin AJ, et al: An electivtitration study of the comparative effectiveness of two angiotensin II-receptor blockers, irbesartan and losartan. Irbesartan/Losartan Study Investigators. *Clin Ther* 20:398, 1998.
61. Souza Dos Santos RA, Passaglio KT, Pesquero JB, et al: Interactions between angiotensin-(1-7), kinins, and angiotensin II in kidney and blood vessels. *Hypertension* 38:660, 2001.
62. Chappell MC, Allred AJ, Ferrario CM: Pathways of angiotensin-(1-7) metabolism in the kidney. *Nephrol Dial Transplant* 16(Suppl 1):22, 2001.
63. Iusuf D, Henning RH, van Gilst WH, Roks AJ. Angiotensin-(1-7): pharmacological properties and pharmacotherapeutic perspectives. *Eur J Pharmacol* 585:303, 2008.
64. White CM: Pharmacologic, pharmacokinetic, and therapeutic differences among ACE inhibitors. *Pharmacotherapy* 18:588, 1998.
65. Cody R: Optimizing ACE inhibitor therapy of congestive heart failure: Insights from pharmacodynamic studies. *Clin Pharmacokinet* 24:59, 1993.
66. Dickstein K: Pharmacokinetics of enalapril in congestive heart failure. *Drugs* 32(Suppl 5):40, 1986.
67. Herman AG: Differences in structure of angiotensin-converting enzyme inhibitors might predict differences in action. *Am J Cardiol* 70:102C, 1992.
68. Salvetti A: Newer ACE inhibitors: A look at the future. *Drugs* 40:800, 1990.
69. Zusman RM: Effects of converting-enzyme inhibitors on the renin-angiotensin-aldosterone, bradykinin, and arachidonic acid-prostaglandin systems: Correlation of chemical structure and biological activity. *Am J Kidney Dis* 10(Suppl 1):13, 1987.
70. Chalmers D, Whitehead A, Lawson DH: Postmarketing surveillance of captopril for hypertension. *Br J Clin Pharmacol* 34:215, 1992.
71. Punzi HD: Safety update: Focus on cough. *Am J Cardiol* 72:45H, 1993.
72. Sharif MN, Evans BL, Pylypchuk GB: Cough induced by quinapril with resolution after changing to fosinopril. *Ann Pharmacother* 28:720, 1994.
73. Zusman RM: Angiotensin-converting enzyme in-

- hibitors: More different than alike. *Am J Cardiol* 72:25H, 1993.
74. Zusman RM, Christensen DM, Higgins J, Boucher CA: Effects of fosinopril on cardiac function in patients with hypertension. Radionuclide assessment of left ventricular systolic and diastolic performance. *Am J Hypertens* 5:219, 1992.
75. Sica DA: Angiotensin-converting enzyme inhibitors: Fosinopril. In: Messerli F, ed. *Cardiovascular Drug Therapy*. 2d ed. Philadelphia: WB Saunders 1996:801–809.
76. Brockmeier D: Tight binding influencing the future of pharmacokinetics. *Methods Find Exp Clin Pharmacol* 20:505–516, 1998.
77. Reid JL: From kinetics to dynamics: Are there differences between ACE inhibitors. *Eur Heart J* 18 (Suppl E): E14, 1997.
78. Hoyer J, Schulte K-L, Lenz T: Clinical pharmacokinetics of angiotensin-converting enzyme inhibitors in renal failure. *Clin Pharmacokinet* 24:230, 1993.
79. Dzau VJ, Bernstein K, Celermajer D, et al: The relevance of tissue angiotensin-converting enzyme: Manifestations in mechanistic and end-point data. *Am J Cardiol* 88 (Suppl 9):1L, 2001.
- 79a. Kostis JB: Differences among ACE inhibitors: *Am J Hypertens* 23: 1156, 2010.
- 79b. Ruzicka M, Coletta E, White R, et al: Effects of ACE inhibitors on cardiac angiotensin II and aldosterone in humans: “relevance of lipophilicity and affinity for ACE”. *Am J Hypertens* 23: 1179, 2010.
80. Sica DA: Kinetics of angiotensin-converting enzyme inhibitors in renal failure. *J Cardiovasc Pharmacol* 20 (Supp 10):S13, 1992.
81. Ebihara A, Fujimura A: Metabolites of antihypertensive drugs. An updated review of their clinical pharmacokinetic and therapeutic implications. *Clin Pharmacokinet* 21:331, 1991.
82. Kelly JG, Doyle GD, Carmody M, et al: Pharmacokinetics of lisinopril, enalapril and enalaprilat in renal failure: Effects of haemodialysis. *Br J Clin Pharmacol* 26:781, 1988.
83. Schunkert H, Kindler J, Gassmann M, et al: Pharmacokinetics of ramipril in hypertensive patients with renal insufficiency. *Eur J Clin Pharmacol* 37:249, 1989.
84. Hui KK, Duchin KL, Kripalani KJ, et al: Pharmacokinetics of fosinopril in patients with various degrees of renal function. *Clin Pharmacol Ther* 49:457, 1991.
85. Danielson B, Querin S, LaRochelle P, et al: Pharmacokinetics and pharmacodynamics oftrandolapril after repeated administration of 2 mg to patients with chronic renal failure and healthy control subjects. *J Cardiovasc Pharmacol* 23(Supp 4):S50, 1994.
86. Kaiser G, Ackermann R, Sioufi A: Pharmacokinetics of a new angiotensin-converting enzyme inhibitor, benazepril hydrochloride, in special populations. *Am Heart J* 117:746, 1989.
87. Noormohamed FH, McNabb WR, Lant AF: Pharmacokinetic and pharmacodynamic actions of enalapril in humans: Effect of probenecid pretreatment. *J Pharmacol Exp Ther* 253:362, 1990.
88. Lin JH, Chen IW, Ulm EH, Duggan DE: Differential renal handling of angiotensin-converting enzyme inhibitors enalaprilat and lisinopril in rats. *Drug Metab Dispos* 16:392, 1998.
89. Sica DA, Cutler RE, Parmer RJ, et al: Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril, and enalapril in patients with chronic renal insufficiency. *Clin Pharmacokinet* 20:420, 1991.
90. Greenbaum R, Zucchelli P, Caspi A, et al: Comparison of the pharmacokinetics of fosinoprilat with enalaprilat and lisinopril in patients with congestive heart failure and chronic renal insufficiency. *Br J Clin Pharmacol* 49:23, 2000.
91. Sica DA, Deedwania PC: Renal considerations in the use of angiotensin-converting enzyme inhibitors in the treatment of congestive heart failure. *Cong Heart Fail* 3:54, 1997.
92. Brown NJ, Vaughn DE: Angiotensin-converting enzyme inhibitors. *Circulation* 97:1411, 1998.
93. Fabris B, Jackson B, Kohzuki M, et al: Increased cardiac angiotensin-converting enzyme in rats with chronic heart failure. *Clin Exp Pharmacol Physiol* 17:309, 1990.
94. Johnston CI, Fabris B, Yamada H, et al: Comparative studies of tissue inhibition by angiotensin-converting enzyme inhibitors. *J Hypertens* 7 (Suppl):S11, 1989.
95. Fabris B, Chen BZ, Pupic V, et al: Inhibition of angiotensin-converting enzyme (ACE) in plasma and tissue. *J Cardiovasc Pharmacol* 15(Supp 2):S6, 1990.
96. Opie LH: ACE Inhibitors: Specific agents and pharmacokinetics. In: Opie LH, ed. *Angiotensin-Converting Enzyme Inhibitors: Scientific Basis for Clinical Use*. New York: Authors’ Publishing House, 1994:171–247.
97. Jackson EK, Garrison JC: Renin and angiotensin. In: Hardman JG, Limbird L, eds. *Goodman & Gilman’s The Pharmacological Basis of Therapeutics*. New York: McGraw-Hill, 1999:743–746.
98. Johnston CI, Fabris B, Yoshida K: The cardiac renin-angiotensin system in heart failure. *Am Heart J* 126:756, 1993.
99. Fabris B, Yamada H, Cubela R, et al: Characterization of cardiac angiotensin-converting enzyme and in vivo inhibition following oral quinapril to rats.

- Br J Pharmacol* 100:651, 1990.
100. Kinoshita A, Urata H, Bumpus FM, Husain A: Measurement of angiotensin I-converting enzyme inhibition in the heart. *Circ Res* 73: 51, 1993.
 101. Leonetti G, Cuspidi C: Choosing the right ACE inhibitor. A guide to selection. *Drugs* 49:516, 1995.
 102. Ruddy MC, Kostis JB, Frishman WH: Drugs that affect the renin-angiotensin system. In: Frishman W, Sonnenblick E, eds. *Cardiovascular Pharmacotherapeutics*. New York: McGraw-Hill, 1998:131–192.
 103. Briscoe TA, Dearing CJ: Clinical and economic effects of replacing enalapril with benazepril in hypertensive patients. *Am J Health Syst Pharm* 53:2191, 1996.
 104. The SOLVD investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 325:293, 1991.
 105. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 329:1456, 1993.
 106. Sica DA: The HOPE Study: ACE inhibitors – are their benefits a class effect or do individual agents differ. *Curr Opin Nephrol Hypertens* 10:597, 2001.
 107. Jafar TH, Stark PC, Schmid CH, et al: Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int* 60:1131, 2001.
 108. Wilson Tang WH, Vagelos RH, et al: Neurohormonal and clinical responses to high- versus low-dose enalapril therapy in chronic heart failure. *J Am Coll Cardiol* 39:70, 2002.
 109. Packer M, Poole-Wilson PA, Armstrong PW, et al: Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 100:2312, 1999.
 110. Massie B: Neurohormonal blockade in chronic heart failure. How much is enough. Can there be too much *J Am Coll Cardiol* 39:79, 2002.
 111. Tang WH, Vagelos RH, Yee YG, et al: Neurohormonal and clinical responses to high- versus low-dose enalapril therapy in chronic heart failure. *J Am Coll Cardiol* 39:70, 2002.
 112. Van Veldhuisen DJ, Genth-Zotz S, Brouwer J, et al: High- versus low-dose ACE inhibition in chronic heart failure. A double-blind, placebo-controlled study of imidapril. *J Am Coll Cardiol* 32:1811, 1998.
 113. The American College of Cardiology/American Heart Association Task Force on Practical Guidelines (Committee on Evaluation and Management of Heart Failure) Guidelines for the evaluation and management of heart failure. *Circulation* 92:2764, 1995.
 114. Sica DA: Pharmacology and clinical efficacy of angiotensin-receptor blockers. *Am J Hypertens* 14:242S, 2001.
 115. Kassler-Taub K, Littlejohn T, Elliott W, et al: Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan, in mild to moderate hypertension. *Am J Hypertens* 11:445, 1998.
 116. Oparil S, Guthrie R, Lewin AJ, et al: An elective-titration study of the comparative effectiveness of two angiotensin II-receptor blockers, irbesartan and losartan. *Clin Ther* 20:398, 1998.
 117. Israili ZH: Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. *J Hum Hypertens* 14 (Suppl 1): S73, 2000.
 - 117a. Azilsartan medoxomil (Edarbi)—the eighth ARB. *The Medical Letter* 43: 39, 2011.
 118. Atacand (candesartan cilexetil). Product information. Wilmington, DE: Astra Zeneca; 1998.
 119. Riddell JG: Bioavailability of candesartan is unaffected by food in healthy volunteers administered candesartan cilexetil. *J Hum Hypertens* 11 (Suppl 2): S29, 1997.
 120. Tenero D, Martin D, Ilson B, et al: Pharmacokinetics of intravenously and orally administered eprosartan in healthy males: Absolute bioavailability and effect of food. *Biopharm Drug Disp* 19:351, 1998.
 121. Cox PJ, Bush BD, Gorycki PD, et al: The metabolic fate of eprosartan in healthy volunteers. *Exp Toxicol Pathol* 48(Suppl II):75, 1996.
 122. Bottorff MB, Tenero DM: Pharmacokinetics of eprosartan in healthy subjects, patients with hypertension, and special populations. *Pharmacotherapy* 19:73S, 1999.
 123. Chapelsky MC, Martin DE, Tenero DM, et al: A dose proportionality study of eprosartan in healthy male volunteers. *J Clin Pharmacol* 38:34, 1998.
 124. Vachharajani NN, Shyu WC, Chando TJ, et al: Oral bioavailability and disposition characteristics of irbesartan, an angiotensin antagonist, in healthy volunteers. *J Clin Pharmacol* 38:702, 1998.
 125. Vachharajani NN, Shyu WC, Mantha S, et al: Lack of effect of food on the oral bioavailability of irbesartan in healthy male volunteers. *J Clin Pharmacol* 38:433, 1998.
 126. Lo MW, Goldberg MR, McCrea JB, et al: Pharmacokinetics of losartan, an angiotensin II receptor antagonist, and its active metabolite, EXP3174 in humans. *Clin Pharmacol Ther* 58:641, 1995.
 127. Cozaar (losartan). Product information. West Point, PA: Merck & Co; 1995.
 128. Laeis P, Puchler K, Kirch W: The pharmacokinetic and metabolic profile of olmesartan medoxomil

- limits the risk of clinically relevant drug interactions. *J Hypertens* 19 (Suppl 1): S21, 2001.
129. Mycardis (telmisartan). Product information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 1998.
 130. Stangier J, Schmid J, Turck D et al: Absorption, metabolism, and excretion of intravenously and orally administered [¹⁴C] telmisartan in healthy volunteers. *J Clin Pharmacol* 40:1312, 2000.
 131. Flesch G, Muller P, Lloyd P: Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist, in man. *Eur J Clin Pharmacol* 52:115, 1997.
 132. Diovan (valsartan). Product information. East Hanover, NJ: Novartis Pharmaceuticals; 1998.
 133. Gillis JC, Markham A: Irbesartan. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in the management of hypertension. *Drugs* 54:885, 1997.
 134. Marino MR, Langenbacher K, Ford NF, et al: Pharmacokinetics and pharmacodynamics of irbesartan in healthy subjects. *J Clin Pharmacol* 38: 246, 1998.
 135. Ludden TM: Nonlinear pharmacokinetics: Clinical implications. *Clin Pharmacokinet* 20: 429, 1991.
 136. Lo MW, Goldberg MR, McCrea JB, et al: Pharmacokinetics of losartan, an angiotensin II receptor antagonist, and its active metabolite, EXP3174 in humans. *Clin Pharmacol Ther* 58:641, 1995.
 137. Lo MW, Toh J, Emmert SE, et al: Pharmacokinetics of intravenous and oral losartan in patients with heart failure. *Clin Pharmacol Ther* 38:525, 1998.
 138. van Lier JJ, Heiningen PNM, Sunzel M: Absorption, metabolism and excretion of ¹⁴C-candesartan and ¹⁴C-candesartan cilexetil in healthy volunteers. *J Hum Hypertens* 11 (Suppl 2): S27, 1997.
 139. Criscione L, Bradley WA, Buylamayer P, et al: Valsartan: Preclinical and clinical profile of an antihypertensive angiotensin II antagonist. *Cardiovasc Drug Rev* 13:230, 1995.
 140. Bergmann K, Laeis P, Puchler K, et al: Olmesartan medoxomil: Influence of age, renal and hepatic function on the pharmacokinetics of olmesartan medoxomil. *J Hypertens* 19 (Suppl 1): S33, 2001.
 141. Christ DD: Human plasma protein binding of the angiotensin II receptor antagonist losartan potassium (DuP 753/MK 954) and its pharmacologically active metabolite EXP3174. *J Clin Pharmacol* 35:515, 1995.
 142. Martin DE, Chapelsky MC, Ilson B, et al: Pharmacokinetics and protein binding of eprosartan in healthy volunteers and in patients with varying degrees of renal impairment. *J Clin Pharmacol* 38:129, 1998.
 143. Colussi DM, Parisot C, Rossolino ML, et al: Protein binding of valsartan, a new angiotensin receptor antagonist. *J Clin Pharmacol* 37: 214, 1997.
 144. van Lier JJ, Heiningen PNM, Sunzel M: Absorption, metabolism and excretion of ¹⁴C-candesartan and ¹⁴C-candesartan cilexetil in healthy volunteers. *J Hum Hypertens* 11(Suppl 2):S27, 1997.
 145. Yun CH, Lee HS, Lee H, et al: Oxidation of the angiotensin II receptor antagonist losartan (DuP 753) in human liver microsomes; role of cytochrome P4503A (4) in formation of the active metabolite EXP3174. *Drug Metab Dispos* 23:285, 1995.
 146. Stearns RA, Chakravarty PK, Chen R, et al: Bio-transformation of losartan to its active carboxylic acid metabolite in human liver microsomes. Role of cytochrome P₄₅₀2C and 3A subfamily members. *Drug Metab Dispos* 23:207, 1995.
 147. McCrea JB, Cribb A, Rushmore T, et al: Phenotypic and genotypic investigations of a healthy volunteer deficient in the conversion of losartan to its active metabolite E-3174. *Clin Pharmacol Ther* 65:348, 1999.
 148. Hubner R, Hogemann AM, Sunzel M, et al: Pharmacokinetics of candesartan after single and multiple doses of candesartan cilexetil in young and elderly healthy volunteers. *J Hum Hypertens* 11 (Suppl 2): S19, 1997.
 149. Kazierad DJ, Martin DE, Blum RA, et al: Effect of fluconazole on the pharmacokinetics of eprosartan and losartan in healthy male volunteers. *Clin Pharmacol Ther* 62:417, 1997.
 150. McCrea JB, Low MW, Furtek CI, et al: Ketoconazole does not effect the systemic conversion of losartan to E-3174. *Clin Pharmacol Ther* 59:A169, 1996.
 151. Yasar U, Tybring G, Hidestrand M, et al: Role of CYP2C9 polymorphism in losartan oxidation. *Drug Metab Dispos* 29:1051, 2001.
 152. Zaidenstein R, Soback S, Gips M, et al: Effect of grapefruit juice on the pharmacokinetics of losartan and its active metabolite E3174 in healthy volunteers. *Ther Drug Monit* 23:369, 2001.
 153. Chando TJ, Everett DW, Kahle AD, et al: Biotransformation of irbesartan in man. *Drug Metab Dispos* 26:408, 1998.
 154. Marino MR, Hammett JL, Ferreira I, et al: Effect of nifedipine on the steady-state pharmacokinetics and pharmacodynamics of irbesartan in healthy subjects. *J Cardiovasc Pharmacol* 3: 111, 1998.
 155. de Zeeuw D, Remuzzi G, Kirch W: The pharmacokinetics of candesartan cilexetil in patients with renal or hepatic impairment. *J Hum Hypertens* 11 (Suppl 2):S37, 1997.
 156. Sica DA, Shaw WC, Lo MW, et al: The pharmaco-

- netics of losartan in renal insufficiency. *J Hypertens* 13 (Suppl 1): S49, 1995.
157. Sica DA, Marino MR, Hammett JL, et al: The pharmacokinetics of irbesartan in renal failure and maintenance hemodialysis. *Clin Pharmacol Ther* 62: 610, 1997.
 158. Stangier J, Su CA, Brickl R, Franke H: Pharmacokinetics of single-dose telmisartan 120 mg given during and between hemodialysis in subjects with severe renal insufficiency: Comparison with healthy volunteers. *J Clin Pharmacol* 40: 1365, 2000.
 159. Prasad P, Mangat S, Choi L, et al: Effect of renal function on the pharmacokinetics of valsartan. *Clin Drug Invest* 13:207, 1997.
 160. Kovacs SJ, Tenero DM, Martin DE, et al: Pharmacokinetics and protein binding of eprosartan in hemodialysis-dependent patients with end-stage renal disease. *Pharmacotherapy* 19:612, 1999.
 161. Martin DE, Chapelsky MC, Ilson B, et al: Pharmacokinetics and protein binding of eprosartan in healthy volunteers and in patients with varying degrees of renal impairment. *J Clin Pharmacol* 38:129, 1998.
 162. Toto R, Shultz P, Jaij L, et al: Efficacy and tolerability of losartan in hypertensive patients with renal impairment. *Hypertension* 31: 684, 1998.
 163. Sharma AM, Hollander A, Koster J, et al. Efficacy and safety in patients with renal impairment; treated with Telmisartan (ESPRIT) Study Group. Telmisartan in patients with mild/moderate hypertension and chronic kidney disease. *Clin Nephrol* 63: 250, 2005.
 164. Schulz EG, Bahri S, Schettler V, et al. Pharmacokinetics and antihypertensive effects of candesartan cilexetil in patients undergoing haemodialysis: an open-label, single-centre study. *Clin Drug Investig* 29:713, 2009.
 165. Plum J, Bünten B, Németh R, Grabensee B. Effects of the angiotensin II antagonist valsartan on blood pressure, proteinuria, and renal hemodynamics in patients with chronic renal failure and hypertension. *J Am Soc Nephrol* 9: 2223, 1998.
 166. De Rosa ML, de Cristofaro A, Rossi M, et al: Irbesartan effects on renal function in patients with renal impairment and hypertension: a drug-withdrawal study. *J Cardiovasc Pharmacol* 38: 482, 2001.
 167. Hunsicker LG, Atkins RC, Lewis JB, et al. Impact of irbesartan, blood pressure control, and proteinuria on renal outcomes in the Irbesartan Diabetic Nephropathy Trial. *Kidney Inter* 66: S99, 2004.
 168. Sica DA, Gehr TW, Fernandez A: Risk-benefit ratio of angiotensin antagonists versus ACE inhibitors in end-stage renal disease. *Drug Saf* 22: 350, 2000.
 169. Brunner HR: The new angiotensin II receptor antagonist, irbesartan. Pharmacokinetic and pharmacodynamic considerations. *Am J Hypertens* 10: 311S, 1997.
 170. Mazzolai L, Maillard M, Rossat J, et al: Angiotensin II receptor blockade in normotensive subjects. A direct comparison of three AT1-receptor antagonists. *Hypertension* 33:850, 1999.
 171. Hodges JC, Hamby JM, Blankey CJ: Angiotensin II receptor binding inhibitors. *Drugs Fut* 17:575, 1992.
 172. Dickinson KE, Cohen RB, Skwish S, et al: BMS 180560, an insurmountable inhibitor of angiotensin-II stimulated responses: Comparison with losartan and EXP-3174. *Br J Pharmacol* 113:179, 1994.
 173. Liu YJ, Shankley NP, Welsh NJ, et al. Evidence that the apparent complexity of receptor antagonism by angiotensin II analogues is due to a reversible and syntopic action. *Br J Pharmacol* 106: 233,1992.
 174. Ojima M, Inada Y, Shibouta Y, et al: Candesartan (CV-11974) dissociates slowly from the angiotensin AT1 receptor. *Eur J Pharmacol* 319:137, 1997.
 175. McConnaughey MM, McConnaughey JS, Ingenito AJ: Practical considerations of the pharmacology of angiotensin receptor blockers. *J Clin Pharmacol* 39:547, 1998.
 176. Hansson L: The relationship between dose and antihypertensive effect for different AT1-receptor blockers. *Blood Press Suppl* 3:33, 2001.
 177. Maillard MP, Wurzner G, Nussberger J, et al: Comparative angiotensin II receptor blockade in healthy volunteers: The importance of dosing. *Clin Pharmacol Ther* 71:68, 2002.
 178. Hollenberg NK: Renal implications of angiotensin receptor blockers. *Am J Hypertens* 14:237S, 2001.
 179. Hodsman GP, Isles CG, Murray GD, et al: Factors related to first-dose hypotensive effect of captopril: Prediction and treatment. *Br Med J* 286:832, 1983.
 180. Muiesan G, Alicandri CL, Agabiti-Rosei E, et al: Angiotensin-converting enzyme inhibition, catecholamines, and hemodynamics in essential hypertension. *Am J Cardiol* 46:1420, 1980.
 181. Saragoca MA, Homsí E, Ribeiro AB, et al: Hemodynamic mechanism of blood pressure response to captopril in human malignant hypertension. *Hypertension* 5 (Suppl I):53, 1983.
 182. Magrini F, Shimizu M, Roberts N, et al: Converting-enzyme inhibition and coronary blood flow. *Circulation* 75:1168, 1987.
 183. Yusuf S, Lonn E: Anti-ischemic effects of ACE inhibitors: Review of current clinical evidence and ongoing clinical trials. *Eur Heart J* 19 (Suppl J): J36,

- 1998.
184. Brugts JJ, den Uil CA, Danser AH, Boersma E. The renin-angiotensin-aldosterone system: approaches to guide angiotensin-converting enzyme inhibition in patients with coronary artery disease. *Cardiology* 112:303, 2009.
185. Waldemar G, Ibsen H, Strandgaard S, et al: The effect of fosinopril sodium on cerebral blood flow in moderate essential hypertension. *Am J Hypertens* 3:464, 1990.
186. Sare GM, Gray LJ, Bath PM. Effect of antihypertensive agents on cerebral blood flow and flow velocity in acute ischaemic stroke: systematic review of controlled studies. *J Hypertens* 26:1058, 2008.
187. Sica DA. Calcium channel blocker-related peripheral edema: can it be resolved? *J Clin Hypertens (Greenwich)* 5: 291, 2003.
188. Morioka S, Simon G, Cohn JN: Cardiac and hormonal effects of enalapril in hypertension. *Clin Pharmacol Ther* 34:583, 1988.
189. Omvik P, Lund-Johansen P: Combined captopril and hydrochlorothiazide therapy in severe hypertension: Long-term haemodynamic changes at rest and during exercise. *J Hypertens* 2:73, 1984.
190. Hollenberg N, Raji L: Angiotensin-converting enzyme inhibition and renal protection. *Arch Intern Med* 153:2426, 1993.
191. Toto RD, Mitchell HC, Lee HC, et al: Reversible renal insufficiency due to angiotensin-converting enzyme inhibitors in hypertensive nephrosclerosis. *Ann Intern Med* 115:513, 1991.
192. Mancia G, De Backer G, Dominiczak A, et al. ESH-ESC Task Force on the Management of Arterial Hypertension. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* 25:1751, 2007.
193. Khan NA, Hemmelgarn B, Herman RJ, et al. Canadian Hypertension Education Program. The 2009 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 2 - therapy. *Can J Cardiol* 25:287, 2009.
194. Sica DA: Old antihypertensive agents - diuretics and beta-blockers: Do we know how and in whom they reduce blood pressure *Curr Hypertens Rep* 1:296, 1999.
195. Julius S, Nesbitt SD, Egan BM, et al for the Trial of Preventing Hypertension (TROPHY) study investigators: Feasibility of treating prehypertension with an angiotensin-receptor blockers. *N Engl J Med* 354: 1685, 2006.
196. Materson BJ, Reda DJ, Cushman WC, et al: Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. *N Engl J Med* 328:914, 1993.
197. Elliott WJ: Therapeutic trials comparing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. *Curr Hypertens Rep* 2:402, 2000.
- 197a. Catanzaro DF, Frishman WH: Angiotensin receptor blockers for management of hypertension. *South Med J* 103: 669, 2010.
198. Caro JJ, Speckman JL, Salas M, et al: Effect of initial drug choice on persistence with antihypertensive therapy: The importance of actual practice data. *CMAJ* 160:41, 1999.
199. Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med* 148:16, 2008.
200. Brenner BM, Cooper ME, de Zeeuw D, et al: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861, 2001.
201. Lewis EJ, Hunsicker LG, Clarke WR, et al: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851, 2001.
202. Halkin A, Keren G: Potential indications for angiotensin-converting enzyme inhibitors in atherosclerotic vascular disease. *Am J Med* 112:126, 2002.
203. Hansson L, Lindholm L, Niskanen L, et al: Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 353:611, 1999.
204. Sica DA. Do pleiotropic effects of antihypertensive medications exist or is it all about the blood pressure? *Curr Hypertens Rep* 10:415, 2008.
205. Smith RD, Franklin SS: Comparison of effects of enalapril plus hydrochlorothiazide versus standard triple therapy on renal function in renovascular hypertension. *Am J Med* 79 (Suppl 3C):14, 1985.
206. Maillard JO, Descombes E, Fellay G, Regamey C: Repeated transient anuria following losartan administration in a patient with a solitary kidney. *Renal Fail* 23:143, 2001.
207. Flack JM, Saunders E, Gradman A, et al: Antihypertensive efficacy and safety of losartan alone and in combination with hydrochlorothiazide in adult African Americans with mild-to-moderate hypertension. *Clin Ther* 23:1193, 2001.
208. Weidmann P, De Myttenaere-Bursztejn S, Maxwell MH: Effect of aging on plasma renin and aldosterone in normal man. *Kidney Int* 8:325, 1975.
209. Gradman AH. Role of angiotensin II type 1 recep-

- tor antagonists in the treatment of hypertension in patients aged > or = 65 years. *Drugs Aging* 26:751, 2009.
210. Sehgal AR. Overlap between whites and blacks in response to antihypertensive drugs. *Hypertension* 43: 566, 2004.
 211. Weir MR, Gray JM, Paster R, et al: Differing mechanisms of action of angiotensin-converting enzyme inhibition in black and white hypertensive patients. *Hypertension* 25:124, 1995.
 212. Agodoa LY, Appel L, Bakris GL, et al: Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: A randomized controlled trial. *JAMA* 285:2719, 2001.
 213. Whitworth JA; World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 21:1983, 2003.
 214. Zannad F: Trandolapril: how does it differ from other angiotensin-converting enzyme Inhibitors. *Drugs* 46 (Suppl 2):172, 1993.
 215. Omboni S, Fogari R, Palatini P, et al: Reproducibility and clinical value of the trough-to-peak ratio of the antihypertensive effect. Evidence from the Sample Study. *Hypertension* 32:424, 1998.
 216. Izzo JL, Sica DA: Antihypertensive drugs: pharmacologic principles and dosing effects. In: Izzo JL, Sica DA, Black HR, eds. *Hypertension Primer*. 4th ed. Philadelphia Lippincott, Williams & Wilkins, 2008:432-435.
 217. Gradman AH, Lewin A, Bowling BT, et al: Comparative effects of candesartan cilexetil and losartan in patients with systemic hypertension. Candesartan Versus Losartan Efficacy Comparison (CANDLE) Study Group. *Heart Dis* 1:52, 1999.
 218. Mancia G, Dell'Oro R, Turri C, Grassi G: Comparison of angiotensin II receptor blockers: impact of missed doses of candesartan cilexetil and losartan in systemic hypertension. *Am J Cardiol* 84:28S, 1999.
 219. Oparil S, Williams D, Chrysant SG, et al: Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. *J Clin Hypertens* 3:283, 2001.
 220. Vidt DG, White WB, Ripley E, et al: A forced titration study of antihypertensive efficacy of candesartan cilexetil in comparison to losartan: CLAIM Study II. *J Hum Hypertens* 15:475, 2001.
 221. Meredith PA: Clinical comparative trials of angiotensin II type 1 (AT1)-receptor blockers. *Blood Press Suppl* 3:11, 2001.
 222. Oparil S: Are there meaningful differences in blood pressure control with current antihypertensive agents. *Am J Hypertens* 15:14S, 2002.
 223. Conlin PR, Spence JD, Williams B, et al: Angiotensin II antagonists for hypertension: Are there differences in efficacy. *Am J Hypertens* 13:418, 2000.
 224. Fogari R, Mugellini A, Zoppi A, et al: A double-blind crossover study of the antihypertensive efficacy of angiotensin II-receptor antagonists and their activation of the renin-angiotensin system. *Curr Ther Res Clin Exp* 61:669, 2000.
 225. Hansson L: The relationship between dose and antihypertensive effect for different AT1-receptor blockers. *Blood Press Suppl* 3:33, 2001.
 226. Veteran's Administration Cooperative Study Group on Antihypertensive Agents. Low-dose captopril for the treatment of mild to moderate hypertension. *Hypertension* 5 (Suppl III): 139, 1983.
 227. Neutel JM, Black HR, Weber MA: Combination therapy with diuretics: An evolution of understanding. *Am J Med* 101:61S, 1996.
 228. Sica DA: Rationale for fixed-dose combinations in the treatment of hypertension: The cycle repeats. *Drugs* 62:443, 2002.
 229. Veteran Administration Cooperative Study Group on Antihypertensive Agents. Racial differences in response to low-dose captopril are abolished by the addition of hydrochloro-thiazide. *Br J Clin Pharmacol* 14:97S, 1982.
 230. Hansson L: Beta blockers with ACE inhibitors - a logical combination. *J Hum Hypertens* 3:97, 1989.
 231. Belz GG, Essig J, Erb K, et al: Pharmacokinetic and pharmacodynamic interactions between the ACE inhibitor cilazapril and beta-adrenoreceptor antagonist propranolol in healthy subjects and in hypertensive patients. *Br J Clin Pharmacol* 27 (Suppl 2): 317S, 1989.
 232. Black HR, Sollins JS, Garofalo JL: The addition of doxazosin to the therapeutic regimen of hypertensive patients inadequately controlled with other antihypertensive medications: A randomized, placebo-controlled study. *Am J Hypertens* 13:468-474, 2000.
 233. Frampton JE, Scott LJ. Amlodipine/valsartan single-pill combination: a review of its use in the management of hypertension. *Am J Cardiovasc Drugs* 9:309, 2009.
 234. Frishman WH, Ram CV, McMahon FG, et al., for the Benazepril/Amlodipine Study Group. Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: A randomized, double-blind, placebo-controlled, parallel-group study. *J Clin Pharmacol* 35:1060, 1995.
 235. DeQuattro V, Lee D: Fixed-dose combination ther-

- apy with trandolapril and verapamil SR is effective in primary hypertension. *Am J Hypertens* 10 (Suppl 2): 138S, 1997.
- 235a. Kostis JB: Antihypertensive therapy with CCB/ARB combination in older individuals: focus on amlodipine/valsartan combination. *Am J Therap* 17: 188, 2010.
 236. Calhoun DA, Lacourcière Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension* 54: 32, 2009.
 237. Fogari R, Malamani G, Corradi L, et al. Effect of valsartan or olmesartan addition to amlodipine on ankle edema in hypertensive patients. *Adv Ther* 27:48, 2010.
 - 237a. Bakris GL, Sarafidis PA, Weir MR, et al for the ACCOMPLISH Trial Investigators: Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomized controlled trial. *Lancet* 375: 1173, 2010.
 238. Sica DA. Combination ACE inhibitor and angiotensin receptor blocker therapy - future considerations. *J Clin Hypertens (Greenwich)* 9:78, 2007.
 239. Doulton TW, He FJ, MacGregor GA. Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. *Hypertension* 45:880, 2005.
 240. Taylor AA: Is there a place for combining angiotensin-converting enzyme inhibitors and angiotensin-receptor antagonists in the treatment of hypertension, renal disease or congestive heart failure. *Curr Opin Nephrol Hypertens* 10:643, 2001.
 241. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 358:1547, 2008.
 242. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 372:547, 2008.
 243. Bevan EG, Pringle SD, Walker PC, et al: Comparison of captopril, hydralazine and nifedipine as third drug in hypertensive patients. *J Hum Hypertens* 7:83, 1993.
 244. Dufloux JJ, Prasquier R, Chatellier G, et al: Effects of captopril and minoxidil on left ventricular hypertrophy in resistant hypertensive patients: A 6-month double-blind comparison. *J Am Coll Cardiol* 16:137, 1990.
 245. Kazerani H, Hajimoradi B, Amini A, et al. Clinical efficacy of sublingual captopril in the treatment of hypertensive urgency. *Singapore Med J* 50:400, 2009.
 246. Hirschl MM, Binder M, Bur A, et al: Impact of the renin-angiotensin-aldosterone system on blood pressure response to intravenous enalaprilat in patients with hypertensive crises. *J Hum Hypertens* 11:177, 1997.
 247. Sica DA: Dosage considerations with perindopril for hypertension. *Am J Cardiol* 88 (Suppl 1):13, 2001.
 248. Schlaich MP, Schmieder RE: Left ventricular hypertrophy and its regression: Pathophysiology and therapeutic approach. *Am J Hypertens* 11:1394, 1998.
 249. Prisant LM. Management of hypertension in patients with cardiac disease: use of renin-angiotensin blocking agents. *Am J Med* 121 (8 Suppl): S8, 2008.
 250. Grandi AM, Laurita E, Solbiati F, et al. Angiotensin-converting enzyme inhibitors influence left ventricular mass and function independently of the antihypertensive effect. *J Cardiovasc Pharmacol* 48: 207, 2006.
 251. Fagard RH, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. *Hypertension* 54:1084, 2009.
 252. Verdecchia P, Sleight P, Mancia G, et al. ONTARGET/TRANSCEND Investigators. Effects of telmisartan, ramipril, and their combination on left ventricular hypertrophy in individuals at high vascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease. *Circulation* 120:1380, 2009.
 253. Os I, Franco V, Kjeldsen SE, et al: Effects of losartan in women with hypertension and left ventricular hypertrophy. Results from the Losartan Intervention for Endpoint Reduction in Hypertension Study. *Hypertension* 51: 1103, 2008.
 254. Koren MJ, Devereux RB, Casale PN, et al: Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 114:345, 1991.
 255. Dahlof B, Devereux RB, Kjeldsen SE, et al: Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet* 359: 995, 2002.
 256. Longobardi G, Corbi G, Cacciatori F, et al: Effect of losartan in treatment of exercise-induced myocardial ischemia. *Am J Cardiol* 100: 1517, 2007.
 257. Daly P, Mettauer B, Rouleau JL, et al: Lack of reflex

- increase in myocardial sympathetic tone after captopril: Potential antianginal mechanism. *Circulation* 71:317, 1985.
258. Chrysant SG: Vascular remodeling: The role of angiotensin-converting enzyme inhibitors. *Am Heart J* 135:S21, 1998.
 259. Schiffrin EL, Park JB, Pu Q: Effect of crossing over hypertensive patients from a beta-blocker to an angiotensin receptor antagonist on resistance artery structure and on endothelial function. *J Hypertens* 20:71, 2002.
 260. Frei A, Muller-Brand J: Cerebral blood flow and antihypertensive treatment with enalapril. *J Hypertens* 4:365, 1986.
 261. Roberts DH, Tsao Y, McLoughlin GA, et al: Placebo-controlled comparison of captopril, atenolol, labetalol, and pindolol in hypertension complicated by intermittent claudication. *Lancet* 2:650, 1987.
 262. Ostergren J, Sleight P, Dagenais G, et al. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *Eur Heart J* 25:17, 2004.
 263. Preston RA: Renoprotective effects of antihypertensive drugs. *Am J Hypertens* 12:19S, 1999.
 264. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 288: 2421, 2002.
 265. Malini P, Stochi E, Ambrosioni E, et al: Long-term antihypertensive, metabolic and cellular effects of enalapril. *J Hypertens* 2 (Suppl 2): 101, 1984.
 266. Abuissa H, Jones PG, Marso SP, O'Keefe JH Jr. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 46: 821, 2005.
 267. Scheen AJ. Renin-angiotensin system inhibition prevents type 2 diabetes mellitus. Part 1. A meta-analysis of randomised clinical trials. *Diabetes Metab* 30: 487, 2004.
 268. The DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med* 355:1551, 2006.
 269. The NAVIGATOR Study Group. Effect of Valsartan on the Incidence of Diabetes and Cardiovascular Events. *N Engl J Med* Mar 16, 2010. [Epub ahead of print]
 270. Sacco RL: Reducing the risk of stroke in diabetes: What have we learned that is new *Diabetes Obes Metab* 4 (Suppl 1):27, 2002.
 271. Bosch J, Yusuf S, Pogue J, et al: Use of ramipril in preventing stroke: Double blind randomised trial. *BMJ* 324:699, 2002.
 272. Leenen FH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension* 48:374, 2006.
 273. Beckett NS, Peters R, Fletcher AE et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 358:1887, 2008.
 274. Dahlöf B, Sever PS, Poulter NR, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering ARM (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 366:895, 2005.
 275. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochloro-thiazide for hypertension in high-risk patients. *N Engl J Med* 359: 2417, 2008.
 276. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 358:1033, 2001.
 277. Lithell H, Hansson L, Skoog I, et al; SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE); principal results of a randomized, double-blind intervention trial. *J Hypertens* 21:875, 2003.
 278. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 363: 2022, 2004.
 279. Yusuf S, Teo K, Anderson C et al. Telmisartan Randomised Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 372:1174, 2008.
 280. Schrader J, Lüders S, Kulschewski A, et al. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. *Stroke* 34: 1699, 2003.
 281. Schrader J, Lüders S, Kulschewski A, et al. Morbidity and Mortality After Stroke, Eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized con-

- trolled study (MOSES). *Stroke* 36:1218, 2005.
282. Yusuf S, Diener HC, Sacco RL, et al; PROFESS Study Group. Telmisartan to prevent recurrent strokes and cardiac events. *N Engl J Med* 359:1225, 2008.
283. Lu GC, Cheng JW, Zhu KM, et al. A systematic review of angiotensin receptor blockers in preventing stroke. *Stroke* 40:3876, 2009.
284. Reboldi G, Angeli F, Cavallini C, et al. Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis. *J Hypertens* 26: 1282, 2008.
285. Parving HH, Lehnert H, Brochner-Mortensen J, et al: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345:870, 2001.
286. Keane WF: Proteinuria: Its clinical importance and role in progressive renal disease. *Am J Kidney Dis* 35 (Suppl 1):S97, 2000.
287. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 139:137, 2003.
288. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy: The Collaborative Study Group. *N Engl J Med* 329:1456, 1993.
289. Ravid M, Lang R, Rachmani R, et al: Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin dependent diabetes mellitus. A 7-year follow-up study. *Arch Intern Med* 156:286, 1996.
290. Viberti G, Mogensen CE, Groop LC, Pauls JF: Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria: European Microalbuminuria Captopril Study Group. *JAMA* 271:275, 1994.
291. Maschio G, Alberti D, Janin G, et al: Effect of the angiotensin-converting enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 334:939, 1996.
292. Uhle BU, Whitworth JA, Shahinfar S, et al: Angiotensin-converting enzyme inhibition in nondiabetic progressive renal insufficiency: A controlled double-blind trial. *Am J Kidney Dis* 27:489, 1996.
293. The Gisen Group: Randomized placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 349:1857, 1997.
294. Giatras I, Lau J, Levey As, et al., for the Angiotensin-Converting Enzyme Inhibition and Progressive Renal Disease Study Group. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: A meta-analysis of randomized trials. *Ann Intern Med* 127:337, 1997.
295. Ruggenenti P, Perna A, Gherardi G, et al: Chronic proteinuric nephropathies: Outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. *Am J Kidney Dis* 35:1155, 2000.
296. Ahmad J, Siddiqui MA, Ahmad H: Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. *Diabetes Care* 20:1576, 1997.
297. Ravid M, Savin H, Jutrin I, et al: Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 118:577, 1993.
298. Mathiesen ER, Hommel R, Giese J, Parving H: Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. *BMJ* 303:81, 1991.
299. The EUCLID Study Group. Randomized placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria and microalbuminuria. *Lancet* 349:1787, 1997.
300. Sano T, Kawamura T, Matsumae H, et al: Effects of long-term enalapril treatment on persistent microalbuminuria in well-controlled hypertensive and normotensive NIDDM patients. *Diabetes Care* 17:420, 1994.
301. Ravid M, Brosh D, Levi Z, et al: Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. *Ann Intern Med* 128: 982-988, 1998.
302. Hou FF, Zhang X, Zhan GH, et al: Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 354: 131, 2006.
303. Lebovitz s, Wiegmann TB, Cnaan A, et al: Renal protective effect of enalapril in hypertensive NIDDM: Role of baseline albuminuria. *Kidney Int* 45 (Suppl):S150, 1994.
304. Fogari R, Zoppi A, Corradi L, et al: Long-term effects of ramipril and nitrendipine on albuminuria in hypertensive patients with type II diabetes and impaired renal function. *J Hum Hypertens* 13:47, 1999.
305. Nielsen FS, Rossing P, Gall MA, et al: Long-term effect of lisinopril and atenolol on kidney function in hypertensive NIDDM subjects with diabetic nephropathy. *Diabetes* 46:1182, 1997.
306. Bakris GL, Copley JB, Vicknair N, et al: Calcium

- channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int* 50:1641, 1996.
307. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 317:703–713, 1998.
 308. Estacio RO, Jeffers BW, Gifford N, Schrier RW: Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 23(Suppl 2):B54, 2000.
 309. Mann JF, Gerstein HC, Pogue J, et al: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134:629, 2001.
 310. Bakris G, Burgess E, Weir M, et al. Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. *Kidney Int* 74:364, 2008.
 311. Burgess E, Muirhead N, Rene de Cotret P, and SMART (Supra Maximal Atacand Renal Trial) Investigators. Supramaximal dose of candesartan in proteinuric renal disease. *J Am Soc Nephrol* 20:893, 2009.
 312. Viberti G, Wheeldon NM; MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation* 106: 672, 2002.
 313. Makino H, Haneda M, Babazono T, et al. Microalbuminuria reduction with telmisartan in normotensive and hypertensive Japanese patients with type 2 diabetes: a post-hoc analysis of The Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study. *Hypertens Res* 31: 657, 2008.
 314. Menne J, Farsang C, Deák L, et al. Valsartan in combination with lisinopril versus the respective high dose monotherapies in hypertensive patients with microalbuminuria: the VALERIA trial. *J Hypertens* 26:1860, 2008.
 315. Hermida RC, Calvo C, Ayala DE, López JE. Decrease in urinary albumin excretion associated with the normalization of nocturnal blood pressure in hypertensive subjects. *Hypertension* 46:960, 2005.
 316. Zatz R, Dunn BR, Meyer TW, et al: Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 77:1925, 1986.
 317. Bakris GL, Weir MR: Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern *Arch Intern Med* 160:685, 2000.
 318. Apperloo AJ, de Zeeuw D, de Jong PE: A short-term antihypertensive-treatment induced drop in glomerular filtration rate predicts long-term stability of renal function. *Kidney Int* 51:793, 1997.
 319. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? *J Am Soc Nephrol* 17: 2974,2006.
 320. Gagliardini E, Benigni A. Therapeutic potential of TGF-beta inhibition in chronic renal failure. *Expert Opin Biol Ther* 7:293, 2007.
 321. Osei SY, Price DA, Laffel LMB, et al: Effect of angiotensin II antagonist eprosartan on hyperglycemia-induced activation of intrarenal renin-angiotensin system in healthy humans. *Hypertension* 36:122, 2000.
 322. Buter H, Hemmelder MH, Navis G, et al. The blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored by hydrochlorothiazide. *Nephrol Dial Transplant* 13:1682, 1998.
 323. Gansevoort RT, de Zeeuw D, de Jong PE: Additive antiproteinuric effect of ACE inhibition and a low protein diet in human renal disease. *Nephrol Dial Transplant* 10:497, 1995.
 324. Chauveau P, Combe C, Rigalleau V, et al. Restricted protein diet is associated with decrease in proteinuria: consequences on the progression of renal failure. *J Ren Nutr* 17:250, 2007.
 325. Rigat B, Hubert C, Alhenc-Gelas F, et al: An insertion-deletion polymorphism in the angiotensin I converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 86:1343, 1990.
 326. Ueda S, Elliott, Morton JJ, et al. Enhanced pressor response to angiotensin I in normotensive men with the deletion genotype (DD) for angiotensin-converting enzyme. *Hypertension* 25:1266, 1995.
 327. Cambien F, Poirier O, Lecerf L, et al: Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. *Nature* 359: 641, 1992.
 328. van Essen GG, Rensma PL, de Zeeuw D, et al: Association between angiotensin-converting enzyme gene polymorphism and failure of renoprotective therapy. *Lancet* 347:94, 1996.
 329. Parving HH, Jacobsen P, Tarnow L, et al: Effect of deletion polymorphism of angiotensin-converting enzyme gene on progression of diabetic nephropathy during inhibition of angiotensin-converting enzyme. Observational follow-up study. *BMJ* 313:591, 1996.

330. Nonoguchi H, Nakayama Y, Shiigai T, et al. Low-responders to angiotensin II receptor blockers and genetic polymorphism in angiotensin-converting enzyme. *Clin Nephrol* 68:209, 2007.
331. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 119:1977, 2009.
332. Howlett JG, McKelvie RS, Arnold JM, et al. Canadian Cardiovascular Society Consensus Conference Guidelines on heart failure, update 2009: diagnosis and management of right-sided heart failure, myocarditis, device therapy and recent important clinical trials. *Can J Cardiol* 25:85, 2009.
333. Remme WJ: Effect of ACE inhibition on neurohormones. *Eur Heart J* 19 (Suppl J): J16, 1998.
334. Flather MD, Yusuf S, Kober L, et al: Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: A systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 355:1575, 2000.
335. Fonarow GC, Yancy CW, Albert NM, et al. Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. *Circ Heart Fail* 1:98, 2008.
336. Philbin EF, Andreou C, Rocco TA, et al: Patterns of angiotensin-converting enzyme inhibitor use in congestive heart failure in two community hospitals. *Am J Cardiol* 77:832, 1996.
337. Bungard TJ, McAlister FA, Johnson JA, Tsuyuki RT: Underutilization of ACE inhibitors in patients with congestive heart failure. *Drugs* 61:2021, 2001.
338. Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS: Renal considerations in angiotensin-converting enzyme inhibitor therapy: A statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation* 104:1985, 2001.
339. Domanski MJ, Exner DV, Borkowf CB, et al: Effect of angiotensin-converting enzyme inhibition on sudden cardiac death following acute myocardial infarction. A meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 33:598, 1999.
340. Megarry M, Sapsford R, Hall AS, et al: Do ACE inhibitors provide protection for the heart in the clinical setting of acute myocardial infarction. *Drugs* 54 (Suppl 5):48, 1997.
341. Perez MI, Musini VM, Wright JM. Effect of early treatment with anti-hypertensive drugs on short and long-term mortality in patients with an acute cardiovascular event. *Cochrane Database Syst Rev* (4):CD006743, 2009.
342. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: Systematic review of individual data from 100,000 patients in randomised trials. *Circulation* 97:2202, 1998.
343. Naccarella F, Naccarelli GV, Maranga SS, et al: Do ACE inhibitors or angiotensin II antagonists reduce total mortality and arrhythmic mortality? A critical review of controlled clinical trials. *Curr Opin Cardiol* 17:6, 2002.
344. Dickstein K, Kjekshus J, OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: The OPTIMAAL randomised trial. *Lancet* 360:752, 2002.
345. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 349:1893, 2003.
346. Pitt B, Segal R, Martinez FA, et al: Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 349: 747-752, 1997.
347. Pitt B, Poole-Wilson PA, Segal R, et al: Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: Randomised trial - the Losartan Heart Failure Survival Study ELITE II. *Lancet* 355:1582, 2000.
348. Cohn JN, Tognoni G: A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 345:1667, 2001.
349. McMurray JJV, Ostergren J, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added Trial. *Lancet* 362,767, 2003.
350. Granger CB, McMurray JJV, Yusuf S et al. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: The CHARM-Alternative Trial. *Lancet* 362,772, 2003.
351. Yusuf S, Pfeffer MA, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and preserved left ventricular systolic function: The CHARM-Preserved Trial. *Lancet* 362,777, 2003.
352. Massie BM, Carson PE, McMurray JJ, et al. Irbe-

- sartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 359:2456, 2008.
353. Shah RV, Desai AS, Givertz MM. The effect of renin-angiotensin system inhibitors on mortality and heart failure hospitalization in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis. *J Card Fail* 16:260, 2010.
- 353a. Zile MR, Gaasch WH, Anand IS, et al: Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve) trial. *Circulation* 121: 1393, 2010.
354. Mochizuki S, Dahlöf B, Shimizu M, et al. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. *Lancet* 369:1431, 2007.
355. Baker WL, Coleman CI, Kluger J, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease. *Ann Intern Med* 151:861, 2009.
356. Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, Weaver WD: Angiotensin converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function. A systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 47: 1576, 2006.
357. Danchin N, Cucherat M, Thuillez C, et al: Angiotensin converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular systolic dysfunction. An overview of long-term randomized controlled trials. *Arch Intern Med* 166: 787, 2006.
358. Dagenais GR, Pogue J, Fox K, et al: Angiotensin converting enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 368: 581, 2006.
359. Solomon SD, Janardhanan R, Verma A, et al: for the Valsartan in Diastolic Dysfunction (VALIDD) investigators: Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. *Lancet* 369: 2079, 2007.
- 359a. Werner C, Pöss J, Böhm M: Optimal antagonism of the renin-angiotensin-aldosterone system. *Drugs* 70: 1215, 2010.
360. Fine EJ. Diuretic renography and angiotensin converting enzyme inhibitor renography. *Radiol Clin North Am* 39:979, 2001.
361. Wu VC, Chang HW, Liu KL, et al. Primary aldosteronism: diagnostic accuracy of the losartan and captopril tests. *Am J Hypertens* 22:821, 2009.
362. Rossi GP, Belfiore A, Bernini G, et al. Comparison of the captopril and the saline infusion test for excluding aldosterone-producing adenoma. *Hypertension* 50: 424, 2007.
363. Plata R, Cornejo A, Arratia C, et al: Angiotensin-converting enzyme inhibition therapy in altitude polycythaemia: A prospective randomised trial. *Lancet* 359:663, 2002.
364. Esposito R, Giammarino A, De Blasio A, et al. Ramipril in post-renal transplant erythrocytosis. *J Nephrol* 20: 57, 2007.
365. Zhu X, Chen J, Han F, et al. Efficacy and safety of losartan in treatment of hyperuricemia and post-transplantation erythrocytosis: results of a prospective, open, randomized, case-control study. *Transplant Proc* 41:3736, 2009.
366. Ohtani K, Egashira K, Ihara Y, et al: Angiotensin II type 1 receptor blockade attenuates in-stent restenosis by inhibiting inflammation and progenitor cells. *Hypertension* 48: 664, 2006.
367. Peters S. Comparison of efficacy of low- (80 mg/day) and high- (160-320 mg/day) dose valsartan in the prevention of in-stent restenosis after implantation of bare-metal stents in type B2/C coronary artery lesions. *Am J Cardiovasc Drugs* 8:83, 2008.
368. Gillis AM: Angiotensin receptor blockers for prevention of atrial fibrillation – a matter of timing or target? *N Engl J Med* 360: 1669, 2009.
369. Ehrlich JR, Hohnloser SH, Nattel R: Role of angiotensin system and effects of its inhibition in atrial fibrillation: clinical and experimental evidence. *Eur Heart J* 27: 512, 2006.
370. Casclang-Verzosa G, Gersh BJ, Tsang TS: Structural and functional remodeling of the left atrium: clinical and therapeutic implications for atrial fibrillation. *J Am Coll Cardiol* 51: 1, 2008.
371. Irvanian S, Dudley SC Jr. The renin angiotensin aldosterone system (RAAS) and cardiac arrhythmias. *Heart Rhythm* 5 Suppl: S12, 2008.
372. Jibrini MB, Molnar J, Arora RR: Prevention of atrial fibrillation by way of abrogation of the renin angiotensin system: a systematic review and meta-analysis. *Am J Therap* 15: 36, 2008.
373. Anand K, Mooss AN, Hee TT, Mohiuddin SM: Meta-analysis: inhibition of renin-angiotensin system prevents new onset atrial fibrillation. *Am Heart J* 152: 217, 2006.
374. Belluzzi F, Sernesi L, Preti P, et al: Prevention of recurrent lone atrial fibrillation by the angiotensin II converting enzyme inhibitor ramipril in normotensive patients. *J Am Coll Cardiol* 53: 24, 2009.
375. Garg S, Narula J, Marelli C, Cesario D: Role of an-

- giotensin receptor blockers in the prevention and treatment of arrhythmias. *Am J Cardiol* 97: 921, 2006.
376. Chrysant SG, Chrysant GS: The pleiotropic effects of angiotensin receptor blockers. *J Clin Hypertens* 8: 261, 2006.
- 376a. Schneider MP, Hua TA, Böhm M, et al: Prevention of atrial fibrillation by renin-angiotensin system inhibition. *J Am Coll Cardiol* 55: 2299, 2010.
377. Salehian O, Healey J, Stambler B, et al on behalf of the HOPE Investigators: Impact of ramipril on the incidence of atrial fibrillation: results of the Heart Outcomes Prevention Evaluation study. *Am Heart J* 154: 448, 2007.
378. GISSI-AF Investigators: Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med* 360: 1606, 2009.
379. Chaturvedi N, Porta M, Klein R, et al for the DIRECT Programme study group: Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. *Lancet* 372: 1394, 2008.
380. Sjølie AK, Klein R, Porta M, et al for the DIRECT Programme study group: Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised, placebo-controlled trial. *Lancet* 372: 1385, 2008.
- 380a. The Navigator Study Group: Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 362: 1477, 2010.
381. Habashi JP, Judge DP, Holm TM, et al: Losartan, an AT1 antagonist prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science* 312: 117, 2006.
382. Hackam DG, Thiruchelvam D, Redelmeier DA: Angiotensin converting enzyme inhibitors and aortic rupture: a population-based case-control study. *Lancet* 368: 659, 2006.
383. The SOLVD investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 325:293, 1991.
384. Bastiaens MT, Zwan NV, Verschuereen GL, et al: Three cases of pemphigus vegetans: Induction by enalapril - association with internal malignancy. *Int J Dermatol* 33:168, 1994.
385. Larbre JP, Nicolas JF, Collet P, et al: Kaposi's sarcoma in a patient with rheumatoid arthritis possible responsibility of captopril in the development of lesions. *J Rheumatol* 18:476, 1991.
386. Vogt B, Frey FJ: Inhibition of angiogenesis in Kaposi's sarcoma by captopril. *Lancet* 349:1148, 1997.
387. Meier CR, Derby LE, Jick SS, Jick H: Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 160:349, 2000.
388. Stahl M, Bulpitt CJ, Palmer AJ, et al: Calcium channel blockers, ACE inhibitors, and the risk of cancer in hypertensive patients: A report from the Department of Health Hypertension Care Computing Project (DHCCP). *J Hum Hypertens* 14:299, 2000.
389. Pahor M, Guralnik JM, Salive ME, et al: Do calcium channel blockers increase the risk of cancer? *Am J Hypertens* 9:695, 1996.
390. Lever AF, Hole DJ, Gillis CR, et al: Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? *Lancet* 352:179, 1998.
391. Sorensen HT, Mellemkjaer L, et al: Angiotensin-converting enzyme inhibitors and the risk of cancer: A population-based cohort study in Denmark. *Cancer* 92:2462, 2001.
392. Friis S, Felmeden DC, Lip GY: Antihypertensive therapy and cancer risk. *Drug Saf* 24:727-739, 2001.
393. Rosenthal T, Gavras I. Angiotensin inhibition and malignancies: a review. *J Hum Hypertens* 23:623, 2009.
- 393a. Sipahi I, Debanne SM, Rowland DY, et al: Angiotensin receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *Lancet Oncol* 11: 627, 2010.
394. Textor SC: Renal failure related to angiotensin-converting enzyme inhibitors. *Semin Nephrol* 17:67, 1997.
395. Textor SC, Bravo EL, Fouad FM, Tarazi RC: Hyperkalemia in azotemic patients during angiotensin-converting enzyme inhibition and aldosterone reduction with captopril. *Am J Med* 73:719, 1982.
396. Garcia NH, Baigorria ST, Juncos LI: Hyperkalemia, renal failure, and converting-enzyme inhibition: An overrated connection. *Hypertension* 38:639, 2001.
397. Bakris GL, Siomos M, Richardson D, et al: ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. VAL-K Study Group. *Kidney Int* 58:2084, 2000.
398. Griffing GT, Sindler BH, Aurecchia SA, Melby JC: Reversal of diuretic-induced secondary hyperaldosteronism and hypokalemia by enalapril (MK-421): A new angiotensin-converting enzyme inhibitor. *Metabolism* 32:711, 1983.
399. Israili ZH, Hall WD: Cough and angioneurotic associated with angiotensin-converting enzyme inhibitor therapy: A review of the literature and pathophysiology. *Ann Intern Med* 117:234, 1992.
400. Chalmers D, Dombey SL, Lawson DH: Post-marketing surveillance of captopril (for hypertension):

- A preliminary report. *Br J Clin Pharmacol* 24:343, 1987.
401. Bensenor IM, Lotufo PA: Headache, hypertension, and irbesartan therapy. *Arch Intern Med* 161:775–776, 2001.
 402. Etminan M, Levine MA, Tomlinson G, Rochon PA: Efficacy of angiotensin II receptor antagonists in preventing headache: A systematic overview and meta-analysis. *Am J Med* 112:642, 2002.
 403. Weber MA, Messerli FH: Angiotensin converting enzyme inhibitors and angioedema. Estimating the risk. *Hypertension* 51: 1465, 2008.
 404. Herkner H, Temmel AF, Mullner M, et al: Different patterns of angioedema in patients with and without angiotensin-converting enzyme inhibitor therapy. *Wien Klin Wochenschr* 113:167, 2001.
 405. Vleeming W, van Amsterdam JG, Stricker BH, et al: ACE inhibitor-induced angioedema. *Drug Saf* 18:171, 1998.
 406. Brown NJ, Snowden M, Griffin MR: Recurrent angiotensin-converting enzyme inhibitor-associated angioedema. *JAMA* 278:232, 1997.
 407. Dobbels P, Van Overbeke L, Vanbeckevoort D, Hiele M. Acute abdomen due to intestinal angioedema induced by ACE inhibitors: not so rare? *Acta Gastroenterol Belg* 72:455, 2009.
 408. Haymore BR, Yoon J, Mikita CP, et al. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. *Ann Allergy Asthma Immunol* 101:495, 2008.
 409. Warner KK, Visconti JA, Tschampel MM: Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. *Ann Pharmacother* 34:526, 2000.
 410. Sica DA, Black HR. Current concepts of pharmacotherapy in hypertension: ACE inhibitor-related angioedema: can angiotensin-receptor blockers be safely used? *J Clin Hypertens (Greenwich)* 4:375, 2002.
 411. Cohen DL, Townsend RR: Can an angiotensin receptor blocker be used in a patient in whom angioedema developed with an angiotensin converting enzyme inhibitor? *J Clin Hypertens* 10: 949, 2008.
 412. Quan A. Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. *Early Hum Dev* 82:23, 2006.
 413. Lambot MA, Vermeylen D, Noel JC: Angiotensin-II-receptor inhibitors in pregnancy. *Lancet* 357:1619, 2001.
 414. Burrows RF, Burrows EA: Assessing the teratogenic potential of angiotensin-converting enzyme inhibitors in pregnancy. *Aust N Z J Obstet Gynaecol* 38:306, 1998.
 415. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 354:2443, 2006.
 416. Magee LA: Treating hypertension in women of childbearing age and during pregnancy. *Drug Saf* 24:457, 2001.
 417. Martin U, Foreman MA, Travis JC, et al. Use of ACE inhibitors and ARBs in hypertensive women of childbearing age. *J Clin Pharm Ther* 33:507, 2008.
 418. Shannon ME, Malecha SE, Cha AJ: Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers and lactation: an update. *J Hum Lact* 16:152, 2000.
 419. Zwanzger P, Marcuse A, Boerner RJ, et al: Lithium intoxication after administration of AT1 blockers. *J Clin Psychiatry* 62:208, 2001.
 420. Juurlink DN, Mamdani MM, Kopp A, et al. Drug-induced lithium toxicity in the elderly: a population-based study. *J Am Geriatr Soc* 52:794, 2004.
 421. Indermitte J, Burkolter S, Drewe J, et al. Risk factors associated with a high velocity of the development of hyperkalaemia in hospitalised patients. *Drug Saf* 30:71, 2007.
 422. Conlin PR, Moore TJ, Swartz SL, et al: Effect of indomethacin on blood pressure lowering by captopril and losartan in hypertensive patients. *Hypertension* 36:461, 2000.
 423. Fricker AF, Nussberger J, Meilenbrock S, et al: Effect of indomethacin on the renal response to angiotensin II receptor blockade in healthy subjects. *Kidney Int* 54: 2089, 1998.
 424. Pavlicević I, Kuzmanić M, Rumboldt M, Rumboldt Z. Interaction between antihypertensives and NSAIDs in primary care: a controlled trial. *Can J Clin Pharmacol* 15:e372, 2008.
 425. Adhiyaman V, Asghar M, Oke A, et al: Nephrotoxicity in the elderly due to co-prescription of angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs. *J R Soc Med* 94:512, 2001.
 426. Samanta A, Burden AC: Fever, myalgia, and arthralgia in a patient on captopril and allopurinol. *Lancet* 1:679,1984.

References for Chapter 10

The Renin-Angiotensin Axis

Direct Renin Inhibition

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1. Chobanian AV, Bakris GL, Black HR, et al.: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 289:2560, 2003.
2. Yusuf S, Sleight P, Pogue J, et al.: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 342: 145, 2000.
3. Staessen J, Lijnen P, Fagard R, et al.: Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. *J Endocrinol*. 91:457, 1981.
4. MacFadyen RJ, Lee AF, Morton JJ, et al.: How often are angiotensin II and aldosterone concentrations raised during chronic ACE inhibitor treatment in cardiac failure? *Heart* 82:57, 1999.
5. Müller DN, Luft FD: Direct renin inhibition with aliskiren in hypertension and target organ damage. *Clin J Am Soc Nephrol* 1: 221, 2006.
6. Bacani C, Frishman WH: Chymase: a new pharmacologic target in cardiovascular disease. *Cardiol in Rev* 14: 187, 2006.
7. Urata H, Healy B, Stewart RW, et al: Angiotensin II-forming pathways in normal and failing human hearts. *Circ Res* 66:883, 1990.
8. Okunishi H, Oka Y, Shiota N, et al: Marked species-difference in the vascular angiotensin II-forming pathways: humans versus rodents. *Jpn J Pharmacol* 62:207, 1993.
9. Hollenberg NK. Pharmacologic interruption of the renin-angiotensin system and the kidney: differential responses to angiotensin-converting enzyme and renin inhibition. *J Am Soc Nephrol* 10 Suppl 11:S239, 1999.
- 9a. Fisher NDL, Danser J, Nussberger J, et al: Renal and hormonal responses to direct renin inhibition with aliskiren in healthy humans. *Circulation* 117: 3199, 2008.
10. Allan DR, Hui KY, Coletti C, et al.: Renin vs. angiotensin-converting enzyme inhibition in the rat: consequences for plasma and renal tissue angiotensin. *J Pharmacol Exp Ther* 283: 661, 1997.
11. Dzau VJ, Burt DW, Pratt RE: Molecular biology of the renin-angiotensin system. *Am J Physiol*. 255(4 Pt 2):F563, 1988.
12. Beierwaltes WH: Prorenin and renin. In Izzo JL Jr, Sica DA, Black HR (eds): *Hypertension Primer 4th ed*. Dallas: American Heart Assn 2008: 44.
13. Kurtz A, Wagner C: Regulation of renin secretion by angiotensin II-AT1 receptors. *J Am Soc Nephrol* 10 Suppl 11:S162, 1999.
14. Pratt RE, Ouellette AJ, Dzau VJ: Biosynthesis of renin: multiplicity of active and intermediate forms. *Proc Natl Acad Sci USA* 80(22):6809, 1983.
15. Galen FX, Devaux C, Houot AM, et al.: Renin biosynthesis by human tumoral juxtaglomerular cells. Evidences for a renin precursor. *J Clin Invest*. 73: 1144, 1984.
16. Corvol P, Chauveau D, Jeunemaitre X, et al.: Human renin inhibitor peptides. *Hypertension* 16:1, 1990.
17. Dhanaraj V, Dealwis CG, Frazao C, et al.: X-ray analyses of peptide-inhibitor complexes define the structural basis of specificity for human and mouse renins. *Nature* 357:466, 1992.
18. Oliver JA: Receptor-mediated actions of renin and prorenin. *Kidney Intl* 69: 13, 2006.
19. Sealey JE, Catanzaro DF, Lavin TN, et al: Specific prorenin/renin binding (ProBP). Identification and characterization of a novel membrane site. *Am*

- J Hypertens* 9: 491, 1996.
- 19a. Reudelhuber TL: Prorenin, renin, and their receptor. Moving targets. *Hypertension* 55: 1071, 2010.
 20. Clauser E, Gaillard I, Wei L, et al.: Regulation of angiotensinogen gene. *Am J Hypertens*. 2(5 Pt 1):403, 1989.
 21. Tewksbury DA, Dart RA, Travis J: The amino terminal amino acid sequence of human angiotensinogen. *Biochem Biophys Res Commun*. 99:1311, 1981.
 22. Kageyama R, Ohkubo H, Nakanishi S: Primary structure of human preangiotensinogen deduced from the cloned cDNA sequence. *Biochemistry* 23:3603, 1984.
 23. Brand M, Lamande N, Sigmund CD, et al.: Angiotensinogen modulates renal vasculature growth. *Hypertension* 47:1067, 2006.
 24. Hilgers KF, Veelken R, Muller DN, et al.: Renin uptake by the endothelium mediates vascular angiotensin formation. *Hypertension* 38:243, 2001.
 25. Turner AJ, Hooper NM: The angiotensin-converting enzyme gene family: genomics and pharmacology. *Trends Pharmacol Sci* 23:177, 2002.
 26. Erdos EG, Deddish PA, Marcic BM: Potentiation of bradykinin actions by ACE inhibitors. *Trends Endocrinol Metab* 10:223, 1999.
 27. Frishman WH, Shanik MH, Lin C: Specific inhibitors of renin in cardiac therapy. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed*. New York: McGraw Hill 2003; 589.
 28. Deodhar SD, Haas E, Goldblatt H: Production of antirenin to homologous renin and its effect of experimental renal hypertension. *J Exp Med* 119:425, 1964.
 29. Helmer OM: Studies on renin antibodies. *Circulation* 17(4, Part 2):648, 1958.
 30. Dzau VJ, Kopelman RI, Barger AC, et al.: Renin-specific antibody for study of cardiovascular homeostasis. *Science* 207:1091, 1980.
 31. Wood JM, Baum HP, Bews JP, et al: Effects of chronic administration of a monoclonal antibody against human renin in the marmoset. *Clin Exp Hypertens* 9:1467, 1987.
 32. Wood JM, Heusser C, Gulati N, et al: Monoclonal antibodies against human renin. Blood pressure effects in the marmoset. *Hypertension* 8:600, 1986.
 33. Evin G, Devin J, Castro B, et al.: Synthesis of peptides related to the prosegment of mouse submaxillary gland renin precursor: an approach to renin inhibitors. *Proc Natl Acad Sci USA* 81:48, 1984.
 34. Cumin F, Evin G, Fehrentz JA, et al.: Inhibition of human renin by synthetic peptides derived from its prosegment. *J Biol Chem* 260:9154, 1985.
 35. Aoyagi T, Kunimoto S, Morishima H, et al.: Effect of pepstatin on acid proteases. *J Antibiot (Tokyo)* 24:687, 1971.
 36. Gross F, Lazar J, Orth H. Inhibition of the renin-angiotensinogen reaction by pepstatin. *Science* 175:656, 1972.
 37. Miller RP, Poper CH, Wilson CW, et al.: Renin inhibition by pepstatin. *Biochem Pharmacol* 21:2941, 1972.
 38. Boger J, Lohr NS, Ulm EH, et al: Novel renin inhibitors containing the amino acid statine. *Nature* 303:81, 1983.
 39. Guegan R, Diaz J, Cazaubon C, et al: Pepstatin analogues as novel renin inhibitors. *J Med Chem* 29:1152, 1986.
 40. Rich DH, Bernatowicz MS, Agarwal NS, et al.: Inhibition of aspartic proteases by pepstatin and 3-methylstatine derivatives of pepstatin. Evidence for collected-substrate enzyme inhibition. *Biochemistry* 24:3165, 1985.
 41. Kokubu T, Ueda E, Fujimoto S, et al.: Peptide inhibitors of the renin-angiotensin system. *Nature* 217:456, 1968.
 42. Poulsen K, Burton J, Haber E: Competitive inhibitors of renin. *Biochemistry* 12:135, 1976.
 43. Burton J, Cody RJ Jr, Herd JA, et al: Specific inhibition of renin by an angiotensinogen analog: studies in sodium depletion and renin-dependent hypertension. *Proc Natl Acad Sci USA* 77:5476, 1980.
 44. Zusman RM, Burton J, Christensen D, et al.: Hemodynamic effects of a competitive renin inhibitory peptide in humans: evidence for multiple mechanisms of action. *Trans Assoc Am Physicians* 96:365, 1983.
 45. Szelke M, Leckie B, Hallett A, et al.: Potent new inhibitors of human renin. *Nature* 299:555, 1982.
 46. Kokubu T, Hiwada K, Nagae A, et al.: Statine-containing dipeptide and tripeptide inhibitors of human renin. *Hypertension* 8(6 Pt 2):II1, 1986.
 47. Kokubu T, Hiwada K, Murakami E, et al.: In vitro inhibition of human renin by statine-containing tripeptide renin inhibitor (ES-1005). *J Cardiovasc Pharmacol* 10 Suppl 7:S88,1987.
 48. Bock MG, DiPardo RM, Evans BE, et al.: Renin inhibitors. Statine-containing tetrapeptides with varied hydrophobic carboxy termini. *J Med Chem* 30: 1853, 1987.
 49. Iizuka K, Kamijo T, Kubota T, et al.: New human renin inhibitors containing an unnatural amino acid, norstatine. *J Med Chem* 31:701, 1988.
 50. Toda N, Miyazaki M, Etoh Y, et al.: Human renin inhibiting dipeptide. *Eur J Pharmacol*. 129:393, 1986.
 51. Thaisrivongs S, Pals DT, Kati WM, et al.: Difluoros-

- tatine- and difluorostatone-containing peptides as potent and specific renin inhibitors. *J Med Chem* 28: 1553, 1985.
52. Thaisrivongs S, Pals DT, Kati WM, et al.: Design and synthesis of potent and specific renin inhibitors containing difluorostatine, difluorostatone, and related analogues. *J Med Chem* 29:2080, 1986.
 53. Boger J, Payne LS, Perlow DS, et al.: Renin inhibitors. Syntheses of subnanomolar, competitive, transition-state analogue inhibitors containing a novel analogue of statine. *J Med Chem* 28:1779, 1985.
 54. Dellaria JF, Maki RG, Bopp BA, et al.: Optimization and in vivo evaluations of a series of small, potent, and specific renin inhibitors containing a novel Leu-Val replacement. *J Med Chem* 30:2137, 1987.
 55. Hui KY, Holtzman EJ, Quinones MA, et al.: Design of rat renin inhibitory peptides. *J Med Chem* 31:1679, 1988.
 56. Hiwada K, Kokubu T, Murakami E, et al.: A highly potent and long-acting oral inhibitor of human renin. *Hypertension* 11(6 Pt 2):708, 1988.
 57. Luly JR, BaMaung N, Soderquist J, et al.: Renin inhibitors. Dipeptide analogues of angiotensinogen utilizing a dihydroxyethylene transition-state mimic at the scissile bond to impart greater inhibitory potency. *J Med Chem* 31: 2264, 1988.
 58. Kleinert HD, Luly JR, Marcotte PA, et al.: Renin inhibitors. Improvements in the stability and biological activity of small peptides containing novel Leu-Val replacements. *FEBS Lett.* 230:38, 1988.
 59. Kempf DJ, de Lara E, Stein HH, et al: Renin inhibitors based on novel dipeptide analogues. Incorporation of the dehydrohydroxyethylene isostere at the scissile bond. *J Med Chem* 30:1978, 1987.
 60. Allen MC, Fuhrer W, Tuck B, et al: Renin inhibitors. Synthesis of transition-state analogue inhibitors containing phosphorus acid derivatives at the scissile bond. *J Med Chem* 32:1652, 1989.
 61. Evin G, Devin J, Castro B, et al: Synthesis of peptides related to the prosegment of mouse submaxillary gland renin precursor: an approach to renin inhibitors. *Proc Natl Acad Sci USA* 81:48, 1984.
 62. Sawyer TK, Pals DT, Mao B, et al.: Design, structure-activity, and molecular modeling studies of potent renin inhibitory peptides having N-terminal Nin-For-Trp (Ftr): angiotensinogen congeners modified by P1-P1' Phe-Phe, Sta, Leu psi[CH(OH)CH₂]Val or leu psi[CH₂NH]Val substitutions. *J Med Chem* 31:18, 1988.
 63. Haber E, Hui KY, Carlson WD, et al.: Renin inhibitors: a search for principles of design. *J Cardiovasc Pharmacol* 10 Suppl 7:S54, 1987.
 64. Bock MG, DiPardo RM, Evans BE, et al.: Renin inhibitors containing hydrophilic groups. Tetra-peptides with enhanced aqueous solubility and nanomolar potency. *J Med Chem* 31:1918, 1988.
 65. Glassman HN, Kleinert HD, Boger RS, et al.: Clinical pharmacology of enalkiren, a novel, dipeptide renin inhibitor. *J Cardiovasc Pharmacol* 16 Suppl 4:S76, 1990.
 66. Paruszewski R, Jaworski P, Winiecka I, et al.: New renin inhibitors with pseudodipeptidic units in P(1)-P(1') and P(2')-P(3') positions. *Chem Pharm Bull* (Tokyo 50:850, 2002.
 67. de Gasparo M, Cumin F, Nussberger J, et al.: Pharmacological investigations of a new renin inhibitor in normal sodium-unrestricted volunteers. *Br J Clin Pharmacol* 27:587,1989.
 68. Boyd SA, Fung AK, Baker WR, et al.: C-terminal modifications of nonpeptide renin inhibitors: improved oral bioavailability via modification of physicochemical properties. *J Med Chem* 35:1735, 1992.
 69. Wood JM, Maibaum J, Rahuel J, et al.: Structure-based design of aliskiren, a novel orally effective renin inhibitor. *Biochem Biophys Res Commun.* 308:698, 2003.
 70. Rahuel J, Rasetti V, Maibaum J, et al. Structure-based drug design: the discovery of novel non peptide orally active inhibitors of human renin. *Chem Biol* 7: 493, 2000.
 71. Nussberger J, Wuerzner G, Jensen C, Brunner HR. Angiotensin II suppression in humans by the orally active renin inhibitor aliskiren (SPP100): comparison with enalapril. *Hypertension* 39:E1, 2003.
 72. Azizi M, Webb R, Nussberger J, Hollenberg NK. Renin inhibition with aliskiren: where are we now and where are we going? *J Hypertens* 24: 243, 2006.
 73. Vaidyanathan S, Warren V, Yeh C, et al: Pharmacokinetics, safety and tolerability of the oral renin inhibitor aliskiren in patients with hepatic impairment. *J Clin Pharmacol* 47: 192, 2007.
 74. Zhao C, Vaidyanathan S, Yeh CM, et al: Aliskiren exhibits similar pharmacokinetics in healthy volunteers and patients with type 2 diabetes mellitus. *Clin Pharmacokinet* 45:1125, 2006.
 75. Gradman AH, Schmieder RE, Lins RL, et al. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation* 111:1012, 2005.
 76. Sica D, Gradman A, Lederballe I, Meyers M, et al. Aliskiren, an oral renin inhibitor, provides long-term antihypertensive efficacy and safety in patients with hypertension. *Eur Heart J* 27 (Supplement): P797, 2006.
 77. Feldman DL, Persohn E, Schutz H, et al. Renal localization of the renin inhibitor aliskiren (abst). *J*

- Clin Hypertens* 8 (Supplement A): A80, 2006.
78. Herron J, Mitchell J, Oh B, et al. The novel renin inhibitor aliskiren is not associated with rebound effects on blood pressure or plasma renin activity following treatment withdrawal (abst). *J Clin Hypertens* 8 (Supplement A): A86, 2006.
 79. Wood JM, Schnell CR, Cumin F, et al: Aliskiren, a novel, orally effective renin inhibitor, lowers blood pressure in marmosets and spontaneously hypertensive rats. *J Hypertens* 23:417, 2005.
 80. Westermann D, Riad A, Lettau O, et al: Renin inhibition improves cardiac function and remodeling after myocardial infarction independent of blood pressure. *Hypertension* 52: 1068, 2008.
 81. Verma S, Gupta MK: Aliskiren improves nitric oxide bioavailability and limits athero-sclerosis. *Hypertension* 52: 467, 2008.
 82. Nussberger J, Aubert JF, Bouzourene K, et al: Renin inhibition by aliskiren prevents atherosclerosis progression. Comparison with irbesartan, atenolol, and amlodipine. *Hypertension* 51: 1306, 2008.
 83. Perlini S, Salinaro F, Fonte ML: Direct renin inhibition. Another weapon to modulate the renin angiotensin system in postinfarction remodeling? *Hypertension* 52: 1019, 2008.
 84. Feldman DL, Jin L, Xuan H, et al: Effects of aliskiren on blood pressure, albuminuria and (pro)renin receptor expression in diabetic TG(mRen-2)27 rats. *Hypertension* 52: 130, 2008.
 85. Carey RM: Antihypertensive and renoprotective mechanisms of renin inhibition in diabetic rats. *Hypertension* 52: 63, 2008.
 86. Sepehrdad R, Frishman WH, Stier CT Jr., Sica DA: Direct inhibition of renin as a cardio-vascular pharmacotherapy. Focus on aliskiren. *Cardiol in Rev* 15: 242, 2007.
 87. Frampton JE, Curran MP: Aliskiren. A review of its use in the management of hypertension. *Drugs* 67: 1767, 2007.
 88. Gradman AH, Schmieder RE, Lins RL, et al: Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation* 111:1012, 2005.
 89. Stanton A, Jensen C, Nussberger J, et al: Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. *Hypertension* 42: 1137, 2003.
 90. Pool JL, Schmieder RE, Azizi M, et al: Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. *Am J Hypertens* 20: 11, 2007.
 91. Strasser R, Puig JG, Farsang C, et al: The oral renin inhibitor aliskiren has comparable safety and efficacy to lisinopril in patients with severe hypertension (abst). *J Hypertens* 24 (Suppl 6): 99, 2006.
 92. Sica D, Gradman A, Lederballe O, et al: Aliskiren, a novel renin inhibitor, is well tolerated and has sustained BP-lowering effects alone and in combination with HCTZ during long-term (52 weeks) treatment of hypertension. Presented at the 15th World Congress of Cardiology, Barcelona, Spain, September 2-6, 2006, p 797.
 93. Azizi M, Menard J, Bissery A, et al: Pharmacologic demonstration of the synergistic effects of a combination of the renin inhibitor aliskiren and the AT1 receptor antagonist valsartan on the angiotensin II-renin feedback interruption. *J Am Soc Nephrol* 15:3126, 2004.
 94. Oparil S, Yarows SA, Patel S, et al: Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 370: 221, 2007.
 95. Uresin Y, Taylor A, Kilo C, et al: Aliskiren, a novel renin inhibitor, has greater BP lowering than ramipril and additional BP lowering when combined with ramipril in patients with diabetes and hypertension. Presented at the 16th Scientific Meeting of the European Society of Hypertension, Madrid, Spain, June 12-15, 2006.
 96. Villamil A, Chrysant SG, Calhoun D, et al: Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens* 25: 217, 2007.
 97. Jordan J, Engeli S, Boye SW, et al: Direct renin inhibition with aliskiren in obese patients with arterial hypertension. *Hypertension* 49: 1047, 2007.
 98. Schmieder RE, Philipp T, Guerediaga J, et al: Long-term antihypertensive efficacy and safety of the oral direct renin inhibition aliskiren. A 12 month randomized, double-blind comparator trial with hydrochlorothiazide. *Circulation* 119: 417, 2009.
 99. Drummond W, Munger MA, Essop MF, et al: Antihypertensive efficacy of the oral direct renin inhibitor aliskiren as add-on therapy in patients not responding to amlodipine monotherapy. *J Clin Hypertens* 9: 742, 2007.
 100. Parving HH, Persson F, Lewis JB, et al for the AVOID study investigators: Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 358: 2433, 2008.
 101. Ingelfinger JR: Aliskiren and dual therapy in type 2 diabetes mellitus. *N Engl J Med* 358: 2503, 2008.
 - 101a. Persson F, Lewis JB, Lewis EJ, et al: Impact of baseline renal function on the efficacy and safety of aliskiren added to losartan in patients with type 2 diabetes and nephropathy. *Diabetes Care* 33: 2304, 2010.

102. Solomon SD, Appelbaum E, Manning WJ, et al for the ALLAY trial investigators: Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation* 119: 530, 2009.
103. Nussberger J, Wuerzner G, Jensen C, et al: Angiotensin II suppression in humans by the orally active renin inhibitor Aliskiren (SPP100): comparison with enalapril. *Hypertension*. 39: E1, 2002.
104. Weir MR, Bush C, Anderson DR, et al: Antihypertensive efficacy, safety, and tolerability of the oral direct renin inhibitor aliskiren in patients with hypertension: a pooled analysis. *J Am Soc Hypertens* 1: 264: 2007.
- 104a. White WB, Bresalier R, Kaplan AP, et al: Safety and tolerability of the direct renin inhibitor aliskiren: a pooled analysis of clinical experience in more than 12,000 patients with hypertension. *J Clin Hypertens* 12: 765, 2010.
- 104b. Duggan ST, Chwieduk CM, Curran MP: Aliskiren. A review of its use as mono-therapy and as combination therapy in the management of hypertension. *Drugs* 70: 2011, 2010.
105. Aliskiren (Tekturna) for hypertension. *The Medical Letter* 49: 29, 2007.
106. Ayalasomayajula S, Yeh CM, Vaidyanathan S, et al: Effects of aliskiren, a direct renin inhibitor, on cardiac repolarization and conduction in healthy subjects. *J Clin Pharmacol* 48: 799, 2008.
107. Dieterle W, Corynen S, Mann J: Effect of the oral renin inhibitor aliskiren on the pharmacokinetics and pharmacodynamics of a single dose of warfarin in healthy subjects. *Br J Clin Pharmacol* 58:433, 2004.
108. Dieterle W, Corynen S, Vaidyanathan S, et al: Pharmacokinetic interactions of the oral renin inhibitor aliskiren with lovastatin, atenolol, celecoxib and cimetidine. *Int J Clin Pharmacol Ther* 43:527, 2005.
109. Vaidyanathan S, Reynolds C, Yeh C-M, et al: Pharmacokinetics, safety, and tolerability of the novel oral direct renin inhibitor aliskiren in elderly healthy subjects. *J Clin Pharmacol* 47: 453, 2007.
110. Aliskiren/hydrochlorothiazide (Tekturna HCT) for hypertension. *The Medical Ltr* 50: 65, 2008.
111. Baldwin CM, Plosker GL: Aliskiren/hydrochlorothiazide combination in mild to moderate hypertension. *Drugs* 69: 833, 2009.
112. Aliskiren/valsartan (Valturna) for hypertension. *The Medical Ltr* 51: 94, 2009.
113. Staessen JA, Li Y, Richart T: Oral renin inhibitors. *Lancet* 368: 1449, 2006.
114. Bergset J, Storozyznsky E, Bisognano JD : Renin inhibition for hypertension : selecting the right role for a new class of drug. *Am J Therap* 17: 182, 2010.
115. McMurray JJV, Pitt B, Latini R, et al for the ALOFT investigators : Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail* 1: 17, 2008.
116. Cleland JGF, Coletta AP, Buga L, et al: Clinical trials update from the American College of Cardiology meeting 2010: DOSE, ASPIRE, CONNECT, STICH, STOP AF, CABANA, RACE II, EVEREST II, ACCORD AND NAVIGATOR. *Eur J Heart Fail* 12: 623, 2010.
117. Novartis six months efficacy and safety of aliskiren therapy on top of standard therapy, on morbidity and mortality in patients with acute decompensated heart failure (ASTRONAUT). Clinicaltrials.gov NCT00894387. US National Institutes of Health. Available from URL: <http://clinicaltrials.gov> (accessed Aug 23 2010)
118. Krum H, Massie B, Abraham WT, et al on behalf of the ATMOSPHERE Investigators: Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with Heart failuRE (ATMOSPHERE) study. *Eur J Heart Fail* 13: 107, 2011.
119. Scirica BM, Morrow DA, Bode C, et al: Patients with acute coronary syndromes and elevated levels of natriuretic peptides: results of the AVANT-GARDE-TIMI 43 trial. *Eur Heart J* 31: 1993, 2010.
120. Parving HH, Brenner BM, McMurray JJ, et al: Aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE): rationale and study design. *Nephrol Dial Transplant* 24: 1663, 2009.

References for Chapter 11

Diuretic Therapy

in Cardiovascular Disease

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1. Dustan H, Rocella EJ, Garrison H: Controlling hypertension. A research success story. *Arch Intern Med* 156:1926, 1996.
2. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 42:1206, 2003.
3. Szady AD, Hill JA: Diuretics in heart failure. A critical appraisal of efficacy and tolerability. *Drugs* 69:2461, 2009.
4. Reddy P, Mooradian AD: Diuretics: an update on the pharmacology and clinical uses. *Am J Therap* 16: 74, 2009.
5. Brater DC: Diuretic therapy. *N Engl J Med* 339:387, 1998.
6. Ichikawa I, Kon V: Role of peritubular capillary forces in the renal action of carbonic anhydrase inhibitor. *Kidney Int* 30:828, 1986.
7. Eveloff J, Warnock DG: Renal carbonic anhydrase. In: Dirks JH, Sutton RA, eds. *Diuretics: Physiology, Pharmacology and Clinical Use*. Philadelphia: WB Saunders, 1986:49–65.
8. Cogan MG, Maddox DA, Warnock DG, et al: Effect of acetazolamide on bicarbonate reabsorption in the proximal tubule of the rat. *Am J Physiol* 237:F447, 1979.
9. Mirza N, Marson AG, Pirmohamed M. Effect of topiramate on acid-base balance: extent, mechanism and effects. *Br J Clin Pharmacol* 68: 655, 2009.
10. Hassan ZU, Kruer JJ, Fuhrman TM. Electrolyte changes during craniotomy caused by administration of hypertonic mannitol. *J Clin Anesth* 19:307, 2007.
11. Weaver A, Sica DA: Mannitol-induced acute renal failure. *Nephron* 45:233, 1987.
12. O'Grady SM, Palfrey HC, Field M: Characteristics and function of Na-K-2Cl cotransport in epithelial tissues. *Am J Physiol* 252:C177, 1987.
13. Radtke HW, Rumrich G, Kinne-Saffran E, Ulrich KJ: Dual action of acetazolamide and furosemide on proximal volume absorption in the rat kidney. *Kidney Int* 1:100, 1972.
14. Duarte CG, Chomety F, Giebisch G: Effect of amiloride, ouabain, and furosemide on distal tubular function in the rat. *Am J Physiol* 221:632, 1971.
15. Jung KY, Endou H: Furosemide acts on short loop of descending thin limb, but not on long loop. *J Pharmacol Exp Ther* 253:1184, 1990.
16. Wilson DR, Honrath U, Sonnenberg H: Furosemide action on collecting ducts: Effect of prostaglandin synthesis inhibition. *Am J Physiol* 244:F666, 1983.
17. White MG, van Gelder J, Eastes G: The effect of loop diuretics on the excretion of Na⁺, Ca²⁺, Mg²⁺, and Cl⁻. *J Clin Pharmacol* 21:610, 1981.
18. Ryan MP, Devane J, Ryan MG, Counihan TB: Effects of diuretics on the renal handling of magnesium. *Drugs* 28(Suppl 1):167, 1984.
19. Steele TH, Oppenheimer S: Factors affecting urate excretion following diuretic administration in man. *Am J Med* 47:564, 1969.
20. Gerber JG: Role of prostaglandins in the hemodynamic and tubular effects of furosemide. *Fed Proc* 42:1707, 1983.
21. Wall GC, Bigner D, Craig S. Ethacrynic acid and the sulfa-sensitive patient. *Arch Intern Med* 163: 116, 2003.
22. Loon NR, Wilcox CS, Unwin RJ: Mechanism of impaired natriuretic response to furosemide during prolonged therapy. *Kidney Int* 36: 682, 1989.
23. Benet LZ: Pharmacokinetics/pharmacodynamics of furosemide in man: A review. *J Pharmacokinetic*

- Biopharm* 7:1, 1979.
24. Murray MD, Haag KM, Black PK, et al: Variable furosemide absorption and poor predictability of response in elderly patients. *Pharmacotherapy* 17:98, 1997.
 25. Bowman RH: Renal secretion of [³⁵S]furosemide and depression by albumin binding. *Am J Physiol* 229:93, 1975.
 26. Takamura N, Maruyama T, Otagiri M: Effects of uremic toxins and fatty acids on serum protein binding of furosemide: Possible mechanism of the binding defect in uremia. *Clin Chem* 43:2274, 1997.
 27. Chennavasin P, Seiwel R, Brater DC, et al: Pharmacodynamic analysis of the furosemide-probenecid interaction in man. *Kidney Int* 16:187, 1979.
 28. Brater DC, Day B, Burdette A, et al: Bumetanide and furosemide in heart failure. *Kidney Int* 26:183, 1984.
 29. Wilcox CS, Mitch WE, Kelly RA, et al: Response of the kidney to furosemide. I. Effects of salt intake and renal compensation. *J Lab Clin Med* 102:450, 1983.
 30. Chennavasin P, Seiwel R, Brater DC: Pharmacokinetic-dynamic analysis of the indomethacin-furosemide interaction in man. *J Pharmacol Exp Ther* 215:77, 1980.
 31. Agarwal R, Gorski JC, Sundblad K, Brater DC: Urinary protein binding does not affect response to furosemide in patients with nephrotic syndrome. *J Am Soc Nephrol* 11:1100, 2000.
 32. Knoben JE, Anderson PO, eds. Diuretics. In: *Clinical Drug Data*. 6th ed. IL: Drug Intelligence Publications; 1988:611-616.
 33. Voelker JR, Brown-Cartwright D, Anderson S, et al: Comparison of loop diuretics in patients with chronic renal insufficiency: Mechanism of difference in response. *Kidney Int* 32:572, 1987.
 34. Marcantonio LA, Auld WH, Murdoch WR, et al: The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in hepatic and renal disease. *Br J Clin Pharmacol* 15:245, 1983.
 35. Rudy DW, Gehr TW, Matzke GR, et al: The pharmacodynamics of IV and oral torsemide in patients with chronic renal insufficiency. *Clin Pharmacol Ther* 56:39, 1994.
 36. Schwartz S, Brater C, Pound D, et al: Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide in patients with cirrhosis. *Clin Pharmacol Ther* 54:90, 1993.
 37. Vargo DL, Kramer WG, Black PK, et al: Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther* 57:601, 1995.
 38. Murray MD, Deer MM, Ferguson JA, et al: Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. *Am J Med* 111:513, 2001.
 39. Ellison DH, Velazquez H, Wright FS: Thiazide-sensitive sodium chloride cotransport in early distal tubule. *Am J Physiol* 253:F546, 1987.
 40. Beyer KH: Chlorothiazide. *Br J Clin Pharmacol* 13:15, 1982.
 41. Wilson DR, Honrath U, Sonnenberg H: Thiazide diuretic effect on medullary collecting duct function in the rat. *Kidney Int* 23:711, 1983.
 42. Seldin DW, Eknayan G, Suki WN, et al: Localization of diuretic action from the pattern of water and electrolyte excretion. *Ann N Y Acad Sci* 139:328, 1966.
 43. Giles TD, Sander GE, Roffidal LE, et al: Comparative effects of nitrendipine and hydrochlorothiazide on calciotropic hormones and bone density in hypertensive patients. *Am J Hypertens* 5:875, 1992.
 44. Weinman EJ, Eknayan G, Suki WN: The influence of the extracellular fluid volume on the tubular reabsorption of uric acid. *J Clin Invest* 55:283, 1975.
 45. Leary WP, Reyes AJ: Diuretic-induced magnesium losses. *Drugs* 28(Suppl 1):182, 1984.
 46. Welling PG: Pharmacokinetics of the thiazide diuretics. *Biopharm Drug Dispos* 7:501, 1986.
 47. Beermann B, Groschinsky-Grind M: Clinical pharmacokinetics of diuretics. *Clin Pharmacokinet* 5:221, 1980.
 48. Knauf H, Mutschler E: Diuretic effectiveness of hydrochlorothiazide and furosemide alone and in combination in chronic renal failure. *J Cardiovasc Pharmacol* 26:394, 1995.
 49. Stern A: Metolazone, a diuretic agent. *Am Heart J* 91:262, 1976.
 50. Suki WN, Dawoud F, Eknayan G, et al: Effects of metolazone on renal function in normal man. *J Pharmacol Exp Ther* 180:6, 1972.
 51. Craswell PW, Ezzat E, Kopstein J, et al: Use of metolazone, a new diuretic, in patients with renal disease. *Nephron* 12:63, 1973.
 52. Sica DA. Metolazone and its role in edema management. *Congest Heart Fail* 9:100-105, 2003.
 53. Wingo CS: Potassium secretion by the cortical collecting tubule: Effect of CI gradients and ouabain. *Am J Physiol* 256:F306, 1989.
 54. Krishna GG, Shulman MD, Narins RG. Clinical use of the potassium sparing diuretics. *Semin Nephrol* 8:354, 1988.
 55. McInnes GT: Relative potency of amiloride and spironolactone in healthy man. *Clin Pharmacol Ther* 31:472, 1982.
 56. Rahn KH. Clinical pharmacology of diuretics. *Clin Exp Hypertens* 5:157, 1983.

57. Andriulli A, Arrighi A, Gindro T, et al: Canrenone and androgen receptor-active materials in plasma of cirrhotic patients during long-term K-canrenoate or spironolactone therapy. *Digestion* 44:155, 1989.
58. Ménard J. The 45-year story of the development of an anti-aldosterone more specific than spironolactone. *Mol Cell Endocrinol* 217:45, 2004.
59. Krum H, Nolly H, Workman D, He W, et al. Efficacy of eplerenone added to renin-angiotensin blockade in hypertensive patients. *Hypertension* 40: 117, 2002.
60. Weinberger MH, Roniker B, Krause SL, Weiss RJ. Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. *Am J Hypertens* 15:709, 2002.
61. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 1:940, 2006.
62. Pitt B, Remme W, Zannad F, Neaton J, et al. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 348:1309, 2003.
63. Teiwees J, Toto RD: Epithelial sodium channel inhibition in cardiovascular disease. A potential role for amiloride. *Am J Hypertens* 20: 109, 2007.
64. Kremer D, Boddy K, Brown JJ, et al. Amiloride in the treatment of primary hyperaldosteronism and essential hypertension. *Clin Endocrinol (Oxford)* 7:151, 1977.
65. Mutschler E, Gilfrich HJ, Knauf H, et al: Pharmacokinetics of triamterene. *Clin Exp Hypertens* 5:249, 1983.
66. Villeneuve JP, Rocheleau F, Raymond G: Triamterene kinetics and dynamics in cirrhosis. *Clin Pharmacol Ther* 35:831, 1984.
67. Knauf H, Mohrke W, Mutschler E: Delayed elimination of triamterene and its active metabolite in chronic renal failure. *Eur J Clin Pharmacol* 24:453, 1983.
68. Sica DA, Gehr TW: Triamterene and the kidney. *Nephron* 51:454, 1989.
69. Kelly RA, Wilcox CS, Mitch WE, et al: Response of the kidney to furosemide. II. Effect of captopril on sodium balance. *Kidney Int* 24:233, 1983.
70. Wilcox CS, Guzman NJ, Mitch WE, et al: Na⁺ and BP homeostasis in man during furosemide: Effects of prazosin and captopril. *Kidney Int* 31:135, 1987.
71. Wilcox CS, Loon NR, Ameer B, et al: Renal and hemodynamic responses to bumetanide in hypertension: effects of nitrendipine. *Kidney Int* 36:719, 1989.
72. Almeshari K, Ahlstrom NG, Capraro FE, et al: A volume-independent component to post-diuretic sodium retention in man. *J Am Soc Nephrol* 3:1878, 1993.
73. Frohlich JC, Hollifield JW, Dormois JC, et al: Suppression of plasma renin activity by indomethacin in man. *Circ Res* 39:447, 1976.
74. Ellison DH, Velazquez H, Wright FS: Adaptation of the distal convoluted tubule of the rat. Structural and functional effects of dietary salt intake and chronic diuretic infusion. *J Clin Invest* 83:113, 1989.
75. Kim J, Welch WJ, Cannon JK, et al: Immunocytochemical response of type A and type B intercalated cells to increased sodium chloride delivery. *Am J Physiol* 262:F288, 1992.
76. Stanton BA, Kaissling B: Adaptation of distal tubule and collecting duct to increase Na⁺ delivery. II. Na⁺ and K⁺ transport. *Am J Physiol* 255:F1269, 1988.
77. Loon NR, Wilcox CS, Unwin RJ: Mechanism of impaired natriuretic response to furosemide during prolonged therapy. *Kidney Int* 36:682, 1989.
78. Idiopathic edema: Role of diuretic abuse. *Kidney Int* 19:881, 1981.
79. Imbs JL, Schmidt M, Velly J, et al: Comparison of the effect of two groups of diuretics on renin secretion in the anesthetized dog. *Clin Sci Mol Med* 52:171, 1977.
80. Wilson TW, Loadholt CB, Privitera PJ, et al: Furosemide increases urine 6-keto-prostaglandin F_{1α}. Relation to natriuresis, vasodilation, and renin release. *Hypertension* 4:634, 1982.
81. Kraus PA, Lipman J, Becker PJ: Acute preload effects of furosemide. *Chest* 98:124, 1990.
82. Ciabattini G, Pugliese F, Cinotti GA, et al: Characterization of furosemide-induced activation of the renal prostaglandin system. *Eur J Pharmacol* 60:181, 1979.
83. Dikshit K, Vyden JK, Forrester JS, et al: Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. *N Engl J Med* 288:1087, 1973.
84. Favre L, Glasson P, Riondel A, et al: Interaction of diuretics and non-steroidal anti-inflammatory drugs in man. *Clin Sci (Colch)* 64:407, 1983.
85. Tiggeler RG, Koene RA, Wijdeveld PG: Inhibition of frusemide-induced natriuresis by indomethacin in patients with nephrotic syndrome. *Clin Sci Mol Med* 52:149, 1977.
86. Kirchner KA, Brandon S, Mueller RA, et al: Mechanism of attenuated hydro-chlorothiazide response during indomethacin administration. *Kidney Int*

- 31:1097, 1987.
87. Cutler JA, Sorlie PD, Wolz M, et al. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. *Hypertension* 52:818, 2008.
 88. Conen D, Bamberg F. Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: a systematic review and meta-analysis. *J Hypertens*. 26:1290, 2008.
 89. Moser M. From JNC I to JNC 7—what have we learned? *Prog Cardiovasc Dis* 48: 303, 2006.
 - 89a. Ernst ME, Moser M: Use of diuretics in patients with hypertension: *N Engl J Med* 361: 2153, 2009.
 90. Roos JC, Boer P, Koomans HA, et al: Haemodynamic and hormonal changes during acute and chronic diuretic treatment in essential hypertension. *Eur J Clin Pharmacol* 19:107, 1981.
 91. Van Brummelen P, Man in't Veld AI, Schalekamp MADH: Hemodynamic changes during long-term thiazide treatment of essential hypertension in responders and non-responders. *Clin Pharmacol Ther* 27:328, 1980.
 92. Tarazi RC, Dustan HP, Frohlich ED: Long-term thiazide therapy in essential hypertension. *Circulation* 41:709, 1970.
 93. Conway J, Lauwers P: Hemodynamic and hypotensive effects of long-term therapy with chlorothiazide. *Circulation* 21:21, 1960.
 94. Uzu T, Kimura G: Diuretics shift circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. *Circulation* 100:1635, 1999.
 95. Shah S, Khatri I, Freis ED: Mechanism of antihypertensive effect of thiazide diuretics. *Am Heart J* 95:611, 1978.
 96. Sica DA. Current concepts of pharmacotherapy in hypertension: thiazide-type diuretics: ongoing considerations on mechanism of action. *J Clin Hypertens (Greenwich)* 6:661, 2004.
 97. Bennett WM, McDonald WJ, Kuehnel E, et al: Do diuretics have antihypertensive properties independent of natriuresis? *Clin Pharmacol Ther* 22:499, 1977.
 98. Sica DA, Gehr TW. Diuretic use in stage 5 chronic kidney disease and end-stage renal disease. *Curr Opin Nephrol Hypertens* 12:483, 2003.
 99. Sica DA. Thiazide and loop diuretics. In Izzo JL Jr., Sica DA, Black HR: *Hypertension Primer 4th ed.* Dallas: American Heart Assn, 2008: 439.
 100. Epstein M: Aldosterone blockers and potassium-sparing diuretics. In Izzo JL Jr., Sica DA, Black HR: *Hypertension Primer 4th ed.* Dallas: American Heart Assn, 2008: 443.
 101. Nelson MR, Reid CM, Krum H, et al. Short-term predictors of maintenance of normotension after withdrawal of antihypertensive drugs in the second Australian National Blood Pressure Study (ANBP2). *Am J Hypertens* 16:39, 2003.
 102. Levinson PD, Khatri IM, Freis ED. Persistence of normal BP after withdrawal of drug treatment in mild hypertension. *Arch Intern Med* 142:2265, 1982.
 103. Holland OB, Gomez-Sanchez CE, Kuhnert LV, et al: Antihypertensive comparison of furosemide with hydrochlorothiazide for black patients. *Arch Intern Med* 139:1015, 1979.
 104. Sica DA, Gehr TWB: Diuretic combination in refractory edema states: Pharmacokinetic and pharmacodynamic relationships. *Clin Pharmacokinet* 30:229, 1996.
 105. Roca-Cusachs A, Aracil-Vilar J, Calvo-Gómez C, et al. Clinical effects of torasemide Prolonged release in mild-to-moderate hypertension: a randomized noninferiority trial versus torasemide immediate release. *Cardiovasc Ther* 26:91, 2008.
 106. Collins R, Peto R, MacMahon S, et al: Blood pressure, stroke, and coronary heart disease. Part 2: Short-term reductions in blood pressure: Overview of randomised drug trials in their epidemiological context. *Lancet* 335:827, 1990.
 107. MacMahon S, Rodgers A: The effects of antihypertensive treatment on vascular disease: reappraisal of the evidence in 1994. *J Vasc Med Biol* 4:265, 1993.
 108. Collins R, MacMahon S: Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 50:272, 1994.
 109. Gueyffier F, Boutitie F, Boissel JP, et al: Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men: A meta-analysis of individual patient data from randomised controlled trials. *Ann Intern Med* 126:761, 1997.
 110. Psaty B, Smith N, Siscovick D, et al: Health outcomes associated with antihypertensive therapies used as first-line agents: A systematic review and meta-analysis. *JAMA* 277:739, 1997.
 111. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 213:1143, 1970.
 112. Hypertension Detection and Follow Up Program Cooperation Group. Five-year findings of the Hypertension Detection and follow up program. I. Reduction in mortality of patients with high blood pressure, including mild hypertension. *JAMA* 242:2562, 1979.
 113. Management Committee: The Australian therapeutic trial in mild hypertension. *Lancet* I:1261,

- 1980.
114. SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older patients with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 265:3255, 1991.
 115. Dahlof B, Lindholm LH, Hansson L, et al: Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 338:1281, 1991.
 116. Wright JM, Lee CH, Chambers GK: Systematic review of antihypertensive therapies: Does the evidence assist in choosing a first-line drug? *CMAJ* 161:25, 1999.
 117. Amery A, Birkenhager W, Brixko R, et al: Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly Trial. *Lancet* 1:1349, 1985.
 118. MRC Working Party: Medical Research Council trial of treatment of hypertension in older adults: Principal results. *BMJ* 304:405, 1992.
 119. Wilhelmssen L, Berglund G, Elmfeld D, et al: Beta-blockers versus diuretics in hypertensive men: Main results from the HAPPHY trial. *J Hypertens* 5:561, 1987.
 120. Blood Pressure Lowering Treatment Trialists Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomised trials. *Lancet* 355:1955, 2000.
 121. Messerli FH, Grossman E, Goldbourt U: Are β blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. *JAMA* 279:1902, 1998.
 122. Wiysonge CS, Bradley H, Mayosi BM, et al. Beta-blockers for hypertension. *Cochrane Database Syst Rev* 24;(1):CD002003, 2007.
 123. Frishman WH, Saunders E, Messerli F: Beta-adrenergic blocking drugs. *J Clin Hypertens* in press.
 124. Hansson L, Lindholm LH, Niskanen L, et al: Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 353:611, 1999.
 125. Hansson L, Lindholm LH, Ekblom T, et al: Randomised trial of old and new antihypertensive drugs in elderly patients: Cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 354:1751, 1999.
 126. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 317:713, 1998.
 127. Brown MJ, Palmer CR, Castaigne A, et al: Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 356:366, 2000.
 128. Hansson L, Hedner T, Lund-Johansen P, et al: Randomised trial of effects of calcium antagonists compared with diuretics and β -blockers on cardiovascular morbidity and mortality in hypertension: The Nordic Diltiazem (NORDIL) study. *Lancet* 356:359, 2000.
 129. Turnbull F, Woodward M, Neal B, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. *Eur Heart J* 29:2669,2008.
 130. Turnbull F, Neal B, Ninomiya T, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 336:1121, 2008.
 131. ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 283:1967, 2000.
 132. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288: 2981, 2002.
 133. Wright JT Jr, Probstfield JL, Cushman WC, et al for the ALLHAT Collaborative Research Group: ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses. *Arch Intern Med* 169: 832, 2009.
 134. Hachamovitch R, Strom JA, Sonnenblick EH, Frishman WH: Left ventricular hypertrophy in hypertension and the effects of antihypertensive drug therapy. *Curr Probl Cardiol* 13:371, 1988.
 135. Levy D, Garrison RJ, Savage DD, et al: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 322:156, 1990.
 136. Moser M, Hebert PR: Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. *J Am Coll Cardiol* 27:1214, 1996.

137. Moser M, Setaro JF: Antihypertensive drug therapy and regression of left ventricular hypertrophy: A review with a focus on diuretics. *Eur Heart J* 12:1034, 1991.
138. Dahlöf B, Pennert K, Hansson L: Reversal of left ventricular hypertrophy in hypertensive patients. A meta-analysis of 109 treatment studies. *Am J Hypertens* 5:95, 1992.
139. Schmieder RE, Martus P, Klingbeil A: Reversal of left ventricular hypertrophy in essential hypertension. *JAMA* 275:1507, 1996.
140. Fagard RH, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. *Hypertension* 2009;54:1084-1091.
141. Neaton JD, Grimm RH Jr, Prineas, et al: Treatment of mild hypertension study (TOMHS): Final results. *JAMA* 270:713, 1993.
142. Gosse P, Sheridan DJ, Zannad F, et al: Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: The LIVE study. *J Hypertens* 18:1465, 2000.
143. Mancia G. Blood pressure reduction and cardiovascular outcomes: past, present and future. *Am J Cardiol* 100 (Suppl):3J, 2007.
144. Materson BJ, Reda DJ, Cushman WC, et al: Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. *N Engl J Med* 328:914, 1993.
145. Coope J, Warrender TS: Randomized trial of treatment of hypertension in elderly in primary care. *Br Med J* 293:1145, 1986.
146. Hampton JR: Comparative efficacy of diuretics: Benefit versus risk: Results of clinical trials. *Eur Heart J* 13 (Suppl G):85, 1992.
147. Manolis A, Doumas M. Sexual dysfunction: the 'prima ballerina' of hypertension-related quality-of-life complications. *J Hypertens* 26: 2074, 2008.
148. The IPPPSH Collaborative Group: Cardiovascular risk and risk factors in a randomised trial of treatment based on the beta blocker oxprenolol: The International Prospective Primary Prevention Study in Hypertension (IPPPSH). *J Hypertens* 3:379, 1985.
149. Wilhelmsen L, Berglund G, Elmfeld D, et al: Beta blockers vs diuretics in hypertensive men: main results from the HAPPHY trial. *J Hypertens* 5: 561, 1987.
150. Pahor M, Shorr RI, Somes GW, et al: Diuretic-based treatment and cardiovascular events in patients with mild renal dysfunction enrolled in the Systolic Hypertension in the Elderly Program. *Arch Intern Med* 158:1340, 1998.
151. Frishman WH: Systemic hypertension in the elderly. In Aronow WS, Fleg JL, Rich MW (ed): *Cardiovascular Disease in the Elderly 4th ed.* New York: Informa 2008:137.
- 151a. ACCF/AHA/NHLBI Expert Consensus Document on Hypertension in the Elderly. A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol* 2011 in press.
- 151b. Fleg JL, Aronow WS, Frishman WH: Cardiovascular drug therapy in the elderly: benefits and challenges. *Nat Rev Cardiol* October 26, 2010 (epub).
152. Douglas JG, Bakris GL, Epstein M, et al. Management of high blood pressure in African Americans: a consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. *Arch Intern Med* 163:525, 2003.
153. Frohlich ED, Messerli FH, Dunn FG, et al: Greater renal vascular involvement in the black patient with essential hypertension: A comparison of systemic and renal hemodynamics in black and white patients. *Miner Electrolyte Metab* 10:173, 1984.
154. INTERSALT Cooperative Research Group: INTERSALT: An international study of electrolyte excretion and blood pressure. Results of 24 h urinary sodium and potassium excretion. *BMJ* 297:319, 1988.
155. Chrysant SG, Danisa K, Kem DC, et al: Racial differences in pressure, volume and renin interrelationships in essential hypertension. *Hypertension* 1:136, 1979.
156. Wilson DK, Sica DA, Miller SB: Effects of potassium on blood pressure in salt-sensitive and salt-resistant black adolescents. *Hypertension* 34:181, 1999.
157. Whelton PK, He J, Cutler JA, et al: Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA* 277:1624, 1997.
158. Freis ED: Age and antihypertensive medication (hydrochlorothiazide, bendroflumethiazide, nadolol and captopril). *Am J Cardiol* 61:117, 1988.
159. Veterans Administration Cooperative Study Group on Antihypertensive Drugs: Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension. I. Results of short term titration with emphasis on racial differences in response. *JAMA* 248:1996, 1982.
160. Moser M, Lunn J: Responses to captopril and hydrochlorothiazide in black patients with hypertension. *Clin Pharmacol Ther* 32:307, 1982.
161. Sica DA: Fixed-dose combination therapy. Is it rational? *Drugs* 48:16, 1994.

162. Wright JT Jr, Dunn JK, Cutler JA, et al. ALLHAT Collaborative Research Group. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA* 293:1595, 2005.
163. Flack JM, Saunders E, Gradman A, et al: Antihypertensive efficacy and safety of losartan alone and in combination with hydrochlorothiazide in adult African Americans with mild to moderate hypertension. *Clin Ther* 23:1193, 2001.
164. Walker WG, Neaton JD, Cutler JA, et al: Renal function change in hypertensive members of the Multiple Risk Factor Intervention Trial: Racial and treatment effects. *JAMA* 268:3085, 1992.
165. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 165:936, 2005.
166. Sica DA: Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. *Drugs* 62:443, 2002.
167. Neldam S, Edwards C, Telmisartan/Hydrochlorothiazide Investigators: Results of increasing doses of hydrochlorothiazide in combination with an angiotensin receptor blocker in patients with uncontrolled hypertension. *J Clin Hypertens* 10: 612, 2008.
168. Hansson L, Zanchetti A, Carruthers SG, et al: Effect of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 351:1755, 1998.
169. Frishman WH, Bryzinski BS, Coulson LR, et al: A multifactorial trial design to assess combination therapy in hypertension: Treatment with bisoprolol and hydrochlorothiazide. *Arch Intern Med* 154:1461, 1994.
170. Moser M: Why are physicians not prescribing diuretics more frequently in the management of hypertension? *JAMA* 270:1813, 1998.
171. Vasan RS, Larson MG, Benjamin EJ, et al: Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: Prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 33:1948, 1999.
172. Gradman AH, Alfayoumi F. From left ventricular hypertrophy to congestive heart failure: management of hypertensive heart disease. *Prog Cardiovasc Dis* 48:326, 2006.
173. Colucci WS: Molecular and cellular mechanisms of myocardial failure. *Am J Cardiol* 80:15L, 1997.
174. LeJemtel TH, Sonnenblick EH, Frishman WH: Diagnosis and management of heart failure. In: Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's The Heart*. 10th ed. New York: McGraw-Hill, 2001:687-724.
175. Givertz MM, Colucci WS: New targets for heart-failure therapy: Endothelin, inflammatory cytokines, and oxidative stress. *Lancet* 352 (Suppl 1):S134, 1998.
176. Francis GS, Benedict C, Johnstone DE, et al: Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: A substudy of the Studies Of Left Ventricular Dysfunction (SOLVD). *Circulation* 82:1724, 1990.
177. Bank AJ, Lee PC, Kubo SH: Endothelial dysfunction in patients with heart failure: Relationship to disease severity. *J Card Fail* 6:29, 2000.
178. Katz SD, Khan T, Zeballos GA, et al: Decreased activity of the L-arginine-nitric oxide metabolic pathway in patients with congestive heart failure. *Circulation* 99:2113, 1999.
179. Sam F, Colucci WS: Role of endothelin-1 in myocardial failure. *Proc Assoc Am Physicians* 111:417, 1999.
180. Moraes DL, Colucci WS, Givertz MM: Secondary pulmonary hypertension in heart failure: The role of the endothelium in pathophysiology and management. *Circulation* 102:1718, 2000.
181. Ichikawa I, Yoshioka T, Fogo A, Kon V: Role of angiotensin II in altered glomerular hemodynamics in congestive heart failure. *Kidney Int Suppl* 30:S123, 1990.
182. Eiskjaer H, Bagger JP, Danielsen J, et al: Mechanisms of sodium retention in heart failure: Relation to the renin-angiotensin-aldosterone system. *Am J Physiol* 260:F883, 1991.
183. Böhm M. Angiotensin receptor blockers versus angiotensin-converting enzyme inhibitors: where do we stand now? *Am J Cardiol* 100:38J, 2007.
184. Cody RJ, Haas GJ, Binkley PF, et al: Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. *Circulation* 85:504, 1992.
185. Chatterjee K. Neurohumoral activation in congestive heart failure and role of vasopressin. *Am J Cardiol* 95:8, 2007.
186. Goldsmith SR: Vasopressin as vasopressor. *Am J Med* 82:1213, 1987.
187. Creager MA, Faxon DP, Cutler SS, et al. Contribution of vasopressin to vasoconstriction in patients with congestive heart failure: comparison with the renin-angiotensin system and the sympathetic nervous system. *J Am Coll Cardiol* 7: 758. 1986.

188. Chatterjee K. Hyponatremia in heart failure. *J Intensive Care Med* 24:347, 2009.
189. Barton M, Yanagisawa M. Endothelin: 20 years from discovery to therapy. *Can J Physiol Pharmacol* 86:485, 2008.
190. Dontas ID, Xanthos T, Dontas I, et al. Impact of nesiritide on renal function and mortality in patients suffering from heart failure. *Cardiovasc Drugs Ther* 23: 221, 2009.
191. Francis GS, Siegel RM, Goldsmith SR, et al: Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med* 103:1, 1985.
192. Wilson JR, Reichek N, Dunkman WB, Goldberg S: Effect of diuresis on the performance of the failing left ventricle in man. *Am J Med* 70:234, 1981.
193. Bauer U, Haerer W, Fehske KJ, et al: Hemodynamic effects of piretanide and methyl digoxine in congestive heart failure: Long-term results of a placebo-controlled randomized double blind study. In: Puschett J, Greenberg A, eds. *Diuretics III: Chemistry, Pharmacology, and Clinical Applications*. New York: Elsevier 1990:316.
194. Vasko MR, Cartwright DB, Knochel JP, et al: Furosemide absorption altered in decompensated congestive heart failure. *Ann Intern Med* 102:314, 1985.
195. Brater DC, Seiwell R, Anderson S, et al: Absorption and disposition of furosemide in congestive heart failure. *Kidney Int* 22:171, 1982.
196. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol* 13:798, 2002.
197. Cook JA, Smith DE, Cornish LA, et al: Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with congestive heart failure. *Clin Pharmacol Ther* 44:487, 1988.
198. Brater DC, Day B, Burdette A, et al: Bumetanide and furosemide in heart failure. *Kidney Int* 26:183, 1984.
199. Dzau VJ, Colucci WS, Williams GH, et al.: Sustained effectiveness of converting-enzyme inhibition in patients with severe congestive heart failure. *N Engl J Med* 302:1373, 1980.
200. McLay JS, McMurray JJ, Bridges AB, et al: Acute effects of captopril on the renal actions of furosemide in patients with chronic heart failure. *Am Heart J* 26:879, 1993.
201. De Pasquale CG, Dunne JS, Minson RB, Arnolda LF. Hypotension is associated with diuretic resistance in severe chronic heart failure, independent of renal function. *Eur J Heart Fail* 7: 888, 2005.
202. Kramer BK, Schweda F, Riegger GAJ: Diuretic treatment and diuretic resistance in heart failure. *Am J Med* 106:90, 1999.
203. Brater DC, Anderson S, Baird B, et al: Effects of ibuprofen, naproxen, and sulindac on prostaglandins in men. *Kidney Int* 27:66, 1985.
204. Marangoni E, Oddone A, Surian M, et al: Effect of high-dose furosemide in refractory congestive heart failure. *Angiology* 41:862, 1990.
205. Gerlag PG, van Meijel JJ: High-dose furosemide in the treatment of refractory congestive heart failure. *Arch Intern Med* 148:286, 1988.
206. Eshaghian S, Horwich TB, Fonarow GC: Relation of loop diuretic dose to mortality in advanced heart failure. *Am J Cardiol* 97: 1759, 2006.
207. Guglin M: Reappraisal of the role of diuretics in heart failure. *Cardiol in Rev* 17: 56, 2009.
- 207a. Allen LA, Turer AT, DeWald T, et al: Continuous versus bolus dosing of furosemide for patients hospitalized for heart failure. *Am J Cardiol* 105: 1794, 2010.
208. Rudy DW, Voelker JR, Greene PK, et al: Loop diuretics for chronic renal insufficiency: A continuous infusion is more efficacious than bolus therapy. *Ann Intern Med* 115:360, 1991.
209. Lahav M, Regev A, Ra'anani P, et al: Intermittent administration of furosemide vs. continuous infusion preceded by a loading dose for congestive heart failure. *Chest* 102:725, 1992.
210. Howard PA: Aggressive diuresis for severe heart failure in the elderly. *Chest* 119:807, 2001.
- 210a. Jentzer JC, DeWald TA, Hernandez AF: Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol* 56: 1527, 2010.
211. Brater DC, Presley RH, Anderson SA: Mechanisms of the synergistic combination of metolazone and bumetanide. *J Pharmacol Exp Ther* 233:70, 1985.
212. Epstein M, Lepp BA, Hoffman DS, et al: Potentiation of furosemide by metolazone in refractory edema. *Curr Ther Res* 21:656, 1977.
213. Channer KS, Richardson M, Crook R, et al: Thiazides with loop diuretics for severe congestive heart failure. *Lancet* 335:922, 1990.
214. Kiyangi A, Field MJ, Pawsey CC, et al: Metolazone in treatment of severe refractory congestive heart failure. *Lancet* 335:29, 1990.
215. Channer KS, McLean KA, Lawson-Matthew P, et al: Combination diuretic treatment in severe heart failure: A randomised controlled trial. *Br Heart J* 71:146, 1994.
216. Van Viet AA, Danker AJM, NAFTA JJ, Overheat FW: Spironolactone in congestive heart failure refractory to high-dose loop diuretic and low-dose angiotensin converting enzyme inhibitor. *Am J Cardiol* 71:21A, 1993.
217. Farquharson CAJ, Struthers AD: Spironolactone

- increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. *Circulation* 101:594, 2000.
218. Weber KT: Aldosterone in congestive heart failure. *N Engl J Med* 345:1689, 2001.
 219. Rocha R, Williams GH: Rationale for the use of aldosterone antagonists in congestive heart failure. *Drugs* 62:723, 2002.
 220. Bauersachs J, Heck M, Fraccarollo D, et al: Addition of spironolactone to angiotensin-converting enzyme inhibition in heart failure improves endothelial vasomotor dysfunction. *J Am Coll Card* 39:351, 2002.
 - 220a. Maron BA, Leopold JA: Aldosterone receptor antagonists. Effective but often forgotten. *Circulation* 121: 934, 2010.
 221. Pitt B, Zannad F, Rime WJ et al: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 341:709, 1999.
 - 221a. Zannad F, McMurray JJ, Drexler H, et al: Rationale and design of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Eur J Heart Fail* 12: 617, 2010.
 222. Keating GM, Plosker GL: Eplerenone. A review of its use in left ventricular systolic dysfunction and heart failure after acute myocardial infarction. *Drugs* 64: 2689, 2004.
 - 222a. Zannad F, McMurray JJV, Krum H, et al: Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* November 14, 2010 (epub).
 - 222b. Armstrong PW: Aldosterone antagonists – last man standing? *N Engl J Med* November 14, 2010 (epub).
 223. Jorde UP, Vittorio T, Katz SD, et al: Elevated plasma aldosterone levels despite complete inhibition of the vascular angiotensin-converting enzyme in chronic heart failure. *Circulation* 106:1055, 2002.
 224. Ayus JC: Diuretic-induced hyponatremia (editorial). *Arch Intern Med* 146:1295, 1986.
 225. Ashraf N, Locksley R, Arieff AI: Thiazide-induced hyponatremia associated with death or neurologic damage in outpatients. *Am J Med* 70:1163, 1981.
 226. Mann SJ. The silent epidemic of thiazide-induced hyponatremia. *J Clin Hypertens (Greenwich)*10:477, 2008.
 227. Szatalowicz VL, Miller PD, Lacher JW, et al: Comparative effect of diuretics on renal water excretion in hyponatraemic oedematous disorders. *Clin Sci (Colch)* 62:235, 1982.
 228. Sonnenblick M, Friedlander Y, Rosin AJ: Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients. *Chest* 103:601, 1993.
 229. Sterns RH: “Slow” correction of hyponatremia: A break with tradition? *Kidney* 23:1, 1991.
 230. Berl T: Treating hyponatremia: What is all the controversy about? [see comments]. *Ann Intern Med* 113:417, 1990.
 231. Morgan DB, Davidson C: Hypokalemia and diuretics: An analysis of publications. *Br Med J* 280:905, 1980.
 232. Khuri RN, Strieder WN, Giebisch G: Effects of flow rate and potassium intake on distal tubular potassium transfer. *Am J Physiol* 228:1249, 1975.
 233. Velazquez H, Wright FS: Control by drugs of renal potassium handling. *Ann Rev Pharmacol Toxicol* 26:293, 1986.
 234. Stanton BA, Giebisch G: Effects of pH on potassium transport by renal distal tubule. *Am J Physiol* 242:F544, 1982.
 235. Wilcox CS: Diuretics and potassium. In: Hoffman JF, Giebisch G, eds. *Current Topics in Membranes and Transport*. Orlando, FL: Academic Press, 1987:250–331.
 236. Freis ED, Papademetriou V: How dangerous are diuretics? *Drugs* 30:469, 1985.
 237. Holland OB, Nixon JV, Kuhnert L: Diuretic-induced ventricular ectopic activity. *Am J Med* 70:762, 1981.
 238. MacMahon S, Collins G, Rautaharju P, et al: Electrocardiographic left ventricular hypertrophy and effects of antihypertensive drug therapy in hypertensive patients in the Multiple Risk Factor Intervention Trial. *Am J Cardiol* 63:202, 1989.
 239. Mann JF, Yi QL, Sleight P, Dagenais GR, et al. Serum potassium, cardiovascular risk, and effects of an ACE inhibitor: results of the HOPE study. *Clin Nephrol* 63:181, 2005.
 240. Madias J, Madias N, Gavras H: Nonarrhythmogenicity of diuretic-induced hypokalemia: Its evidence in patients with uncomplicated essential hypertension. *Arch Intern Med* 144:2171, 1984.
 241. Papademetriou V, Fletcher R, Khatri IM, et al: Diuretic-induced hypokalemia in uncomplicated systemic hypertension. Effect of plasma potassium correction in cardiac arrhythmias. *Am J Cardiol* 52:1017, 1983.
 242. Medical Research Council, Working Party on Mild to Moderate Hypertension: Ventricular extrasystole during thiazide treatment: Substudy of MRC Mild Hypertension Trial. *Br Med J* 287:1249, 1983.
 243. Kafka H, Langevin L, Armstrong P: Serum magnesium and potassium in acute myocardial infarction: Influences on ventricular arrhythmia. *Arch Intern Med* 147:465, 1987.

244. Packer M: Potential role of potassium as a determinant of morbidity and mortality in patients with systemic hypertension and congestive heart failure. *Am J Cardiol* 65:45E, 1990.
245. Dargie HJ, Cleland J, Leckie B, et al: Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure. *Circulation* 75(Suppl IV):IV98, 1987.
246. Franse LV, Pahor M, DiBari M, et al: Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. *Hypertension* 35:1025, 2000.
247. Siscovick DS, Raghunathan TE, Psaty BM, et al: Diuretic therapy and the risk of primary cardiac arrest. *N Engl J Med* 330:1852, 1994.
248. Cooper HW, Dries DL, Davis CE, et al: Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. *Circulation* 100:1311, 1999.
249. Seigel D, Hulley SB, Black DM, et al: Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *JAMA* 267:1083, 1992.
250. Knochel JP, Schlein EM: On the mechanism of rhabdomyolysis in potassium depletion. *J Clin Invest* 51:1750, 1972.
251. Relman AS, Schwartz WB: The nephropathy of potassium depletion: A clinical and pathological entity. *N Engl J Med* 255:195, 1956.
252. Sica DA, Gehr TW, Yancy C. Hyperkalemia, congestive heart failure, and aldosterone receptor antagonism. *Congest Heart Fail* 9: 224, 2003.
253. Quamme GA: Effect of furosemide on calcium and magnesium transport in the rat nephron. *Am J Physiol* 241:F340, 1981.
254. Kroenke K, Wood DR, Hanley JF: The value of serum magnesium determination in hypertensive patients receiving diuretics. *Arch Intern Med* 147:1553, 1987.
255. Petri M, Cumber P, Grimes L, et al: The metabolic effects of thiazide therapy in the elderly: A population study. *Age Aging* 15:151, 1986.
256. Dyckner T, Wester PO: Effects of magnesium infusions in diuretic induced hyponatraemia. *Lancet* 1:585, 1981.
257. Whang R, Oei TO, Aikawa JK, et al: Predictors of clinical hypomagnesemia. Hypokalemia, hypophosphatemia, hyponatremia, and hypocalcemia. *Arch Intern Med* 144:1984.
258. Wester PO, Dyckner T: Intracellular electrolytes in cardiac failure. *Acta Med Scand* 707(Suppl): 33, 1986.
259. Eichhorn EJ, Tandon PK, DiBianco R, et al: Clinical and prognostic significance of serum magnesium concentration in patients with severe chronic congestive heart failure: The PROMISE study. *J Am Coll Cardiol* 21:634, 1993.
260. Cannon PJ, Heineman HO, Albert MS, et al: "Contraction" alkalosis after diuresis of edematous patients with ethacrynic acid. *Ann Intern Med* 62:979, 1965.
261. Loon NR, Wilcox CS, Nelson R, Mounts M: Metabolic alkalosis impairs the response to bumetanide. *Kidney Int* 33:200A, 1988.
262. O'Connell JE, Colledge NR. Type IV renal tubular acidosis and spironolactone therapy in the elderly. *Postgrad Med J* 69:887, 1993.
263. Report of Medical Research Council Working Party on Mild to Moderate Hypertension. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. *Lancet* 2:539, 1981.
264. Furman BL: Impairment of glucose intolerance produced by diuretics and other drugs. *Pharmacol Ther* 12:613, 1981.
265. Dornhorst A, Powell SH, Pensky J: Aggravation by propranolol of hyperglycaemic effect of hydrochlorothiazide in type II diabetics without alteration of insulin secretion. *Lancet* 1:123, 1985.
266. Palmer BF, Naderi ASA: Metabolic complications associated with use of thiazide diuretics. *J Am Soc Hypertens* 1: 381, 2007.
267. Zillich AJ, Garg J, Basu S, et al: Thiazide diuretics, potassium, and the development of diabetes. A quantitative review. *Hypertension* 48: 219, 2006.
268. Carter BL, Einhorn PT, Brands M, et al. Thiazide-induced dysglycemia: call for research from a working group from the national heart, lung, and blood institute. *Hypertension* 52:30, 2008.
269. Cooper-DeHoff RM, Wen S, Beitelshes AL, et al. Impact of abdominal obesity on incidence of adverse metabolic effects associated with antihypertensive medications. *Hypertension* 55:61, 2010.
270. Sowers JR, Bakris GL: Antihypertensive therapy and the risk of type 2 diabetes mellitus. *N Engl J Med* 342:969, 2000.
271. Jeunemaitre X, Charru A, Chatellier G, et al: Long-term metabolic effects of spironolactone and thiazides combined with potassium-sparing agents for treatment of essential hypertension. *Am J Cardiol* 62:1072, 1988.
272. Cooper-DeHoff RM, Pacanowski MA, Pepine CJ. Cardiovascular therapies and associated glucose homeostasis: implications across the dysglycemia continuum. *J Am Coll Cardiol* 53 (5 Suppl):S28, 2009.
273. Ruppert M, Overlack A, Kolloch R, et al: Neurohormonal and metabolic effects of severe and mod-

- erate salt restriction in non-obese normotensive adults. *J Hypertens* 11:743, 1993.
274. Mantel-Teeuwisse AK, Kloosterman JM, Maitland-van der Zee AH, et al: Drug-Induced lipid changes: A review of the unintended effects of some commonly used drugs on serum lipid levels. *Drug Saf* 24:443, 2001.
 275. Lakshman MR, Reda DJ, Materson BJ, et al: Diuretics and β blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. *Arch Intern Med* 159:551, 1999.
 276. Kasiske BL, Ma JZ, Kalil RS, et al. Effects of anti-hypertensive therapy on serum lipids. *Ann Intern Med* 122::133, 1995.
 277. Hypertension Detection and Follow-Up Program Cooperation Group. 1979. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of patients with high blood pressure, including mild hypertension. *JAMA* 277:157, 1997.
 278. Ljunghall S, Backman U, Danielson BG, et al: Effects of bendroflumethiazide on urate metabolism during treatment of patients with renal stones. *J Urol* 127:1207, 1982.
 279. Sica DA, Schoolwerth A. Renal handling of organic anions and cations and renal excretion of uric acid. In: Brenner B, Rector F, eds. *The Kidney* 7th ed. Philadelphia: WB Saunders; 2004:637–662.
 280. Weinman EJ, Eknoyan G, Suki WN. The influence of the extracellular fluid volume on the tubular reabsorption of uric acid. *J Clin Invest* 55:283, 1975.
 281. Franse LV, Pahor M, Di Bari M, et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens* 18:1149, 2000.
 282. Young JL Jr, Boswell RB, Nies AS. Severe allopurinol hypersensitivity. Association with thiazides and prior renal compromise. *Arch Intern Med* 134: 553, 1974.
 283. Shahinfar RL, Simpson RL, Carides AD, et al. Safety of losartan in hypertensive patients with thiazide-induced hyperuricemia. *Kidney Int* 56:1879, 1999.
 284. Lim LS, Fink HA, Kuskowski MA, et al for the Osteoporotic Fractures in Men (MrOS) Study Group: Loop diuretic use and increased rates of hip bone loss in older men. *Arch Intern Med* 168: 735, 2008.
 285. Chang SW, Fine R, Siegel D, et al: The impact of diuretic therapy on reported sexual function [see comments]. *Arch Intern Med* 151:2402, 1991.
 286. Bansal S. Sexual dysfunction in hypertensive men. A critical review of the literature. *Hypertension* 12:1, 1988.
 287. Grimm RH Jr, Grandits GA, Prineas RJ, et al. Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Treatment of Mild Hypertension Study (TOMHS). *Hypertension* 29:8, 1997.
 288. Wassertheil-Smoller S, Blaufox MD, Oberman A, et al. Effect of antihypertensives on sexual function and quality of life: the TAIM study. *Ann Intern Med* 114:613, 1991.
 289. Kloner RA, Brown M, Prisant LM, et al. Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. Sildenafil Study Group. *Am J Hypertens* 14:70, 2001.
 290. Jeunemaitre X, Chatellier G, Kreft-Jais C, et al. Efficacy and tolerance of spironolactone in essential hypertension. *Am J Cardiol* 60: 820, 1987.
 291. Spironolactone and endocrine dysfunction. *Ann Intern Med* 85:630, 1976.
 292. Williams GH, Burgess E, Kolloch RE, et al. Efficacy of eplerenone versus enalapril as monotherapy in systemic hypertension. *Am J Cardiol* 93:990, 2004.
 293. Rybak LP: Ototoxicity of loop diuretics. *Otolaryngology Clin* 26:829, 1993.
 294. Rybak LP: Pathophysiology of furosemide ototoxicity. *J Otolaryngol* 11:127, 1982.
 295. Tuzel IH: Comparison of adverse reactions to bumetanide and furosemide. *J Clin Pharmacol* 21:615, 1981.
 296. Reineck HJ: Diuretic use in renal failure. In: Eknoyan G, Martinez-Maldonado M, eds. *The Physiological Basis of Diuretic Therapy in Clinical Medicine*. Orlando, FL: Grune & Stratton, 1986:298.
 297. Heidland A, Wigand ME: The effect of furosemide at high doses on auditory sensitivity in patients with uremia. *Klin Wochenschr* 48:1052, 1970.
 298. Fries D, Pozet N, Dubois N, et al: The use of large doses of frusemide in acute renal failure. *Postgrad Med J* 47:(Suppl):18, 1971.
 299. Beermann B, Dalen E, Lindstrom B, Rosen A: On the fate of furosemide in man. *Eur J Clin Pharmacol* 9:51, 1975.
 300. Brown CG, Ogg CS, Cameron JS, Bewick M: High-dose furosemide in acute reversible intrinsic renal failure. *Scot Med J* 19(Suppl):35, 1974.
 301. Addo HA, Ferguson J, Frain Bell W: Thiazide-induced photosensitivity: A study of 33 subjects. *Br J Dermatol* 116:749, 1987.
 302. Diffey BL, Langtry J: Phototoxic potential of thiazide diuretics in normal subjects. *Arch Dermatol* 125:1355, 1989.
 303. Frommer JP, Wesson DE, Eknoyan G: Side effects and complications of diuretic therapy. In: Eknoyan G, Martinez-Maldonado M, eds. *The Physiological Basis of Diuretic Therapy in Clinical Medicine*. Or-

- lando, FL: Grune & Stratton, 1986:293–309.
304. Schwarz A, Krause PH, Kunzendorf U, et al: The outcome of acute interstitial nephritis: Risk factors for the transition from acute to chronic interstitial nephritis. *Clin Nephrol* 54:179, 2000.
 305. Magil AB, Ballon HS, Cameron EC, Rae A: Acute interstitial nephritis associated with thiazide diuretics. Clinical and pathologic observations in three cases. *Am J Med* 69:939, 1980.
 306. Grossman E, Messerli FH, Goldbourt U: Does diuretic therapy increase the risk of renal cell carcinoma? *Am J Cardiol* 83:1090, 1999.
 307. Tenenbaum A, Grossman E, Fisman EZ, et al: Long-term diuretic therapy in patients with coronary disease: Increased colon cancer-related mortality over a 5-year follow up. *J Hum Hypertens* 15:373, 2001.
 308. Grossman E, Messerli FH, Goldbourt U. Carcinogenicity of cardiovascular drugs. *Curr Hypertens Rep* 1: 212, 1999.
 309. Corrao G, Scotti L, Bagnardi V, Sega R. Hypertension, antihypertensive therapy and renal-cell cancer: a meta-analysis. *Curr Drug Saf* 2:125, 2007.
 310. Lawson DH, Macadam RF, Singh MH, et al: Effect of furosemide on antibiotic-induced renal damage in rats. *J Infect Dis* 126:593, 1972.
 311. Shapiro S, Slone D, Lewis GP, et al: The epidemiology of digoxin toxicity. A study in three Boston hospitals. *J Chronic Dis* 22:361, 1969.
 312. Petersen V, Hvidt S, Thomsen K, et al: Effect of prolonged thiazide treatment on renal lithium clearance. *Br Med J* 3:143, 1974.
 313. Boer WH, Loomans HA, Dorhout Mees EJ: Effects of thiazides with and without carbonic-anhydrase inhibiting activity on free water and lithium clearance. In: Puschett J, Greenberg A, eds. *Diuretics III: Chemistry, Pharmacology, and Clinical Applications*. New York: Elsevier Science Publishing, 1990:31–33.
 314. Shirley DG, Walter SJ, Sampson B: A micropuncture study of renal lithium reabsorption: Effects of amiloride and furosemide. *Am J Physiol* 263:F1128, 1992.
 315. Bridgman JF, Rosen SM, Thorp JM: Complications during clofibrate treatment of nephrotic-syndrome hyperlipoproteinaemia. *Lancet* 2:506, 1972.
 316. Weinberg MS, Quigg RJ, Salant DJ, Bernard DB: Anuric renal failure precipitated by indomethacin and triamterene. *Nephron* 40:216, 1985.
 317. Packer M, Lee WH, Kessler P, et al: Identification of hyponatremia as a risk factor for the development of functional renal insufficiency during converting enzyme inhibition in severe chronic heart failure. *J Am Coll Cardiol* 10:837, 1987.
 318. Packer M Lee WH, Medina, et al: Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. *Ann Intern Med* 106:346, 1987.
 319. Schlondorff D: Renal prostaglandin synthesis: Sites of production and specific actions of prostaglandins. *Am J Med* 81:1, 1985.
 320. Sica DA: Dosage considerations with perindopril for systemic hypertension. *Am J Cardiol* 88(Suppl 7):13i, 2001.

References for Chapter 12

Magnesium, Potassium, and Calcium as Cardiovascular Disease Therapies

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1. Saris NE, Mervaala E, Karppanen H, et al: Magnesium: An update on physiological, clinical, and analytical aspects. *Clin Chim Acta* 294: 1, 2000.
2. Reinhart RA: Magnesium metabolism: A review with special reference to the relationship between intracellular content and serum levels. *Arch Intern Med* 148:2415, 1988.
3. Wacker WE, Parisi AF: Magnesium metabolism. *N Engl J Med* 278:658, 1968.
4. Altura BM, Altura BT: Role of magnesium in the pathogenesis of hypertension updated: relationship to its actions on cardiac, vascular smooth muscle, and endothelial cells. In: Laragh JN, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis and Management*. New York: Raven Press, 1995:1213.
5. Reinhart RA: Clinical correlates of the molecular and cellular actions of magnesium on the cardiovascular system. *Am Heart J* 121:1513, 1991.
6. Fox C, Ramsomair D, Carter C: Magnesium: Its proven and potential clinical significance. *South Med J* 94:1195, 2001.
7. Mroczek WJ, Lee WR, Davidov ME: Effect of magnesium sulfate on cardiovascular hemodynamics. *Angiology* 28:720, 1977.
8. Laurant P, Touyz RM: Physiological and pathophysiological role of magnesium in the cardiovascular system: Implications in hypertension. *J Hypertens* 18: 1177, 2000.
9. Iseri LT, French JH: Magnesium: nature's physiologic calcium blocker. *Am Heart J* 108:188, 1984.
10. Vigorito C, Giordano A, Ferraro P, et al: Hemodynamic effects of magnesium sulfate on the normal human heart. *Am J Cardiol* 67:1435, 1991.
11. Turlapaty PD, Altura BM: Magnesium deficiency produces spasms of coronary arteries: Relationship to etiology of sudden death ischemic heart disease. *Science* 208:198, 1980.
12. Arsenian MA: Magnesium and cardiovascular disease. *Prog Cardiovasc Dis* 35:271, 1993.
13. Satake K, Lee JD, Shimizu H, et al: Relation between severity of magnesium deficiency and frequency of anginal attacks in men with variant angina. *J Am Coll Cardiol* 28:897, 1996.
14. Cermuzynski L, Gebalska J, Wolk R, Makowska E: Hypomagnesemia in heart failure with ventricular arrhythmias. Beneficial effects of magnesium supplementation. *J Intern Med* 247:78, 2000.
15. Sheu JR, Hsiao G, Shen MY, et al. Mechanisms involved in the antiplatelet activity of magnesium in human platelets. *Br J Haematol* 119:1033, 2002.
16. Ravn HB. Pharmacological effects of magnesium on arterial thrombosis-mechanisms of action? *Magnes Res* 12 : 191, 1999.
17. Shechter M: The role of magnesium as antithrombotic therapy. *Wien Med Wochenschr* 150:343, 2000.
18. Sherer Y, Bitzur R, Cohen H, et al: Mechanisms of action of the anti-atherogenic effect of magnesium: Lessons from a mouse model. *Magnes Res* 14:173, 2001.
19. Shechter M, Sharir M, Labrador MJ, et al: Oral magnesium therapy improves endothelial function in patients with coronary artery disease. *Circulation* 102:2353, 2000.
20. Mazur A, Maier JA, Rock E, et al. Magnesium and the inflammatory response: potential pathophysiological implications. *Arch Biochem Biophys* 458: 48, 2007.
21. Leary WP, Reyes AJ, Lockett CJ, et al: Magnesium and deaths ascribed to ischaemic heart disease in South Africa. A preliminary report. *S Afr Med J*

- 64:775, 1983.
22. Yamori Y, Mizushima S: A review of the link between dietary magnesium and cardiovascular risk. *J Cardiovasc Risk* 7:31, 2000.
 23. Chipperfield B, Chipperfield JR: Heart-muscle magnesium, potassium, and zinc concentrations after sudden death from heart-disease. *Lancet* 2:293, 1973.
 24. Johnson CJ, Peterson DR, Smith EK: Myocardial tissue concentrations of magnesium and potassium in men dying suddenly from ischemic heart disease. *Am J Clin Nutr* 32:967, 1979.
 25. Abraham AS, Bar-On E, Eylath U: Changes in the magnesium content of tissues following myocardial damage in rats. *Med Biol* 59:99, 1981.
 26. Chang C, Bloom S: Interrelationship of dietary magnesium intake and electrolyte homeostasis in hamsters: I. Severe magnesium deficiency, electrolyte homeostasis, and myocardial necrosis. *J Am Coll Nutr* 4:173, 1985.
 27. Chakraborti S, Chakraborti T, Mandal M, et al. Protective role of magnesium in cardiovascular diseases: a review. *Mol Cell Biochem* 238:163, 2002.
 28. Steurer G, Yang P, Rao V, et al: Acute myocardial infarction, reperfusion injury, and intravenous magnesium therapy: Basic concepts and clinical implications. *Am Heart J* 132: 478, 496, 1996.
 29. Teo KK, Yusuf S, Collins R, et al: Effects of intravenous magnesium in suspected acute myocardial infarction: Overview of randomised trials. *BMJ* 303:1499, 1991.
 30. Woods KL, Fletcher S, Roffe C, Haider Y: Intravenous magnesium sulphate in suspected acute myocardial infarction: Results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 339:1553, 1992.
 31. ISIS-4: A randomized factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 345:669, 1995.
 32. Ziegelstein RC, Hilbe JM, French WJ, et al: Magnesium use in the treatment of acute myocardial infarction in the United States (Observations from the Second National Registry of Myocardial Infarction). *Am J Cardiol* 87:7, 2001.
 33. Woods KL, Fletcher S: Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: The second Leicester Intravenous magnesium Intervention Trial (LIMIT-2). *Lancet* 343:816, 1994.
 34. Roffe C, Fletcher S, Woods KL: Investigation of the effects of intravenous magnesium sulphate on cardiac rhythm in acute myocardial infarction. *Br Heart J* 71:141, 1994.
 35. Shechter M, Hod H, Kaplinsky E, Rabinowitz B: The rationale of magnesium as alternative therapy for patients with acute myocardial infarction without thrombolytic therapy. *Am Heart J* 132:483, 1996.
 36. Antman EM: Magnesium in acute myocardial infarction: Overview of available evidence. *Am Heart J* 132:487, 1996.
 37. Woods KL, Abrams K: The importance of effect mechanism in the design and interpretation of clinical trials: The role magnesium in acute myocardial infarction. *Prog Cardiovasc Dis* 44:267, 2002.
 38. Shechter M, Hod H, Chouraqui P, et al: Magnesium therapy in acute myocardial infarction when patients are not candidates for thrombolytic therapy. *Am J Cardiol* 75:321, 1995.
 39. Caspi J, Rudis E, Bar I, et al: Effects of magnesium on myocardial function after coronary artery bypass grafting. *Ann Thorac Surg* 59:942, 1995.
 40. Toraman F, Karabulut EH, Alhan HC, et al: Magnesium infusion dramatically decreases the incidence of atrial fibrillation after coronary artery bypass grafting. *Ann Thorac Surg* 72:1256, 2001.
 41. Kinoshita K, Oe M, Tokunaga K: Superior protective effect of low-calcium, magnesium-free potassium cardioplegic solution on ischemic myocardium. Clinical study in comparison with St. Thomas' Hospital solution. *J Thorac Cardiovasc Surg* 101:695, 1991.
 42. Demmy TL, Haggerty SP, Boley TM, Curtis JJ: Lack of cardioplegia uniformity in clinical myocardial preservation. *Ann Thorac Surg* 57:648, 1994.
 43. Santoro GM, Antonucci D, Bolognese L, et al: A randomized study of intravenous magnesium in acute myocardial infarction treated with direct coronary angioplasty. *Am Heart J* 140:891, 2000.
 44. Magnesium in Coronaries (MAGIC) Trial Investigators. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the Magnesium in Coronaries (MAGIC) Trial: a randomised controlled trial. *Lancet* 360:1189, 2002.
 45. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction—Executive Summary. *Circulation*. 110:588, 2004.
 46. Li J, Zhang Q, Zhang M, Egger M. Intravenous magnesium for acute myocardial infarction. *Cochrane Database Syst Rev* 18: (2): CD002755, 2007.
 47. Jackson CE, Meier DW: Routine serum magnesium analysis. Correlation with clinical state in 5,100 patients. *Ann Int Med* 69:743, 1968.

48. Tosiello L: Hypomagnesemia and diabetes mellitus. A review of clinical implications. *Arch Intern Med* 156:1143, 1996.
49. Lima MD, Cruz T, Pousada JC, et al: The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. *Diabetes Care* 21:682, 1998.
50. Sjogren A, Floren CH, Nilsson A: Magnesium, potassium and zinc deficiency in subjects with type II diabetes mellitus. *Acta Med Scand* 224:461, 1988.
51. Agus ZS: Hypomagnesemia. *J Am Soc Nephrol* 10:1616, 1999.
52. Leier CV, Dei Cas L, Metra M: Clinical relevance and management of the major electrolyte abnormalities in congestive heart failure: Hyponatremia, hypokalemia, and hypomagnesemia. *Am Heart J* 128:564, 1994.
53. Cohen N, Alon I, Almozni-Sarafian D, et al: Metabolic and clinical effects of oral magnesium supplementation in furosemide-treated patients with severe congestive heart failure. *Clin Cardiol* 23:433, 2000.
54. Wester PO, Dyckner T: Diuretic treatment and magnesium losses. *Acta Med Scand* 647(Suppl):145, 1981.
55. Chase LR, Slatopolsky E: Secretion and metabolic efficiency of parathyroid hormone in patients with severe hypomagnesemia. *J Clin Endocrinol Metab* 38:363, 1974.
56. Leicht E, Schmidt-Gayk H, Langer HJ, et al: Hypomagnesaemia-induced hypocalcaemia: Concentrations of parathyroid hormone, prolactin and 1,25-dihydroxyvitamin D during magnesium replenishment. *Magnes Res* 5:33, 1992.
57. Dyckner T, Wester PO, Widman L: Amiloride prevents thiazide-induced intracellular potassium and magnesium losses. *Acta Med Scand* 224: 25, 1988.
58. Bo S, Pisu E. Role of dietary magnesium in cardiovascular disease prevention, insulin sensitivity and diabetes. *Curr Opin Lipidol* 19:50, 2008.
59. Belin RJ, He K. Magnesium physiology and pathogenic mechanisms that contribute to the development of the metabolic syndrome. *Magnes Res* 20: 107, 2007.
60. Wester PO: Electrolyte balance in heart failure and the role for magnesium ions. *Am J Cardiol* 70:44C, 1992.
61. Eichhorn EJ, Tandon PK, DiBianco R, et al: Clinical and prognostic significance of serum magnesium concentration in patients with severe chronic congestive heart failure: The PROMISE Study. *J Am Coll Cardiol* 21:634, 1993.
- 61a. Peacock JM, Ohira T, Post W, et al: Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 160: 464, 2010.
62. Gottlieb SS, Fisher ML, Pressel MD, et al: Effects of intravenous magnesium sulfate on arrhythmias in patients with congestive heart failure. *Am Heart J* 125:1645, 1993.
63. Sueta CA, Clarke SW, Dunlap SH, et al: Effect of acute magnesium administration on the frequency of ventricular arrhythmia in patients with heart failure. *Circulation* 89:660, 1994.
64. Bashir Y, Sneddon JF, Staunton HA, et al: Effects of long-term oral magnesium chloride replacement in congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 72:1156, 1993.
65. Cohen L, Kitzes R: Magnesium sulfate and digitalis-toxic arrhythmias. *JAMA* 249:2808, 1983.
66. Crippa G, Sverzellati E, Giorgi-Pierfranceschi M, Carrara GC: Magnesium and cardiovascular drugs: Interactions and therapeutic role. *Ann Ital Med Int* 14:40, 1999.
67. Dyckner T, Wester PO: Ventricular extrasystoles and intracellular electrolytes before and after potassium and magnesium infusions in patients on diuretic treatment. *Am Heart J* 97:12, 1979.
68. McLean RM: Magnesium and its therapeutic uses: A review. *Am J Med* 96:63, 1994.
69. Ho KM. Intravenous magnesium for cardiac arrhythmias: jack of all trades. *Magnes Res* 21: 65, 2008.
70. Hirahara K, Matsubayashi T, Matsuura H, Ehara T: Intracellular magnesium depletion depresses the delayed rectifier potassium current in guinea pig ventricular myocytes. *Jpn J Physiol* 48:81, 1998.
71. Ghani MF, Rabah M: Effect of magnesium chloride on electrical stability of the heart. *Isr Heart J* 94:600, 1977.
72. McDaniel WC, Curtis JJ, Walls JT, Madsen RW. Effects of magnesium sulfate on electrical ventricular defibrillation of dogs. *J Electrocardiol* 31:137, 1998.
73. Dyckner T, Wester PO: Magnesium deficiency contributing to ventricular tachycardia. Two case reports. *Acta Med Scand* 212:89, 1982.
74. Iseri LT: Magnesium and cardiac arrhythmias. *Magnesium* 5:111, 1986.
75. Tsuji H, Venditti FJ Jr, Evans JC, et al: The association of levels of serum potassium and magnesium with ventricular premature complexes (the Framingham Heart Study). *Am J Cardiol* 74: 232, 1994.
76. Shiga T, Wajima Z, Inoue T, Ogawa R: Magnesium prophylaxis for arrhythmias after cardiac surgery: a meta-analysis of randomized controlled trial. *Am J Med* 117: 325, 2004.
77. Hoes AW, Grobbee DE, Lubsen J, et al: Diuretics, β -blockers, and the risk for sudden cardiac death

- in hypertensive patients. *Ann Intern Med* 123:481, 1995.
78. Allegra J, Lavery R, Cody R, et al: Magnesium sulfate in the treatment of refractory ventricular fibrillation in the pre-hospital setting. *Resuscitation* 49:245, 2001.
 79. Allen BJ, Brodsky MA, Capparelli EV, et al: Magnesium sulfate therapy for sustained monomorphic ventricular tachycardia. *Am J Cardiol* 15:64:1202, 1989.
 80. Ramee SR, White CJ, Svinarich JT, et al: Torsades de pointes and magnesium deficiency. *Am Heart J* 109:164, 1985.
 81. Tzivoni D, Banai S, Schuger C, et al: Treatment of torsades de pointes with magnesium sulfate. *Circulation* 77:392, 1988.
 82. Shingu T, Matsuura H, Kusaka M, et al: Significance of intracellular free calcium and magnesium and calcium-regulating hormones with sodium chloride loading in patients with essential hypertension. *J Hypertens* 9:1021, 1991.
 83. Hatzistavri LS, Sarafidis PA, Georgianos PI, et al: Oral magnesium supplementation reduces ambulatory blood pressure in patients with mild hypertension. *Am J Hypertens* 22:1070, 2009.
 84. McCarron DA: Calcium and magnesium nutrition in human hypertension. *Ann Intern Med* 98:800, 1983.
 85. Joffres MR, Reed DM, Yano K: Relationship of magnesium intake and other dietary factors to blood pressure: The Honolulu Heart Study. *Am J Clin Nutr* 45:469; 1987.
 86. Peacock JM, Folsom AR, Arnett DK, et al: Relationship of serum and dietary magnesium to incident hypertension: The Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol* 9:159, 1999.
 87. Houston MC, Harper KJ. Potassium, magnesium, and calcium: their role in both the cause and treatment of hypertension. *J Clin Hypertens (Greenwich)* 10(7 Suppl 2):3, 2008.
 88. Resnick LM, Gupta RK, Laragh JH: Intracellular free magnesium in erythrocytes of essential hypertension: Relation to blood pressure and serum divalent cations. *Proc Natl Acad Sci U S A* 81: 6511, 1984.
 89. Vollmer WM, Sacks FM, Ard J, et al: Effects of diet and sodium intake on blood pressure: Subgroup analysis of the DASH-Sodium Trial. *Ann Intern Med* 135:1019, 2001.
 90. Ascherio A, Hennekens C, Willett WC, et al: Prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertension* 27:1065, 1996.
 91. Yamamoto ME, Applegate WB, Klag MJ, et al: Lack of blood pressure effect with calcium and magnesium supplementation in adults with high-normal blood pressure. Results from Phase I of the Trials of Hypertension Prevention (TOHP). Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 5:96, 1995.
 92. Lind L, Lithell H, Pollare T, Ljunghall S: Blood pressure response during long-term treatment with magnesium is dependent on magnesium status. A double-blind, placebo-controlled study in essential hypertension and in subjects with high normal blood pressure. *Am J Hypertens* 4:674, 1991.
 93. Cappuccio FP, Markandu ND, Benynon GW, et al: Lack of effect of oral magnesium on high blood pressure: A double blind study. *BMJ* 291:235, 1985.
 94. Henderson DG, Schierup J, Schodt J: Effect of magnesium supplementation on blood pressure and electrolyte concentrations in hypertensive patients receiving long-term diuretic treatment. *BMJ* 293: 664, 1986.
 95. Nowson CA, Morgan TO: Magnesium supplementation in mild hypertensive patients on a moderately low sodium diet. *Clin Exp Pharmacol Toxicol* 16:299, 1989.
 96. Ferrara LA, Iannuzzi R, Castaldo A, et al: Long-term magnesium supplementation in essential hypertension. *Cardiology* 81:25, 1992.
 97. Hatzistavri LS, Sarafidis PA, Georgianos PI, et al. Oral magnesium supplementation reduces ambulatory blood pressure in patients with mild hypertension. *Am J Hypertens* 22:1070, 2009.
 98. Harlan WR, Harlan LC: Blood pressure and calcium and magnesium intake. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis and Management*. New York: Raven Press, 1995:1143.
 99. Lu JF, Nightingale CH: Magnesium sulfate in eclampsia and pre-eclampsia: Pharmacokinetic principles. *Clin Pharmacokinet* 38:305, 2000.
 100. Witlin AG, Sibai BM: Magnesium sulfate in pre-eclampsia and eclampsia. *Obstet Gynecol* 92:883, 1998.
 101. Simunic M, Rumboldt Z, Ljutic D, et al. Ramipril decreases chlorthalidone-induced loss of magnesium and potassium in hypertensive patients. *J Clin Pharmacol* 35:1150, 1995.
 102. Keyrouz SG, Diringer MN. Clinical review: Prevention and therapy of vasospasm in subarachnoid hemorrhage. *Crit Care* 11; 220, 2007
 103. Vink R, Cook NL, van den Heuvel C. Magnesium in acute and chronic brain injury: an update. *Magnes Res* 22:158S, 2009.
 104. Larsson SC, Virtanen MJ, Mars M, et al: Magne-

- sium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. *Arch Intern Med* 168: 459, 2008.
105. Muir KW: Magnesium for neuroprotection in ischaemic stroke: Rationale for use and evidence of effectiveness. *CNS Drugs* 15:921, 2001.
 106. Lampl Y, Gilad R, Geva D, et al: Intravenous administration of magnesium sulfate in acute stroke: A randomized double-blind study. *Clin Neuropharmacol* 24:1, 2001.
 107. Cortés YE, Moses L. Magnesium disturbances in critically ill patients. *Compend Contin Educ Vet* 29: 420, 2007.
 108. Elliott C, Newman N, Madan A: Gentamicin effects on urinary electrolyte excretion in healthy subjects. *Clin Pharmacol Ther* 67:16, 2000.
 109. Kingston ME, Al-Siba'i MB, Skooge WC: Clinical manifestations of hypomagnesemia. *Crit Care Med* 14:950, 1986.
 110. Gettes LS: Electrolyte abnormalities underlying lethal and ventricular arrhythmias. *Circulation* 85(Suppl I):I70, 1992.
 111. Chen WC, Fu XX, Pan ZJ, Qian SZ: ECG changes in early stage of magnesium deficiency. *Am Heart J* 104:1115, 1982.
 112. Iseri LT, Freed J, Bures AR: Magnesium deficiency and cardiac disorders. *Am J Med* 58:837, 1975.
 113. Gullestad L, Midtvedt K, Dolva LO, et al: The magnesium-loading test: Reference values in healthy subjects. *Scand J Clin Lab Invest* 54:23, 1994.
 114. Rob PM, Dick K, Bley N, et al: Can one really measure magnesium deficiency using the short-term magnesium loading test? *J Intern Med* 246:373, 1999.
 115. Martin KJ, González EA, Slatopolsky E. Clinical consequences and management of hypomagnesemia. *J Am Soc Nephrol* 20:2291, 2009.
 116. He K, Liu K, Daviglius ML, et al: Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation* 113: 1675, 2006.
 117. Sica DA, Struthers AD, Cushman WC, et al: Importance of potassium in cardiovascular disease. *J Clin Hypertens* 4:1, 2002.
 - 117a. Bowling CB, Pitt B, Ahmed MI, et al: Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease. Findings from propensity-matched studies. *Circ Heart Fail* 3: 253, 2010.
 - 117b. Chatterjee R, Yeh H-C, Shafi T, et al: Serum and dietary potassium and risk of incident type 2 diabetes mellitus. The Atherosclerosis Risk in Communities (ARIC) Study. *Arch Intern Med* 170: 1745, 2010.
 118. Young DB: Control, cardiovascular, and renal effects of potassium. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis and Management*. New York: Raven Press, 1995:1503.
 119. Young DB, Lin H, McCabe RD: Potassium's cardiovascular protective mechanisms. *Am J Physiol* 268:R825, 1995.
 120. Fang J, Madhavan S, Alderman MH: Dietary potassium intake and stroke mortality. *Stroke* 31:1532, 2000.
 121. Bazzano LA, he J, Ogden LG, et al: Dietary potassium intake and risk of stroke in US men and women. National Health and Nutrition Examination Survey I Epidemiologic Follow-Up Study. *Stroke* 32:1473, 2001.
 122. Cohen HW, Madhavan S, Alderman MH: High and low serum potassium associated with cardiovascular events in diuretic-treated patients. *J Hypertens* 19:1315, 2001.
 123. Franse LV, Pahor M, DiBari M, et al: Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. *Hypertension* 35:1025, 2000.
 124. Sanguinetti MC: Modulation of potassium channels by antiarrhythmic and antihypertensive drugs. *Hypertension* 19:228, 1992.
 125. Singh H, Linas SL: Potassium therapy and hypertension. *Miner Electrolyte Metab* 19:57, 1993.
 126. Morris RC Jr, Sebastian A: Potassium-responsive hypertension. In: Laragh, JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis and Management*, 2nd ed. New York: Raven Press, 1995:2715.
 127. Tobian L: The protective effects of high-potassium diets in hypertension, and the mechanisms by which high-NaCl diets produce hypertension—a personal view. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis and Management*, 2nd ed. New York: Raven Press, 1995:299.
 128. Siani A, Strazzullo P: Relevance of dietary potassium intake to antihypertensive drug treatment. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis and Management*, 2nd ed. New York: Raven Press, 1995:2727.
 129. Khaw KT, Barrett-Connor E: Dietary potassium and blood pressure in a population. *Am J Clin Nutr* 39: 963; 1984.
 130. Khaw KT, Rose G: Population study of blood pressure and associated factors in St. Lucia, West Indies. *Int J Epidemiol* 11:372, 1982.
 131. Reed D, McGee D, Yano K, Hankin J: Diet, blood pressure, and multicollinearity. *Hypertension* 7:405, 1985.
 132. Cook NR, Obarzanek E, Cutler JA, et al. Trials of Hypertension Prevention Collaborative Research Group. Joint effects of sodium and potassium in-

- take on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. *Arch Intern Med* 169:32, 2009.
133. Pietinen PI, Wong O, Altschul AM: Electrolyte output, blood pressure, and family history of hypertension. *Am J Clin Nutr* 32:997, 1979.
 134. Grim CE, Luft FC, Miller JZ, et al: Racial differences in blood pressure in Evans County, Georgia: Relationship to sodium and potassium intake and plasma renin activity. *J Chronic Dis* 33:87, 1980.
 135. Turban S, Miller ER 3rd, Ange B, Appel LJ: Racial differences in urinary potassium excretion. *J Am Soc Nephrol* 19:1396, 2008.
 136. Whelton PK: Potassium and blood pressure. In Izzo JL Jr., Sica DA, Black HR (eds): *Hypertension Primer 4th ed.* American Heart Assn, Dallas 2008:305.
 137. Appel LJ, on behalf of the American Society of Hypertension Writing Group: ASH position paper: dietary approaches to lower blood pressure. *J Clin Hypertens* 11:358, 2009.
 138. Fujita T, Ando K: Hemodynamic and endocrine changes associated with potassium supplementation in sodium-loaded hypertensives. *Hypertension* 6:184, 1984.
 139. Young DB, McCaa RE, Pan YJ, Guyton AC: The natriuretic and hypotensive effects of potassium. *Circ Res* 38(Suppl 2):84, 1976.
 140. Wilson DK, Sica DA, Miller SB: Effects of potassium on blood pressure in salt-sensitive and salt-resistant black adolescents. *Hypertension* 34:181, 1999.
 141. Cappuccio FP, MacGregor GA: Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *J Hypertens* 9:465, 1991.
 142. Kawano Y, Minami J, Takishita S, Omae T: Effects of potassium supplementation on office, home, and 24-h blood pressure in patients with essential hypertension. *Am J Hypertens* 11:1141, 1998.
 143. Gu D, He J, Wu X, et al: Effect of potassium supplementation on blood pressure in Chinese: A randomized, placebo-controlled trial. *J Hypertens* 19:1325, 2001.
 144. Whelton PK, He J, Cutler JA, et al: Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA* 277:1624, 1997.
 145. Smith SR, Klotman PE, Svetkey LP: Potassium chloride lowers blood pressure and causes natriuresis in older patients with hypertension. *J Am Soc Nephrol* 2:1302, 1992.
 146. Fotherby MD, Potter JF: Potassium supplementation reduces clinic and ambulatory blood pressure in elderly patients. *J Hypertens* 10:1403, 1992.
 147. Svetkey LP, Simons-Morton D, Vollmer WM, et al: Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Arch Intern Med* 159:285, 1999.
 148. Sacks FM, Svetkey LP, Vollmer WM, et al: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 344:3, 2001.
 149. Kaplan NM, Carnegie A, Ruskin P, et al: Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. *N Engl J Med* 312:746, 1985.
 150. Salvetti A, Bishisao E, Caiazza A, et al: The combination of a low Na/high K salt with metoprolol in the treatment of mild-moderate hypertension. A multicenter study. *Am J Hypertens* 1:201S, 1988.
 151. Khaw KT, Barrett-Connor E: Dietary potassium and stroke-associated mortality. A 12-year prospective population study. *N Engl J Med* 316:235, 1987.
 152. Ascherio A, Rimm EB, Hernan MA, et al: Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation* 98:1198, 1998.
 153. Fang J, Madhavan S, Alderman MH: Dietary potassium intake and stroke mortality. *Stroke* 31:1532, 2000.
 154. Larsson SC, Virtanen MJ, Mars M, Männistö S, et al: Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. *Arch Intern Med* 168:459, 2008.
 155. US FDA Center for Food Safety and Applied Nutrition Health claim notification for potassium-containing foods. Available at [http://www.fda.gov/Food/LabelingNutrition/LabelClaims/FDA Modernization Act FD AMAClaims/ucm073606.htm](http://www.fda.gov/Food/LabelingNutrition/LabelClaims/FDA%20Modernization%20Act%20FD%20AMAClaims/ucm073606.htm). Accessed 1/31/10.
 156. Steinberg D, Parthasarathy S, Carew TE, et al: Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 320:915, 1989.
 157. Steinbrecher UP, Zhang H, Longheed M: Role of oxidative modification of low-density lipoprotein in atherosclerosis. *Free Radic Biol Med* 9:155, 1990.
 158. Tobian L, Jahner TM, Johnson MA: High potassium diets markedly reduce atherosclerotic cholesterol ester deposition in aortas of rats with hypercholesterolemia and hypertension. *Am J Hypertens* 3:133, 1990.
 159. Young DB, Ma G: Vascular protective effects of potassium. *Semin Nephrol* 19:477, 1999.
 160. Cavusoglu E, Chopra V, Gupta A, et al: Relation of

- baseline serum potassium levels to angiographic findings in patients with known or suspected coronary artery disease. *Am J Hypertens* 22: 754, 2009.
161. Fang J, Madhavan S, Cohen H, Alderman MH: Serum potassium and cardiovascular mortality. *J Gen Intern Med* 15: 885, 2000.
 162. Rardon DP, Fisch C: Electrolytes and the heart. In: Schlant RC, Alexander RW, eds. *Hurst's The Heart*, 8th ed. New York: McGraw Hill, 1994:768.
 163. Diercks DB, Shumaik GM, Harrigan RA, et al. Electrocardiographic manifestations: electrolyte abnormalities. *J Emerg Med* 27:153, 2004.
 164. Surawicz B: Electrolytes, hormones, temperature, and miscellaneous factors. In: *Electrophysiologic Basis of ECG and Cardiac Arrhythmias*. Baltimore: Williams Wilkins, 1995:426.
 165. Wahr JA, Parks R, Boisvert D, et al: Preoperative serum potassium levels and perioperative outcomes in cardiac surgery patients. Multicenter Study of Perioperative Ischemia Research Group. *JAMA* 281:2203, 1999.
 166. Reid JL, Whyte KF, Struthers AD: Epinephrine-induced hypokalemia: The role of beta adrenoceptors. *Am J Cardiol* 57:23F, 1986.
 167. Newhouse MT, Chapman KR, McCallum AL, et al: Cardiovascular safety of high doses of inhaled fenoterol and albuterol in acute severe asthma. *Chest* 110:595, 1996.
 168. Salerno DM, Murakami M, Elsperger KJ: Effects of pretreatment with propranolol on potassium, calcium, and magnesium shifts after ventricular fibrillation in dogs. *J Lab Clin Med* 114:595, 1989.
 169. Wijesinghe M, Weatherall M, Perrin K, et al. Risk of mortality associated with formoterol: a systematic review and meta-analysis. *Eur Respir J* 34: 803, 2009.
 170. Cohn JN, Kowey PR, Whelton PK, Prisant LM: New guidelines for potassium replacement in clinical practice: A contemporary review by the National Council on potassium in Clinical Practice. *Arch Intern Med* 160: 2429, 2000.
 171. Norris W, Kunzelman KS, Bussell S, et al Potassium supplementation, diet vs pills. A randomized trial of postoperative cardiac surgery patients. *Chest* 125: 404, 2004.
 172. Perezella MA: Drug-induced hyperkalemia: Old culprits and new offenders. *Am J Med* 109:307, 2000.
 173. Schepkens H, Vanholder R, Billiow JM, Lameire N: Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: An analysis of 25 cases. *Am J Med* 110:438, 2001.
 174. Kruse JA, Clark VL, Carlson RW, Geheb MA: Concentrated potassium chloride infusions in critically ill patients with hypokalemia. *J Clin Pharmacol* 34:1077, 1994.
 175. Kruse JA, Carlson RW: Rapid correction of hypokalemia using concentrated intravenous potassium chloride infusions. *Arch Intern Med* 150:613, 1990.
 176. Famularo G, Corsi FM, Giacanelli M: Iatrogenic worsening of hypokalemia and neuromuscular paralysis associated with the use of glucose solutions for potassium replacement in a young woman with licorice intoxication and furosemide abuse. *Acad Emerg Med* 6:960, 1999.
 177. He FJ, MacGregor GA: Beneficial effects of potassium. *BMJ* 323:497, 2001.
 178. Gennari FJ: Hypokalemia. *N Engl J Med* 339:451, 1998.
 179. Macdonald JE, Struthers AD: What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* 43: 155, 2004.
 180. Hatton DC, Young EW, Bukoski RD, McCarron DA: Calcium metabolism in experimental genetic hypertension. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis and Management*. New York: Raven Press, 1995:1193.
 181. Oparil S: Diet-micronutrients—special foods. In: Oparil S, Weber M, eds. *Hypertension: A Companion to the Kidney*. Philadelphia: Saunders, 2000:433.
 182. Fleckenstein-Grun G, Frey M, Thimm F, et al: Calcium overload—an important cellular mechanism in hypertension and arteriosclerosis. *Drugs* 44(Suppl 1):23, 1992.
 183. Sowers JR, Standley PR, Tuck ML, Ram JL: Calcium and calcium-regulatory hormones in hypertension. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis and Management*. New York: Raven Press, 1995:1155.
 184. Zemel MB: Calcium modulation of hypertension and obesity: Mechanisms and implications. *J Am Coll Nutr* 20 (Suppl 5): 428S, 2001.
 185. Sica DA, Harford AM, Zawada ET: Hypercalcemic hypertension in hemodialysis. *Clin Nephrol* 22:102, 1984.
 186. Quereda C, Orte L, Sabater J, et al: Urinary calcium excretion in treated and untreated essential hypertension. *J Am Soc Nephrol* 7:1058, 1996.
 187. Yamakawa H, Suzuki H, Nakamura M, et al: Disturbed calcium metabolism in offspring of hypertensive parents. *Hypertension* 19:528, 1992.
 188. Jorde R, Sundsfjord J, Haug E, Bonna KH: Relation between low calcium intake, parathyroid hormone, and blood pressure. *Hypertension* 35:1154, 2000.
 189. Jorde R, Bonna KH, Sundsfjord J: Population based study on serum ionized calcium, serum parathyroid hormone, and blood pressure. The Tromso

- study. *Eur J Endocrinol* 141:350, 1999.
190. Hagstrom E, Hellman P, Larsson TE, et al: Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. *Circulation* 119:2765, 2009.
 191. Bucher HC, Cook RJ, Guyatt GH, et al: Effects of dietary calcium supplementation on blood pressure. A meta-analysis of randomized controlled trials. *JAMA* 275:1016, 1996.
 192. Allender PS, Cutler JA, Follmann D, et al: Dietary calcium and blood pressure: A meta-analysis of randomized clinical trials. *Ann Intern Med* 124:825, 1996.
 193. Pikilidou MI, Befani CD, Sarafidis PA, Oral calcium supplementation ambulatory blood pressure and relation to changes in intracellular ions and sodium-hydrogen exchange. *Am J Hypertens* 22:1263, 2009.
 194. Griffith LE, Guyatt GH, Cook RJ, et al: The influence of dietary and non-dietary calcium supplementation on blood pressure: An updated meta-analysis of randomized controlled trials. *Am J Hypertens* 12:84, 1999.
 195. Domrongkitchaiporn S, Ongphiphadhanakul B, Stitchantrakul W, et al: Risk of calcium oxalate nephrolithiasis after calcium or combined calcium and calcitriol supplementation in postmenopausal women. *Osteoporosis Int* 11:486, 2000.
 196. Bucher HC, Guyatt GH, Cook RJ, et al: Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: A meta-analysis of randomized controlled trials. *JAMA* 275:1113, 1996.
 197. Niromanesh S, Laghahi S, Mosavi-Jarrahi A: Supplementary calcium in prevention of pre-eclampsia. *Int J Gynaecol Obstet* 74:17, 2001.
 198. Hofmyr GJ, Duley L, Atallah A. Dietary calcium supplementation for prevention of pre-eclampsia and related problems: a systematic review and commentary. *BJOG* 114:933, 2007.
 199. LeWinter MM, Osol G: Normal physiology of the cardiovascular system. In: Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's the Heart*, 10th ed. New York: McGraw Hill, 2001:63-94.
 200. Figueredo VM, Camacho SA: Basic mechanisms of myocardial dysfunction: Cellular pathophysiology of heart failure. *Curr Opin Cardiol* 9:272, 1994.
 201. Dhalla NS, Afzal N, Beamish RE, et al: Pathophysiology of cardiac dysfunction in congestive heart failure. *Can J Cardiol* 9:873, 1993.
 202. Ornato JP, Gonzalez ER, Morkunas AR, et al: Treatment of presumed asystole during pre-hospital cardiac arrest: Superiority of electrical countershock. *Am J Emer Med* 3:395, 1985.
 203. Stempien A, Katz AM, Messineo FC: Calcium and cardiac arrest. *Ann Intern Med* 105:603, 1986.
 204. Kelsch T, Kikuchi K, Vahdat S, Frishman WH: Innovative pharmacologic approaches to cardiopulmonary resuscitation. *Heart Dis* 3:46, 2001.
 205. Kirsch JR, Dean JM, Rogers MC: Current concepts in brain resuscitation. *Arch Intern Med* 146:1413, 1986.
 206. Dembo DH: Calcium in advanced life support. *Crit Care Med* 9:358, 1981.
 207. Follette DM, Fey K, Buckberg GD, et al: Reducing postischemic damage by temporary modification of reperfusate calcium, potassium, pH, and osmolarity. *J Thorac Cardiovasc Surg* 82:221, 1981.
 208. Hessen SE, Michelson EL: Mechanisms of ventricular arrhythmias: From laboratory to bedside. *Am Coll Cardiol Curr J Rev* 4:11, 1995.
 209. White RD, Goldsmith RS, Rodriguez R, et al: Plasma ionic calcium levels following injection of chloride, gluconate, and gluceptate salts of calcium. *J*

References for Chapter 13

Inotropic Agents

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1. Warner Stevenson L: Inotropic therapy for heart failure. *N Engl J Med* 339:1848, 1998.
2. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure: *J Am Coll Cardiol* 46: e1, 2005.
 - 2a. Jefferies JL, Towbin JA: Dilated cardiomyopathy. *Lancet* 375: 752, 2010.
 - 2b. Goldhaber JJ, Hamilton MA: Role of inotropic agents in the treatment of heart failure. *Circulation* 121: 1655, 2010.
3. LeJemtel TH, Sonnenblick EH, Frishman WH: Diagnosis and management of heart failure. In: Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's The Heart*, 11th ed. New York: McGraw-Hill, 2004:723.
4. Ferguson DW: Digitalis and neurohormonal abnormalities in heart failure and implications for therapy. *Am J Cardiol* 69:24G, 1992.
5. Felker GM, O'Connor CM: Inotropic therapy for heart failure: An evidence-based approach. *Am Heart J* 142:393, 2001.
6. Burger AJ, Elkayam U, Neibaur MT, et al: Comparison of the occurrence of ventricular arrhythmias in patients with acutely decompensated congestive heart failure receiving dobutamine versus nesiritide therapy. *Am J Cardiol* 88:35, 2001.
7. Patel MB, Kaplan IV, Patni RN, et al: Sustained improvement in flow mediated vasodilation after short-term administration of dobutamine in patients with severe congestive heart failure. *Circulation* 99:60, 1999.
8. Drazner MH, Solomon MA, Thompson B, Yancy CW: Tailored therapy using dobutamine and nitroglycerin in advanced heart failure. *Am J Cardiol* 84:941, 1999.
9. Withering W: *An Account of the Foxglove, And Some of Its Medical Uses: With Practical Remarks on Dropsy and other Diseases*. London: GGJ and J Robinson, 1785.
10. Fothergill JM: *Digitalis: Its Mode of Action*. London, 1871.
11. Dock W, Tainter ML: The circulatory changes after full therapeutic doses of digitalis, with critical discussion of views on cardiac output. *J Clin Invest* 8:467, 1929.
12. Fisch C: William Withering: An account of the foxglove and some of its medical uses, 1785–1985. *J Am Coll Cardiol* 5:1A, 1985.
13. Gillis RA, Quest JA: The role of the nervous system in the cardiovascular effects of digitalis. *Pharmacol Rev* 31:19, 1980.
14. Rahimtoola SH, Tak T: The use of digitalis in heart failure. *Curr Probl Cardiol* 21:785, 1996.
15. Fozzard HA, Sheets MF: Cellular mechanism of action of cardiac glycosides. *J Am Coll Cardiol* 5:10A, 1985.
16. Charlemagne D: Molecular and cellular level of action of digitalis. *Herz* 18:79, 1993.
17. Scholz H: Inotropic drugs and their mechanisms of action. *J Am Coll Cardiol* 4:389, 1984.
18. Siri FM, Krueger JW, Nordin C, et al: Depressed intracellular calcium transients and contraction in myocytes from hypertrophied and failing guinea pig hearts. *Am J Physiol* 261:H514, 1991.
19. Li P, Park C, Micheletti R, et al: Myocyte performance during evolution of myocardial infarction in rats: Effects of propionyl-L-carnitine. *Am J*

- Physiol* 268:H1702, 1995.
20. Rosen MR: Cellular electrophysiology of digitalis toxicity. *J Am Coll Cardiol* 5:22A, 1985.
 21. Smith TW, Antman EM, Friedman PL, et al: Digitalis glycosides: Mechanisms and manifestations of toxicity. Parts I, II, III. *Prog Cardiovasc Dis* 26:413, 495; 27:21, 1984.
 22. Wantanabe AM: Digitalis and the autonomic nervous system. *J Am Coll Cardiol* 5:35A, 1985.
 23. Newton GE, Tong JH, Schofield AM, et al: Digoxin reduces cardiac sympathetic activity in severe congestive heart failure. *J Am Coll Cardiol* 28:155, 1996.
 24. Wenger T, Butler VP Jr., Haber E, Smith TW: Digoxin-specific antibody treatment of digitalis toxicity. In: Erdmann E, Greeff K, Skou JC, eds. *Update in Cardiac Glycosides 1785–1985*. New York: Springer-Verlag, 1986:377–388.
 25. Braunwald E, Ross J Jr, Sonnenblick EH: *Mechanisms of Contraction of the Normal and Failing Heart*, 2nd ed. Boston: Little, Brown, 1976.
 26. Mason DT, Braunwald E, Karsh RB, Bullock FA: Studies on digitalis. X: Effects of ouabain on forearm vascular resistance and venous tone in normal subjects and in patients with heart failure. *J Clin Invest* 43:532, 1964.
 27. Eberhardt RT, Frishman WH, Landau A, et al: Increased mortality incidence in elderly individuals receiving digoxin therapy: Results of the Bronx Longitudinal Aging Study. *Cardiol Elderly* 3:177, 1995.
 28. Packer M, Gheorghide M, Young JB, et al: Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med* 329:1, 1993.
 29. Uretsky BF, Young JB, Shahidi FE, et al: Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: Results of the PROVED Trial. *J Am Coll Cardiol* 22:955, 1995.
 30. Adams KF Jr, Gheorghide M, Uretsky BF, et al: Clinical predictors of worsening heart failure during withdrawal from digoxin therapy. *Am Heart J* 135:389–397, 1998.
 31. Captopril-Digoxin Multicenter Research Group: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 259:539, 1988.
 32. Tauke J, Goldstein S, Gheorghide M: Digoxin for chronic heart failure: A review of the randomized controlled trials with special attention to the PROVED and RADIANCE Trials. *Prog Cardiovasc Dis* 37:49, 1994.
 33. Kraus F, Rudolph C, Rudolph W: Efficacy of digitalis in patients with chronic congestive heart failure and sinus rhythm: An overview of randomized, double-blind, placebo-controlled studies. *Herz* 18:95, 1993.
 34. The Digitalis Investigation Group: The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 336:525, 1997.
 35. Wirth KE: Relevant metabolism of cardiac glycosides. In: Erdmann E, Greeff K, Skou JC, eds. *Update in Cardiac Glycosides, 1785–1985*. New York: Springer-Verlag, 1986:257–262.
 36. Adams KF Jr., Gheorghide M, Uretsky BF, et al: Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 39:946, 2002.
 37. van Veldhuisen DJ: Low-dose digoxin in patients with heart failure: Less toxic and at least as effective? *J Am Coll Cardiol* 39:954, 2002.
 38. Marcus FI: Pharmacokinetic interactions between digoxin and other drugs. *J Am Coll Cardiol* 5:82A, 1985.
 39. Sonnenblick EH, LeJemtel TH: Heart failure: Its progression and its therapy. *Hosp Pract* 28:121, 1993.
 40. Fauchier L, Grimard C, Pierre B, et al: Comparison of beta blocker and digoxin alone and in combination for management of patients with atrial fibrillation and heart failure. *Am J Cardiol* 103: 248, 2009.
 41. Hauptman PJ, Kelly RA: Digitalis. *Circulation* 99:1265, 1999.
 42. Muller JE, Turi ZG, Stone PH, et al for the MILIS Group: Digoxin therapy and mortality following confirmed or suspected myocardial infarction: experience in the MILIS Study. In: Erdmann E, Greeff JC, Skou JC, eds. *Update in Cardiac Glycosides 1785–1985*. New York: Springer-Verlag, 1986:493.
 43. Ahmed A, Gambassi G, Weaver MT, et al: Effects of discontinuation of digoxin versus continuation at low serum digoxin concentrations in chronic heart failure. *Am J Cardiol* 100: 280, 2007.
 44. Spargias KS, Hall AS, Ball SG: Safety concerns about digoxin after acute myocardial infarction. *Lancet* 354:391, 1999.
 45. Lewis RP: Clinical use of serum digoxin concentrations. *Am J Cardiol* 69:97G, 1992.
 46. Steimer W, Muller C, Eber B: Digoxin assays: Frequent, substantial and potentially dangerous interference by spironoactone, canrenone, and other steroids. *Clin Chem* 48:507, 2002.
 47. Kelley RA, Smith TW: Recognition and treatment of digitalis toxicity. *Am J Cardiol* 69:108G, 1992.
 48. Marcus FI: Digitalis. In: Schlant RC, Alexander RW, eds. *Hurst's The Heart*, 8th ed. New York: McGraw-Hill, 1994:573–588.
 49. Williamson KM, Thrasher KA, Fulton KB, et al:

- Digoxin toxicity. An evaluation in current clinical practice. *Arch Intern Med* 158:2444, 1998.
50. Cardiac glycosides interact with many drugs. *Drugs Ther Perspect* 6(3):11, 1995.
 51. Eddleston M, Rajapakse S, Rajakanthan SJ, et al: Anti-digoxin Fab fragments in cardiotoxicity induced by ingestion of yellow oleander: A randomised controlled trial. *Lancet* 355:767, 2000.
 52. Marik PE, Fromm L: A case series of hospitalized patients with elevated digoxin levels. *Am J Med* 105:110, 1998.
 53. Benovic JL, Bouvier M, Caron MG, Lefkowitz RJ: Regulation of adenylyl cyclase-coupled β -adrenergic receptors. *Am Rev Cell Biol* 4:405, 1988.
 54. Kelly RB: Storage and release of neurotransmitters. *Cell/Neuron* 72(Suppl. 72):443, 1993.
 55. Hoffman BB, Taylor P: Neurotransmission. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York: McGraw-Hill, 2001:115–153.
 56. Spann JF, Sonnenblick EH, Cooper T, et al: Cardiac norepinephrine stores and the contractile state of the heart. *Circ Res* 19:317, 1966.
 57. Francis GS, Goldsmith SR, Levine TB, et al: The neurohumoral axis in congestive heart failure. *Ann Intern Med* 101:370, 1984.
 58. Insel PA: Adrenergic receptors—evolving concepts and clinical implications. *N Engl J Med* 334:580, 1996.
 59. Movsesian MA: Beta-adrenergic receptor agonists and cyclic nucleotide phosphodiesterase inhibitors: Shifting the focus from inotropy to cyclic adenosine monophosphate *J Am Coll Cardiol* 34:318–324, 1999.
 60. Pagel PS, Haikala H, Pentikainen PJ, et al: Pharmacology of levosimendan: A new myofilament calcium sensitizer. *Cardiovasc Drugs Rev* 14:286, 1996.
 61. Micheletti R, Mattera GG, Rocchetti M, et al: Pharmacological profile of the novel inotropic agent (E,Z)-3-((2-aminoethoxy)imino)androstane-6,17-dione hydrochloride (PST2744). *J Pharm Exp Thera* 303:592, 2002.
 62. Goldberg LI, Rajfer SI: Dopamine receptors: Applications in clinical cardiology. *Circulation* 72:245, 1985.
 63. Leclerc KM, Steele NP, Levy WC: Norepinephrine alters exercise oxygen consumption in heart failure patients. *Med Sci Sports Exerc* 32:2029, 2000.
 64. van de Borne P, Oren R, Somers VK: Dopamine depresses minute ventilation in patients with heart failure. *Circulation* 98:126, 1998.
 65. Elkayam U, Ng TMH, Hatamizadeh P, et al: Renal vasodilatory action of dopamine in patients with heart failure. Magnitude of effect and site of action. *Circulation* 117: 200, 2008.
 66. Hoogenberg K, Smit AJ, Girbes ARJ: Effects of low-dose dopamine on renal and systemic hemodynamics during incremental norepinephrine infusion in healthy volunteers. *Crit Care Med* 26:260, 1998.
 67. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. *Lancet* 356:2139, 2000.
 68. DeBacker D, Biston P, Devriendt J, et al for the SOAP II Investigators: Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 362: 779, 2010.
 69. Ruffolo RR Jr.: Review: The pharmacology of dobutamine. *Am J Med Sci* 294:244, 1987.
 70. Sonnenblick EH, Frishman WH, LeJemtel TH: Dobutamine: A new synthetic cardioactive sympathetic amine. *N Engl J Med* 300:17, 1979.
 71. Tisdale JE, Patel R, Webb CR, et al: Electrophysiologic and proarrhythmic effects of intravenous inotropic agents. *Progr Cardiovasc Dis* 38:167, 1995.
 72. Oliva F, Latini R, Politi A, et al for the DICE (Dobutamina nell'Insufficienza Cardiaca Estrema) Investigators: Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE Multicenter Trial. *Am Heart J* 138:247, 1999.
 73. Silver MA: Intermittent inotropes for advanced heart failure: Inquiring minds want to know. *Am Heart J* 138:191, 1999.
 74. Nanas JN, Kontoyannis DA, Alexopoulos GP, et al: Long-term intermittent dobutamine infusion combined with oral amiodarone improves the survival of patients with severe congestive heart failure. *Chest* 119:1173, 2001.
 75. Parmley WW, Sonnenblick EH: A role for glucagon in cardiac therapy. *Am J Med Sci* 258:224, 1969.
 76. Braunwald E, Sonnenblick EH, Chakrin LW, Schwarz RP Jr., eds. *Milrinone Investigation: A New Inotropic Therapy for Congestive Heart Failure*. New York: Raven Press, 1984.
 77. Grose R, Strain J, Greenberg M, LeJemtel TH: Systemic and coronary effects of intravenous milrinone and dobutamine in congestive heart failure. *J Am Coll Cardiol* 7:1107, 1986.
 78. Harris AL, Silver PJ, Lemp BM, Evans DB: The vasorelaxant effects of milrinone and other vasodilators are attenuated by ouabain. *Eur J Pharmacol* 145:133–139, 1988.
 79. Nielsen-Kudsk JE, Aldershvile J: Will calcium sensitizers play a role in the treatment of heart failure? *J Cardiovasc Pharmacol* 26 (Suppl 1):577, 1995.
 80. Packer M, Carver JR, Rodeheffer RJ, et al: Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 325:1468, 1991.

81. Fleming GA, Murray KT, Yu C, et al: Milrinone use is associated with postoperative atrial fibrillation after cardiac surgery. *Circulation* 118: 1619, 2008.
82. Baruch L, Patacsil P, Hameed A, et al: Pharmacodynamic effects of milrinone with and without a bolus loading infusion. *Am Heart J* e6:141, 2000.
83. Givertz MM, Hare JM, Loh E, et al: Effect of bolus milrinone on hemodynamic variables and pulmonary vascular resistance in patients with severe left ventricular dysfunction: A rapid test for reversibility of pulmonary hypertension. *J Am Coll Cardiol* 28:1775, 1996.
84. Yano M, Kohno M, Ohkusa T, et al: Effect of milrinone on left ventricular relaxation and Ca²⁺ uptake function of cardiac sarcoplasmic reticulum. *Am J Physiol* 279:H1898, 2000.
85. Tanigawa T, Yano M, Kohno M, et al: Mechanism of preserved positive lusitropy by cAMP-dependent drugs in heart failure. *Am J Physiol* 278:H313, 2000.
86. Hatzizacharias A, Makris T, Krespi P, et al: Intermittent milrinone effect on long-term hemodynamic profile in patients with severe congestive heart failure. *Am Heart J* 138:241, 1999.
87. Milfred-LaForest SK, Shubert J, Mendoza B, et al: Tolerability of extended duration intravenous milrinone in patients hospitalized for advanced heart failure and the usefulness of uptitration of oral angiotensin-converting enzyme inhibitors. *Am J Cardiol* 84:894, 1999.
88. Ewy GA: Inotropic infusions for chronic congestive heart failure. Medical miracles or misguided medicinal? *J Am Coll Cardiol* 33:572, 1999.
89. Cesario D, Clark J, Maisel A: Beneficial effects of intermittent home administration of the inotrope/vasodilator milrinone in patients with end-stage congestive heart failure: A preliminary study. *Am Heart J* 135:121, 1998.
90. Mehra MR, Ventura HO, Kapoor C, et al: Safety and clinical utility of long-term intravenous milrinone in advanced heart failure. *Am J Cardiol* 80:61, 1997.
91. Canver CC, Chanda J: Milrinone for long-term pharmacologic support of the status of heart transplant candidates. *Ann Thorac Surg* 69:1823, 2000.
92. Cusick DA, Pfeifer PB, Quigg RJ: Effects of intravenous milrinone followed by titration of high-dose oral vasodilator therapy on clinical outcome and rehospitalization rates in patients with severe heart failure. *Am J Cardiol* 82:1060, 1998.
93. Cuffe MS, Califf RM, Adams KF Jr. et al: Short-term intravenous milrinone for acute exacerbation of chronic heart failure. A randomized, controlled trial. *JAMA* 287:1541, 2002.
94. Lowes BD, Higginbotham M, Petrovich L, et al: Low-dose enoximone improves exercise capacity in chronic heart failure. *J Am Coll Cardiol* 36:501, 2000.
95. Shakar SF, Bristow MR: Low-level inotropic stimulation with type III phosphodiesterase inhibitors in patients with advanced symptomatic chronic heart failure receiving β -blocking agents. *Curr Cardiol Rep* 3:224, 2001.
96. Metra M. ESSENTIAL: the Studies of Oral Enoximone Therapy in Advanced Heart Failure. Presented at: European Society of Cardiology Congress; September 5–8, 2005; Stockholm, Sweden: Late Breaking Clinical Trials.
97. Causoglu E, Frishman WH, Klapholz M: Vesnarinone: A new inotropic agent for treating congestive heart failure. *J Card Fail* 1:249, 1995.
98. Matsumori A, Shioi T, Yamada T, et al: Vesnarinone, a new inotropic agent, inhibits cytokine production by stimulated human blood from patients with heart failure. *Circulation* 89:955, 1994.
99. OPC 8212 Multicenter Research Group: A placebo-controlled, randomized, double-blind study of OPC 8212 in patients with mild chronic heart failure. *Cardiovasc Drugs Ther* 4:419, 1990.
100. Feldman AM, Bristow MR, Parmley WW, et al for the Vesnarinone Study Group: Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 329:149, 1993.
101. Cohn JN, Goldstein SO, Greenberg BH et al: A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. *N Engl J Med* 339:1810, 1998.
102. Sugiyama A, Satoh Y, Hashimoto K: Electropharmacologic effects of a new phosphodiesterase III inhibitor, toborinone (OPC-18790), assessed in an in vivo canine model. *J Cardiovasc Pharmacol* 38:268, 2001.
103. Yu Y, Mizushige K, Ueda T, et al: Effect of olprinone, phosphodiesterase III inhibitor, on cerebral blood flow assessed with technetium-99m-ECD SPECT. *J Cardiovasc Pharmacol* 35:422, 2000.
104. Slawsky MT, Colucci WS, Gottlieb SS, et al: Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. *Circulation* 102:2222, 2001.
105. Kivikko M, Lehtonen L, Colucci WS, et al. Sustained hemodynamic effects of intravenous levosimendan. *Circulation* 2003;107:81-6.
106. Fuhrmann JT, Schmeisser A, Schulze MR, et al: Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction. *Crit Care Med* 36: 2257, 2008.
107. Russ MA, Prondzinsky R, Christoph A, et al: Hemodynamic improvement following levosimendan

- treatment in patients with acute myocardial infarction and cardiogenic shock. *Crit Care Med* 35: 2732, 2007.
108. Lehtonen L: Levosimendan: A promising agent for the treatment of hospitalized patients with decompensated heart failure. *Curr Cardiol Rep* 2:233, 2000.
 109. Figgitt DP, Gillies PS, Goa KL: Levosimendan. *Drugs* 61:613, 2001.
 110. Folláth F, Hinkka S, Jäger D, et al: Dose-ranging and safety with intravenous levosimendan in low-output heart failure: Experience in three pilot studies and outline of the levosimendan infusion versus dobutamine (LIDO) trial. *Am J Cardiol* 83:211, 1999.
 111. Ukkonen H, Saraste M, Akkila J, et al: Myocardial efficiency during levosimendan infusion in congestive heart failure. *Clin Pharmacol Ther* 68:522, 2000.
 112. Harjola V-P, Peuhkurinen K, Nieminen MS, et al: Oral levosimendan improves cardiac function and hemodynamics in patients with severe congestive heart failure. *Am J Cardiol* 83:4I, 1999.
 113. Nijhawan N, Nicolosi AC, Montgomery MW, et al: Levosimendan enhances cardiac performance after cardiopulmonary bypass: A prospective, randomized placebo-controlled trial. *J Cardiovasc Pharmacol* 34:219, 1999.
 114. Hosenpud JD, for the Oral Levosimendan Study Group: Levosimendan, a novel myofilament calcium sensitizer, allows weaning of parenteral inotropic therapy in patients with severe congestive heart failure. *Am J Cardiol* 83:9I, 1999.
 115. Follath F, Cleland JGF, Just H, et al: Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): A randomised double-blind study. *Lancet* 360:196, 2002.
 116. Moiseyev VS, Pöder P, Andrejevs N, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). *Eur Heart J* 23:1422, 2002.
 117. Lehtonen L, Pöder P: The utility of levosimendan in the treatment of heart failure. *Ann Med* 39: 2, 2007.
 - 117a. REVIVE-II summary data. <http://www.cardiosource.com/pops/trialSum.asp?trialID=1378>; accessed February 17, 2010.
 118. Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. *JAMA* 297:1883, 2007.
 119. Fujimoto S, Matsuda T. Effects of pimobendan, a cardiotonic and vasodilating agent with phosphodiesterase inhibiting properties, on isolated arteries and veins of rats. *J Pharmacol Exp Ther* 1990; 252(3): 1304-11.
 120. Matsui K, Kiyosue T, Wang JC, et al. Effects of pimobendan on the L-type Ca²⁺ current and developed tension in guinea-pig ventricular myocytes and papillary muscle: comparison with IBMX, milrinone, and cilostazol. *Cardiovasc Drugs Ther* 13:105, 1999.
 121. Kuriya S, Ohmori S, Hino M, et al. Identification of cytochrome P-450 isoform(s) responsible for the metabolism of pimobendan in human liver microsomes. *Drug Metab Dispos* 28:73, 2000.
 122. Chu KM, Shieh SM, Hu OY. Pharmacokinetics and pharmacodynamics of enantiomers of pimobendan in patients with dilated cardiomyopathy and congestive heart failure after single and repeated oral dosing. *Clin Pharmacol Ther* 57: 610, 1995.
 123. Chu KM, Shieh SM, Hu OY. Pharmacokinetics and pharmacodynamics of enantiomers of pimobendan in patients with dilated cardiomyopathy and congestive heart failure after single and repeated oral dosing. *Clin Pharmacol Ther* 57: 610, 1995.
 124. Hagemeyer F. Calcium sensitization with pimobendan: pharmacology, haemodynamic improvement, and sudden death in patients with chronic congestive heart failure. *Eur Heart J* 14:551, 1993.
 125. Sasayama S, Asanoi H, Kihara Y, et al. Clinical effects of long-term administration of pimobendan in patients with moderate congestive heart failure. *Heart Vessels* 9:113, 1994.
 126. Katz SD, Kubo SH, Jessup M, et al. A multicenter, randomized, double-blind, placebo-controlled trial of pimobendan, a new cardiotonic and vasodilator agent, in patients with severe congestive heart failure. *Am Heart J* 123:95, 1992.
 127. Kubo SH, Gollub S, Bourge R, et al. Beneficial effects of pimobendan on exercise tolerance and quality of life in patients with heart failure: results of a multicenter trial. The Pimobendan Multicenter Research Group. *Circulation* 85:942, 1992.
 128. The Pimobendan in Congestive Heart Failure (PICO) investigators. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart* 76:223, 1996.
 129. The EPOCH study group. Effects of pimobendan on adverse cardiac events and physical activities in patients with mild to moderate chronic heart failure – The Effects of Pimobendan on Chronic Heart Failure Study (EPOCH Study). *Circ J* 66:149, 2002.
 130. Sasaki T, Kubo T, Komamura K, Nishikimi T. Effects of long-term treatment with pimobendan on neurohormonal factors in patients with non-ischemic chronic moderate heart failure. *J Cardiol* 33:317, 1999.
 131. Iwasaki A, Matsumori A, Yamada T, et al: Pimo-

- bendan inhibits the production of proinflammatory cytokines and gene expression of inducible nitric oxide synthase in a murine model of viral myocarditis. *J Am Coll Cardiol* 33:1400, 1999.
132. Dorigo P, Floreani M, Santostasi G, et al: Pharmacological characterization of a new Ca²⁺sensitizer. *J Pharmacol Exp Ther* 295:994, 2000.
 133. Brixius K, Reicke S, Reuter H, Schwinger RH. Effects of the Ca²⁺ sensitizers EMD 57033 and CGP 48506 on myocardial contractility and Ca²⁺ transients in human ventricular and atrial myocardium. *Z Kardiol* 91:312,2002
 134. Yang G, Liu L, Xu J, Li T. Effects of MCI-154 on vascular reactivity and its mechanisms after hemorrhagic shock in rats. *J Cardiovasc Pharmacol* 47:751, 2006.
 135. Müller-Ehmsen J, Brixius K, Schwinger RHG: Positive inotropic effects of a novel Na⁺-channel modulator BDF 9198 in human nonfailing and failing myocardium. *J Cardiovasc Pharmacol* 31:684, 1998.
 136. Doggrel S.A.: Effects of BDF 9198 on left ventricular contractility in advanced spontaneously hypertensive rats with heart failure. *J Pharmacy Pharmacol* 54: 1097, 2002.
 137. Satoh N, Sato T, Shimada M, et al. Lusitropic effect of MCC-135 is associated with improvement of sarcoplasmic reticulum function in ventricular muscles of rats with diabetic cardiomyopathy. *J Pharm Exper Ther*298:1161, 2001.
 138. Kawasumi H, Satoh N, Kitada Y: Caldaret, an intracellular Ca²⁺ handling modulator, limits infarct size of reperfused canine heart. *J Pharmacol Sci* 103: 222, 2007.
 139. Bär FW, Tzivoni D, Dirksen MT, et al. Results of the first clinical study of adjunctive Caldaret (MCC-135) in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: the randomized multicentre CASTEMI study. *Eur Heart J* 27:2516,2006.
 140. Tzivoni D, Balkin J, Bär FW, et al: Effect of Caldaret on the incidence of severe left ventricular dysfunction in patients with ST-elevation myocardial infarction undergoing primary coronary intervention. *Am J Cardiol* 103; 1,2009.
 141. Shah SJ, Blair JEA, Filippatos GS, et al for the HORIZON-HF Investigators: Effects of istaroxime on diastolic stiffness in acute heart failure syndromes: results from the hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: a randomized controlled trial in patients hospitalized with heart failure (HORIZON-HF) trial. *Am Heart J* 157: 1035, 2009.
 142. Micheletti R, Mattera GG, Rocchetti M, et al. Pharmacological profile of the novel inotropic agent (E,Z)-3-((2-aminoethoxy)imino)androstane-6,17-dione hydrochloride (PST2744). *J Pharm Exp Thera* 303:592,2002.
 143. Adamson PB, Vanoli E, Mattera GG, et al. Hemodynamic effects of a new inotropic compound, PST-2744, in dogs with chronic ischemic heart failure. *J Cardiovasc Pharmacol* 42:169,2003.
 144. Gheorghide M, Blair JEA, Filippatos GS, et al. Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent. *J Am Coll Cardiol* 51:2276,2008.
 145. McMurray J, Pfeffer MA: New therapeutic options in congestive heart failure, Part II. *Circulation* 105:2223, 2002.
 146. Maurice JP, Hata JA, Shah AS, et al: Enhancement of cardiac function after adenoviral-mediated in vivo intracoronary β_2 -adrenergic receptor gene delivery. *J Clin Invest* 104:21, 1999.
 147. Weig H-J, Laugwitz K-L, Moretti A, et al: Enhanced cardiac contractility after gene transfer of V2 vasopressin receptors in vivo by ultrasound-guided injection or transcatheter delivery. *Circulation* 101:1578, 2000.
 148. del Monte F, Harding SE, Schmidt U, et al: Restoration of contractile function in isolated cardiomyocytes from failing human hearts by gene transfer of SERCA2a. *Circulation* 100:2308, 1999.
 149. del Monte F, Williams E, Lebeche D, et al: Improvement in survival and cardiac metabolism after gene transfer of sarcoplasmic reticulum Ca²⁺-ATPase in a rat model of heart failure. *Circulation* 104:1424, 2001.
 150. Sakata S, Lebeche D, Sakata Y, et al: Transcatheter gene transfer of SERCA2a increases coronary blood flow and decreases cardiomyocyte size in a type 2 diabetic rat model. *Am J Physiol Heart Circ Physiol*. 292:H1204,2007.
 151. Sakata S, Lebeche D, Sakata N, et al: Targeted gene transfer increases contractility and decreases oxygen cost of contractility in normal rat hearts. *Am J Physiol Heart Circ Physiol*. 292:H2356,2007.
 152. Sakata S, Lebeche D, Sakata N, et al: Restoration of mechanical and energetic function in failing aortic-banded rat hearts by gene transfer of calcium cycling proteins. *J Mol Cell Cardiol*. 42:852,2007.
 153. Calcium Up-Regulation by Percutaneous Administration of Gene therapy In Cardiac Disease (CUPID Trial) -Presented at American Heart Association Meeting 2008. *J Card Fail* 14:355,2008.
 154. Late Breaking Clinical Trials. *Circulation* 118:2309,2008.
 155. Leri A, Anversa P, Frishman WH: *Cardiovascular Regeneration and Stem Cell Therapy*. UK: Blackwell

References for Chapter 14

The Organic Nitrates and Nitroprusside

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- Publishing, 2007.
1. Fung H-L, Chung S-J, Bauer JA, et al: Biochemical mechanism of organic nitrate action. *Am J Cardiol* 70:4B, 1992.
2. Kukovetz WR, Holzmann S, Schmidt K: Cellular mechanisms of action therapeutic nitric oxide donors. *Eur Heart J* 12(suppl E):16, 1991.
3. Harrison DG, Bates JN: The nitrovasodilators: New ideas about old drugs. *Circulation* 87:1461, 1993.
4. Torfgard KE, Ahlner J: Mechanisms of action of nitrates. *Cardiovasc Drugs Ther* 8:701, 1994.
5. Loscalzo J: Antiplatelet and antithrombotic effects of organic nitrates. *Am J Cardiol* 70:18B, 1992.
6. Diodati J, Theroux P, Latour J-G, et al: Effects of nitroglycerin at therapeutic doses on platelet aggregation in unstable angina pectoris and acute myocardial infarction. *Am J Cardiol* 66:683, 1996.
7. Folts JD, Stamler J, Loscalzo J: Intravenous nitroglycerin infusion inhibits blood flow responses caused by periodic platelet thrombus formation in stenosed canine coronary arteries. *Circulation* 83:2122, 1991.
8. Lam JYT, Chesebro JH, Fuster V: Platelets, vasoconstriction and nitroglycerin during arterial wall injury: A new antithrombotic role for an old drug. *Circulation* 78:712, 1988.
9. Fye WB: Nitroglycerin: A homeopathic remedy. *Circulation* 73:21, 1986.
10. Whitmont RD, Mamtani R: Homeopathy with a special focus on treatment of cardio-vascular diseases. In Frishman WH, Weintraub MI, Micozzi MS: *Complementary and Integrative Therapies for Cardiovascular Disease*. St. Louis: Elsevier/Mosby 2005: 232-47.
11. Seth P, Fung H-L: Biochemical characterization of a membrane-bound enzyme responsible for generating nitric oxide from nitroglycerin in vascular smooth muscle cells. *Biochem Pharmacol* 64:1481, 1993.
12. Watanabe H, Kakihana M, Ohtsuka S, et al: Platelet cyclic GMP. A potentially useful indicator to evaluate the effects of nitroglycerin and nitrate tolerance. *Circulation* 88:29, 1993.
13. Gori T, Parker JD: The puzzle of nitrate tolerance. Pieces smaller than we thought? *Circulation* 106: 2404, 2002.
14. Gori T, Parker JD: Nitrate tolerance. A unifying hypothesis. *Circulation* 106: 2510, 2002.
15. Sage PR, de la Lande IS, Stafford I: Nitroglycerin tolerance in human vessels. Evidence for impaired nitroglycerin bioconversion. *Circulation* 102:2810, 2000.
16. Boesgaard S, Aldershvile J, Lofts S, et al: Nitrate tolerance in vivo is not associated with depletion of arterial or venous thiol levels. *Circ Res* 74:115, 1994.
- 16a. Fung H-L: Personal Communication.
- 16b. Munzel T, Wenzel P, Daiber A: Do we still need organic nitrates? (editorial comment). *J Am Coll Cardiol* 49: 1296: 2007.
17. Kim D, Rybalkin SD, Pi X, et al: Upregulation of phosphodiesterase 1A1 expression is associated with the development of nitrate tolerance. *Circulation* 104:2338, 2001.
18. Bassenge E: Coronary vasomotor responses: Role of endothelium and nitrovasodilators. *Cardiovasc Drugs Ther* 8:601, 1994.
19. Kurz MA, Lamping KG, Bates JN, et al: Mechanisms responsible for the heterogeneous coronary microvascular response to nitroglycerin. *Circ Res* 68:847, 1991.
20. Chiariello M, Gold HK, Leinbach RC, et al: Com-

- parison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction. *Circulation* 54:766, 1976.
21. Abrams J: Mechanisms of action of the organic nitrates in the treatment of myocardial ischemia. *Am J Cardiol* 70:30B, 1992.
 22. Loos D, Schneider R, Schorner W: Changes in regional body blood volume caused by nitroglycerin. *Z Kardiol* 72(Suppl 3):29, 1983.
 23. Vatner SF, Pagani M, Rutherford JD, et al: Effects of nitroglycerin on cardiac performance and regional blood flows distribution in conscious dogs. *Am J Physiol* 234(3):H244, 1978.
 24. Leier CV, Huss P, Bambach D, et al: Central and regional hemodynamic effects of intravenous isosorbide dinitrate, nitroglycerin and nitroprusside in patients with congestive heart failure. *Am J Cardiol* 48:1115, 1981.
 25. Abrams J: Beneficial actions of nitrates in cardiovascular disease. *Am J Cardiol* 77:31C, 1996.
 26. Pupita G, Maseri A, Kaski JC, et al: Myocardial ischemia caused distal coronary-artery constriction in stable angina pectoris. *N Engl J Med* 323:514, 1990.
 27. Brown BG, Bolson EL, Dodgett T: Dynamic mechanisms in human coronary stenosis. *Circulation* 70:917, 1984.
 28. Bassenge E, Zanzinger J: Nitrates in different vascular beds, nitrate tolerance, and interactions with endothelial function. *Am J Cardiol* 70:23B, 1992.
 29. Dupuis J: Nitrates in congestive heart failure. *Cardiovasc Drugs Ther* 8:501, 1994.
 30. Schwarz M, Katz SD, Demopoulos L, et al: Enhancement of endothelium dependent vasodilation by low-dose nitroglycerin in patients with congestive heart failure. *Circulation* 89:1609, 1994.
 31. Luscher TF, Noll G: The endothelium in coronary vascular control, update 3. In: Braunwald E, ed. *Heart Disease*. Philadelphia: Saunders, 1995:1.
 32. Gage JE, Hess OM, Murakami T, et al: Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: Reversibility by nitroglycerin. *Circulation* 73:865, 1986.
 33. Ludmer PL, Selwyn AP, Shook TL, et al: Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic arteries. *N Engl J Med* 315:1046, 1986.
 34. Paulus WJ: Endothelial control of vascular and myocardial function in heart failure. *Cardiovasc Drugs Ther* 8:437, 1994.
 35. Sonnenblick EH, Lejemtel TH, Frishman WH: Inotropic agents. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed*. New York: McGraw Hill 2003: 191.
 36. Rafflenbeul W, Bassenge E, Lichtlen P: Competition between endothelium-dependent and nitroglycerin-induced coronary vasodilation. *Z Kardiol* 78(Suppl 2):45, 1989.
 37. Luscher TF: Endothelium-derived nitric oxide: The endogenous nitrovasodilator in the human cardiovascular system. *Eur Heart J* 12(Suppl E):2, 1991.
 38. Münzel T, Giaid A, Kurz S, et al: Evidence for a role of endothelin 1 and protein kinase C in nitroglycerin tolerance. *Proc Natl Acad Sci USA* 92:5244, 1995.
 39. Gori T, Mak SS, Kelly S, Parker JD: Evidence supporting abnormalities in nitric oxide synthase function induced by nitroglycerin in humans. *J Am Coll Cardiol* 38:1096, 2001.
 40. Münzel T, Sayegh H, Freeman BA, et al: Evidence for enhanced vascular superoxide anion production in nitrate tolerance. A novel mechanism underlying tolerance and cross-tolerance. *J Clin Invest* 95 (1):187, 1995.
 41. Heizer T, Just H, Brockhoff C et al: Long-term nitroglycerin treatment is associated with supersensitivity to vasoconstrictors in men with stable coronary artery disease: Prevention by concomitant treatment with captopril. *J Am Coll Cardiol* 31(1):83, 1998.
 42. Caramori PR, Adelman AG, Azevedo ER, et al: Therapy with nitroglycerin increases coronary vasoconstriction in response to acetylcholine. *J Am Coll Cardiol* 32(7):1969, 1998.
 43. Gori T, Parker JD: Nitrate-induced toxicity and preconditioning. A rationale for reconsidering the use of these drugs. *J Am Coll Cardiol* 52: 251, 2008.
 44. Jugdutt BI, Tymchak WJ, Burton JR: Preservation of left ventricular geometry and function after late reperfusion and intravenous nitroglycerin in acute transmural myocardial infarction. *Circulation* 84:II-683, 1991.
 45. McDonald KM, Francis GS, Matthews J, et al: Long-term oral nitrate therapy prevents chronic ventricular remodeling in the dog. *J Am Coll Cardiol* 21:514, 1993.
 46. Jugdutt BI, Warnica JW: Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications: Effect on timing, dosage and infarct location. *Circulation* 78:906, 1988.
 47. Yusuf S, Collins R, MacMahon S, Peto R: Effect of intravenous nitrates on mortality in acute myocardial infarction: An overview of the randomized trials. *Lancet* 2:1088, 1988.
 48. Beltrame JF, Stewart S, Leslie S, et al: Resolution of ST segment elevation following intravenous administration of nitroglycerin and verapamil. *Am J Cardiol* 89:452, 2002.

49. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3): Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 343:1115, 1994.
50. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group (ISIS-4): A randomized factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 345:669, 1995.
51. Leeser MA, Stoddard MF, Dawn B, et al: Delayed preconditioning-mimetic action of nitroglycerin in patients undergoing coronary angioplasty. *Circulation* 103:2935, 2001.
52. Heusch G: Nitroglycerin and delayed preconditioning in humans. Yet another new mechanism for an old drug? *Circulation* 103:2876, 2001.
53. Henrikson CA, Howell EE, Bush DE, et al: Chest pain relief by nitroglycerin does not predict active coronary artery disease. *Ann Intern Med* 139: 979, 2003.
54. Nesbitt SD: Nitrates as adjunct hypertensive treatment. A possible answer to resistant systolic hypertension. *Hypertension* 45: 352, 2005.
55. Pickering TG: Why don't we use nitrates to treat older hypertensive patients? *J Clin Hypertens* 7: 685, 2005.
56. Duchier J, Iannascoli F, Safor M: Antihypertensive effect of sustained release isosorbide dinitrate for isolated systolic systemic hypertension in the elderly. *Am J Cardiol* 60:99, 1987.
57. Ito Y, Isotani E, Mizuno Y, et al: Effective improvement of the cerebral vasospasm after subarachnoid hemorrhage with low-dose nitroglycerin. *J Cardiovasc Pharmacol* 35:45, 2000.
58. Abrams J, Schroeder J, Frishman WH, Freedman J: Pharmacologic options for treatment of ischemic disease. In Antman EM (ed): *Cardiovascular Therapeutics. A Companion to Braunwald's Heart Disease, 3rd ed.*. Philadelphia: Saunders/Elsevier 2007: 77.
59. Abrams J: Nitrates and nitrate tolerance in congestive heart failure. *Coron Artery Dis* 4:27, 1993.
60. Mehra A, Ostrzega E, Shotan A, et al: Persistent hemodynamic improvement with short-term nitrate therapy in patients with chronic congestive heart failure already treated with captopril. *Am J Cardiol* 70:1310, 1992.
61. Parker JD, Parker JO: Effect of therapy with an angiotensin converting enzyme inhibitor on hemodynamic and counterregulators responses during continuous therapy with nitroglycerin. *J Am Coll Cardiol* 21:1445, 1993.
62. Elkayam U, Johnson JV, Shotan A, et al: Double-blind, placebo-controlled study to evaluate the effect of organic nitrates in patients with chronic heart failure treated with angiotensin-converting enzyme inhibition. *Circulation* 99:2652, 1999.
63. Elkayam U, Mehra A, Shotan A, Ostrzega E: Nitrate resistance and tolerance: Potential limitations in the treatment of congestive heart failure. *Am J Cardiol* 70:98B, 1992.
64. Abrams J: The mystery of nitrate resistance. *Am J Cardiol* 68: 1393, 1991.
65. Leier CB, Magorien RD, Desch CE, et al: Hydralazine and isosorbide dinitrate: comparative central and regional hemodynamic effects when administered alone or in combination. *Circulation* 63: 102: 1981.
66. Gogia H, Mehra A, Parikh S, et al: Prevention of tolerance to hemodynamic effects of nitrates with concomitant use of hydralazine in patients with chronic heart failure. *J Am Coll Cardiol* 26: 1575, 1995.
67. Elkayam U, Canetti M, Wani DR, et al: Hydralazine induced prevention of nitrate tolerance: experimental and clinical evidence and potential mechanism. *Am J Cardiol* 81; 44A, 1998.
68. Munzel T, Kurz S, Rajagopalan S, et al: Hydralazine prevents nitroglycerin tolerance by inhibiting activation of a membrane-bound NADH oxidase: a new action for an old drug. *J Clin Invest* 98: 1465, 1996.
69. Daiber A, Oelze M, Coldewey M, et al: Hydralazine is a powerful inhibitor of peroxy-nitrite formation as a possible explanation for its beneficial effects on prognosis in patients with congestive heart failure. *Biochem Biophys Res Commun* 338: 1865, 2005.
70. Cohn JN, Archibald DG, Ziesche S, et al: Effect of vasodilator therapy on mortality in chronic congestive heart failure: Results of a Veterans Administration Cooperative Study. *N Engl J Med* 314:1547, 1986.
71. Cohn JN, Johnson G, Ziesche S, et al: A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 325:303, 1991.
72. Carson P, Ziesche S, Johnson G, Cohn JN: Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. *J Card Fail* 5: 178, 1999.
73. Cheng JW: A review of isosorbide dinitrate and hydralazine in the management of heart failure in black patients, with a focus on a new fixed-dose combination. *Clin Ther* 28: 666, 2006.

74. Taylor AL, Ziesche S, Yancy C, et al: African-American Heart Failure Trial Investigators: Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 351: 2049, 2004.
75. Mullens W, Abrahams Z, Francis GS, et al: Usefulness of isosorbide dinitrate and hydralazine as add-on therapy in patients discharged for advanced decompensated heart failure. *Am J Cardiol* 103: 1113, 2009.
76. Carmody MS, Anderson JR: BiDil (isosorbide dinitrate and hydralazine): a new fixed-dose combination of two older medications for the treatment of heart failure in black patients. *Cardiol in Rev* 15: 46, 2007.
77. Temple R, Stockbridge NL: BiDil for heart failure in black patients: the US Food and Drug Administration perspective. *Ann Intern Med* 146: 57, 2007.
78. Wilson RM, DeSilva DS, Sato K, et al: Effects of fixed-dose isosorbide dinitrate/hydralazine on diastolic function and exercise capacity in hypertension-induced diastolic heart failure. *Hypertension* 54: 583, 2009.
79. Mahmarian JJ, Fenimore NL, Marks GF, et al: Transdermal nitroglycerin patch therapy reduces the extent of exercise-induced myocardial ischemia: Results of a double-blind, placebo-controlled trial using quantitative thallium-201 tomography. *J Am Cardiol* 24:25, 1994.
80. Fallen EL, Nahmia SC, Scheffel A, et al: Redistribution of myocardial blood flow with topical nitroglycerin in patients with coronary arterial disease. *Circulation* 91:1381, 1995.
81. Parker JO, Amies MH, Hawkinson RW, et al: Intermittent transdermal nitroglycerin therapy in angina pectoris: Clinically effective without tolerance or rebound. *Circulation* 91:1368, 1995.
82. DeMots H, Glasser SP: Intermittent transdermal nitroglycerin therapy in the treatment of chronic stable angina. *J Am Coll Cardiol* 13:786, 1989.
83. Freedman SB, Daxini BV, Noyce D, Kelly DT: Intermittent transdermal nitrates do not improve ischemia in patients taking beta-blockers or calcium antagonists: Potential role of rebound ischemia during the nitrate-free period. *J Am Coll Cardiol* 25:349, 1995.
84. Bogaert MG: Clinical pharmacokinetics of nitrates. *Cardiovasc Drugs Ther* 8:693, 1994.
85. Schaumann W: Pharmacokinetics of isosorbide dinitrate and isosorbide-5-mononitrate. *Int J Clin Pharmacol Ther Toxicol* 27:445, 1989.
86. Parker JO and the Isosorbide-5-Mononitrate Study Group: Eccentric dosing with isosorbide-5-mononitrate in angina pectoris. *Am J Cardiol* 73:871, 1993.
87. Abrams J: The role of nitrates in coronary heart disease. *Arch Intern Med* 155:357, 1995.
88. Gunasekara NS, Noble S: Isosorbide 5-mononitrate. A review of a sustained-release formulation (Imdur) in stable angina pectoris. *Drugs* 57:261, 1999.
89. Chrysant SG, Glasser SP, Bittar N, et al: Efficacy and safety of extended release isosorbide mononitrate for stable effort angina pectoris. *Am J Cardiol* 72:1249, 1993.
90. Prakash A, Markham A: Long-acting isosorbide mononitrate. *Drugs* 57:93, 1999.
91. Waller DG: Optimal nitrate therapy with a once-daily sustained-release formulation of isosorbide mononitrate. *J Cardiovasc Pharmacol* 34 (Suppl 2):S21, 1999.
92. Webb DJ, Muirhead GJ, Wulff M, et al: Sildenafil citrate potentiates the hypotensive effect of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 36:25, 2000.
93. Col J, Col-Debeys C, Lavenne-Pardonge E, et al: Propylene glycol induced heparin resistance during nitroglycerin infusion. *Am Heart J* 110:171, 1986.
94. Becker RC, Jeanne CM, Corrao JM, et al: Intravenous nitroglycerin induced heparin resistance: A qualitative antithrombin III abnormality. *Am Heart J* 119:1254, 1990.
95. Bode V, Weizel D, Franz G, et al: Absence of drug interaction between heparin and nitroglycerin: Randomized placebo-controlled crossover study. *Arch Intern Med* 150(10):2117, 1990.
96. Nicolini FA, Ferrini D, Ottani F, et al: Concurrent nitroglycerin therapy impairs tissue-type plasminogen activator-induced thrombolysis in patients with acute myocardial infarction. *Am J Cardiol* 74:662, 1994.
97. Death AK, Nakhla S, McGrath KCY, et al: Nitroglycerin upregulates matrix metalloproteinase expression in human macrophages. *J Am Coll Cardiol* 39:1943, 2002.
98. Thadani U, Ripley TL: Side effects of using nitrates to treat heart failure and the acute coronary syndromes, unstable angina and acute myocardial infarction. *Expert Opin Drug Saf* 6: 385, 2007.
99. Elkayam V: Tolerance to organic nitrates: Evidence, mechanisms, clinical relevance, and strategies for prevention. *Ann Intern Med* 114: 667, 1991.
100. Fung H-L, Bauer JA: Mechanisms of nitrate tolerance. *Cardiovasc Drugs Ther* 94-8:489, 1993.
101. Steering Committee, Transdermal Nitroglycerin Cooperative Study: Acute and chronic antianginal efficacy in continuous twenty-four hour application of transdermal nitroglycerin. *Am J Cardiol*

- 68:1263, 1991.
102. Thadani U, Fung H-L, Darke AC, Parker JO: Oral isosorbide dinitrate in angina pectoris: Comparison of duration of action and dose response relationship during acute and sustained therapy. *Am J Cardiol* 49:411, 1982.
 103. Münzel T, Mollnau H, Hartmann M et al: Effects of a nitrate-free interval on tolerance, vasoconstrictor sensitivity and vascular superoxide production. *J Am Coll Cardiol* 36(2):628, 2000.
 104. Abrams J, Elkayam U, Thadani U, Fung H: Nitrate tolerance: An historical overview. *Am J Cardiol* 81(1A):3-14A, 1998.
 105. Glasser S: Prospects for therapy of nitrate tolerance. *Lancet* 353:1545, 1999.
 106. Elkayam U, Roth A, Mehra A, et al: Randomized study to evaluate the relation between oral isosorbide dinitrate dosing interval and the development of early tolerance to its effect on left ventricular filling pressure in patients with chronic heart failure. *Circulation* 84:2040, 1991.
 107. Frishman WH: Tolerance, rebound and time-zero effect of nitrate therapy. *Am J Cardiol* 70:436, 1992.
 108. Ferratini M, Pirelli S, Merlini P, et al: Intermittent transdermal nitroglycerin monotherapy in stable exercise-induced angina: A comparison with a continuous schedule. *Eur Heart J* 10:998, 1989.
 109. Abou-Mohamed G, Kaesemeyer WH, Caldwell RB, Caldwell RW: Role of L-arginine in the vascular actions and development of tolerance to nitroglycerin. *Br J Pharmacol* 130(2):211, 2000.
 110. Gruhn N, Aldershvile J, Boesgaard S: Tetrahydrobiopterin improves endothelium-dependent vasodilation in nitroglycerin-tolerant rats. *Eur J Pharmacol* 416(3):245, 2001.
 111. Milone SD, Pace-Asciak CR, Reynaud D, et al: Biochemical, hemodynamic, and vascular evidence concerning the free radical hypothesis of nitrate tolerance. *J Cardiovasc Pharmacol* 33(5):685, 1999.
 112. Dikalov S, Fink B, Skatchkov M, Bassenge E: Comparison of glyceryl trinitrate-induced with pentacerythrityl tetranitrate-induced in vivo formation of superoxide radicals: Effect of vitamin C. *Free Radic Biol Med* 27(1-2):170, 1999.
 113. Bassenge E, Fink N, Skatchkov M, Fink B: Dietary supplement with vitamin C prevents nitrate tolerance. *J Clin Invest* 102(1):67, 1998.
 114. Watanabe H, Kakihana M, Ohtsuka S, Sugishita Y: Randomized, double-blind, placebo-controlled study of the preventive effect of supplemental oral vitamin C on attenuation of development of nitrate tolerance. *J Am Coll Cardiol* 31(6):1323, 1998.
 115. Gori T, Burstein JM, Ahmed S, et al: Folic acid prevents nitroglycerin-induced nitric oxide synthase dysfunction and nitrate tolerance. *Circulation* 104:1119, 2001.
 116. Loscalzo J: Folate and nitrate-induced endothelial dysfunction: A simple treatment for complex pathology. *Circulation* 104:1086, 2001.
 117. Hirai N, Kawano H, Yasue H, et al: Attenuation of nitrate tolerance and oxidative stress by an angiotensin II receptor blocker in patients with coronary spastic angina. *Circulation* 108: 1446, 2003.
 118. Zimmet JM, Hare JM: Nitroso-redox interactions in the cardiovascular system. *Circulation* 114: 1531, 2006.
 119. Thomas GR, DiFabio JM, Gori T, Parker JD: Once daily therapy with isosorbide-5-mononitrate causes endothelial dysfunction in humans. *J Am Coll Cardiol* 49: 1289, 2007.
 120. Berkenboom G, Fontaine D, Unger P, et al: Absence of nitrate tolerance after long-term treatment with ramipril: An endothelium-dependent mechanism. *J Cardiovasc Pharmacol* 34:517, 1999.
 121. Munzel T: Does nitroglycerin therapy hit the endothelium? (editorial). *J Am Coll Cardiol* 38:1102, 2001.
 122. Hebert D, Lam JYT: Nitroglycerin rebound associated with vascular, rather than platelet, hypersensitivity. *J Am Coll Cardiol* 36:2311, 2000.
 123. Kanamasa K, Hayashi T, Takenaka T, et al: Continuous long-term dosing with oral slow-release isosorbide dinitrate does not reduce incidence of cardiac events in patients with healed myocardial infarction. *Clin Cardiol* 24:608, 2001.
 124. Nakamura Y, Moss AJ, Brown MW, et al: Long-term nitrate use may be deleterious in ischemic heart disease: A study using the databases from two large-scale post-infarction studies. Multicenter Myocardial Ischemia Research Group. *Am Heart J* 138:577, 1999.
 125. Khot WN, Novaro GM, Popvic ZB, et al: Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med* 348: 1756, 2003.
 126. Miller RR, Vismara LA, Zelis R, et al: Clinical use of sodium nitroprusside in chronic ischemic heart disease: Effect on peripheral vascular resistance and venous tone on ventricular volume, pump and mechanical performance. *Circulation* 51:328, 1975.
 127. Mullens W, Abrahams Z, Francis GS: Sodium nitroprusside for advanced low-output heart failure. *J Am Coll Cardiol* 52: 200, 2008.
 128. Zile MR, Gaasch WH: Heart failure in aortic stenosis – improving diagnosis and treatment. *N Engl J Med* 348: 1735, 2003.
 129. Mann T, Cohn P, Holman BL, et al: Effect of nitroprusside on regional myocardial blood flow in

- coronary artery disease: Results in 25 patients and comparison with nitroglycerin. *Circulation* 52:732, 1978.
130. Macho P, Vatner SF: Effects of nitroglycerin and nitroprusside on large and small coronary vessels in conscious dogs. *Circulation* 64:1101, 1981.
 131. Flaherty JT, Magee PA, Gardner TJ, et al: Comparison of intravenous nitroglycerin and sodium nitroprusside for the treatment of acute hypertension developing after coronary artery bypass surgery. *Circulation* 65:1172, 1981.
 132. Cohn JN, Franciosa JA, Francis GS, et al: Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure. *N Engl J Med* 306:1129, 1982.
 133. Durrer JD, Lie KI, van Chapelle FJL, Durrer D: Effect of sodium nitroprusside on mortality in acute myocardial infarction. *N Engl J Med* 306:1121, 1982.
 134. Flaherty JT: Role of nitrates in acute myocardial infarction. In: Abrams J, Pepine C, Thadani U, eds. *Medical Therapy of Ischemic Heart Disease*. Boston, Little Brown, 1992:309.
 135. Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST elevation myocardial infarction – executive summary of a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol* 44: 671, 2004.
 136. Darius H: Role of nitrates for the therapy of coronary artery disease patients in the years beyond 2000. *J Cardiovasc Pharmacol* 34(Suppl 2): S15, 1999.

References for Chapter 15

Ranolazine

A Piperazine Derivative

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1. American Heart Association. Heart disease and stroke statistics – 2005 update. Dallas, TX: American Heart Association; 2005.
2. Fraker TD Jr., Fihn SD. Focused update of the 2002 ACC/AHA guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines. *J Am Coll Cardiol* 50: 2264, 2007.
3. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 41: 159, 2003.
4. Hueb W, Soares PR, Gersh BJ, et al. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease. One year results. *J Am Coll Cardiol* 43:1743,2004.
5. Holubkov R, Laskey WK, Haviland A. Angina 1 year after percutaneous coronary intervention: a report from the NHLBI dynamic registry. *Am Heart J* 144:826,2002.
6. Anderson JR, Nawarskas JJ: Ranolazine. A metabolic modulator for the treatment of chronic stable angina. *Cardiol in Rev* 13: 202, 2005.
7. Goldschmidt M, Frishman WH: Ranolazine: a new anti-ischemic drug which affects myocardial energetics. *Am J Therap* 2: 269, 1995.
8. Frishman WH, Retter A, Misailidis, et al: Innovative pharmacologic approaches to the treatment of myocardial ischemia. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed.* New York: McGraw Hill 2003: 855.
9. Siddiqui MAA, Keam SJ: Ranolazine. A review of its use in chronic stable angina pectoris. *Drugs* 66: 693, 2006.
10. Keating GM: Ranolazine. A review of its use in chronic stable angina. *Drugs* 68: 2483, 2008.
11. Scirica BM, Morrow DA: Ranolazine in patients with angina and coronary artery disease. *Curr Cardiol Rep* 9: 272, 2007.
12. Shyroock JC, Belardinelli L: Inhibition of late sodium current to reduce electrical and mechanical dysfunction of ischaemic myocardium. *Br J Pharmacol* 153: 1128, 2008.
13. Hale SL, Shyroock JC, Belardinelli L, et al: Late sodium current inhibition as a new cardioprotective approach. *J Molec Cell Cardiol* 44: 954, 2008.13a. Hwang H, Arcidi JM Jr., Hale SL, et al: Ranolazine as a cardioplegia additive improves recovery of diastolic function in isolated rat hearts. *Circulation* 120 Suppl 1: S16, 2009.
14. Saint DA: The cardiac persistent sodium current: an appealing therapeutic target? *Br J Pharmacol* 153: 1133, 2008.
15. Theroux P. Protection of the myocardial cell during ischemia. *Am J Cardiol* 83:3G,1999.
16. Stanley WC, Chandler MP. Energy metabolism in the normal and failing heart: potential for therapeutic interventions. *Heart Fail Rev* 7:115,2002.
17. Hutter JE, Piper HM, Spieckermann PG. Effects of fatty acid oxidation on efficiency of energy production in rat heart. *Am J Physiol* 249:H723,1985.
18. Lopaschuk GD, Belke DD, Gamble J, et al. Regu-

- lation of fatty acid oxidation in the mammalian heart in health and disease. *Biochem Biophys Acta* 1994;1213:263,1994.
19. Steinberg D, Khoo JC. Hormone-sensitive lipase of adipose tissue. *Fed Proc* 36: 1986,1977.
 20. MacInnes A, Fairman DA, Binding P, et al: The antianginal agent trimetazidine does not exert its functional benefit via inhibition of mitochondrial long-chain-3-ketoacyl coenzyme A thiolase. *Circ Res* 93: e26, 2003.
 21. Wang P, Fraser H, Lloyd SG, et al: A comparison between ranolazine and CVT-4325, a novel inhibitor of fatty acid oxidation, on cardiac metabolism and left ventricular function in rat isolated perfused heart during ischemia and reperfusion. *J Pharmacol Exp Ther* 321: 213, 2007.
 22. Létienné R, Vié B, Puech A, et al: Evidence that ranolazine behaves as a weak β 1- and β 2-adrenoceptor antagonist in the rat cardiovascular system. *Naunyn Schmiedebergs Arch Pharmacol* 363: 464, 2001.
 23. Pepine CJ, Wolff AA: A controlled trial with a novel anti-ischemic agent, ranolazine, in chronic stable angina pectoris that is response to conventional antianginal agents. Ranolazine Study Group. *Am J Cardiol* 84:46, 1999.
 24. Rousseau MF, Pouleur H, Cocco G, et al: Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. *Am J Cardiol* 95: 311, 2005.
 25. Sossalla S, Wagner S, Rasenack ECL, et al: Ranolazine improves diastolic dysfunction in isolated myocardium from failing human hearts: role of late sodium current and intracellular ion accumulation. *J Molec Cell Cardiol* 45: 32, 2008.
 26. Moss AJ, Zareba W, Schwarz KQ, et al: Ranolazine shortens repolarization in patients with sustained inward sodium current due to type-3 long-QT syndrome. *J Cardiovasc Electrophysiol* 19:1294, 2008.
 27. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol* 43:1375, 2004.
 28. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA* 291:309, 2004.
 29. Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. *Circulation* 110:904,2004.
 30. Wu L, Shryock JC, Song Y, et al. Antiarrhythmic effects of ranolazine in a guinea pig in vitro model of long-QT syndrome. *JPET* 310:599,2004.
 31. Song Y, Shryock JC, Wu L, Belardinelli L. Antagonism by ranolazine of the pro-arrhythmic effects of increasing late I_{Na} in guinea pig ventricular myocytes. *J Cardiovasc Pharmacol* 44:192,2004.
 - 31a. Carvas M, Nascimento BCG, Acar M, et al: Intrapericardial ranolazine prolongs atrial refractory period and markedly reduces atrial fibrillation inducibility in the intact porcine heart. *J Cardiovasc Pharmacol* 55: 286, 2010.
 32. Fenichel RR, Malik M, Antzelevitch C, et al. Drug-induced torsades de pointes and implications for drug development. *J Cardiovasc Electrophysiol* 15:475,2004.
 33. Belardinelli L, Antzelevitch C, Vos MA. Assessing predictors of drug-induced torsade de pointes. *Trends Pharmacol Sci* 24:619,2003.
 34. Cocco G, Rousseau MF, Bouvy T, et al. Effects of a new metabolic modulator, ranolazine, on exercise tolerance in angina pectoris patients treated with β -blocker or diltiazem. *J Cardiovasc Pharmacol* 20:131,1992.
 35. Herron WJ, Eadie J, Penman AD. Estimation of ranolazine and eleven phase I metabolites in human plasma by liquid chromatography-atmospheric pressure chemical ionization mass spectrometry with selected-ion monitoring. *J Chromatogr A* 712:55,1995.
 36. Pepine CJ, Wolff AA. A controlled trial with a novel anti-ischemic agent, ranolazine, in chronic stable angina pectoris that is responsive to conventional antianginal agents. *Am J Cardiol*. 84:46,1999.
 37. Anderson JR, Khou S, Nawarskas JJ. Ranolazine: a potential new treatment for chronic stable angina. *Heart Dis* 3:263,2001.
 38. Jain D, Dasgupta P, Hughes LO, et al. Ranolazine (RS-43285): A preliminary study of a new antianginal agent with selective effect of ischaemic myocardium. *Eur J Clin Pharmacol* 38:111,1990.
 39. Thadani U, Ezekowitz M, Fenney L, et al. Double-blind efficacy and safety study of a novel anti-ischemic agent, ranolazine, versus placebo in patients with chronic stable angina pectoris. *Circulation* 90:726,1994.
 40. Rousseau MF, Pouleur H, Cocco G, Wolff AA. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. *Am J Cardiol* 95; 311, 2005.
 41. Stone PH, Gratsiansky NA, Blokhin A, et al: Anti-anal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol* 48: 566, 2006.
 42. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al: Effects of ranolazine on recurrent

- cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. *JAMA* 297: 1775, 2007.
43. DeQuattro V, Skettino S, Chaitman BR, et al. Comparative antianginal efficacy and tolerability of ranolazine in diabetic and nondiabetic patients: results of the MARISA trial. *J Am Coll Cardiol* 37: 338A, 2001.
 44. Chaitman BR, Skettino S, DeQuattro V. Improved exercise performance on ranolazine in patients with chronic angina and a history of heart failure: the MARISA trial. *J Am Coll Cardiol* 37: 149A, 2001.
 45. Koren MJ, Crager MR, Sweeney M. Long-term safety of a novel antianginal agent in patients with severe chronic stable angina: the Ranolazine Open Label Experience (ROLE). *J Am Coll Cardiol* 49: 1027, 2007.
 46. Chaitman BR, Skettino S, Pepine CJ, et al. Ranolazine increases exercise performance and decreases hemoglobin A1C in angina patients with diabetes. *J Am Coll Cardiol* 41: 378A, 2003.
 47. White HD, Skettino S, Chaitman BR, et al. Antianginal efficacy of ranolazine addition to beta blocker or calcium antagonist therapy in patients with a history of heart failure. *Circulation* 106:II-349, 2002.
 48. Scirica BM, Morrow DA, Hod H, et al. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndromes: results from the Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis In Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. *Circulation* 116: 1647, 2007.
 49. Scirica BM, Morrow DA, Budaj A, et al. Ischemic detected on continuous electrocardiography after acute coronary syndrome: observations from the MERLIN-TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 36) trial *J Am Coll Cardiol* 53: 1411, 2009.
 50. Wilson SR, Scirica BM, Braunwald E, et al. Efficacy of ranolazine in patients with chronic angina: observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation Acute Coronary Syndromes 36) trial. *J Am Coll Cardiol* 53: 1510, 2009.
 51. Mega JL, Hochman JS, Scirica BM, et al. Clinical features and outcomes of women with unstable ischemic heart failure. Observations from Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI36). *Circulation* 121: 1809, 2010.
 52. Morrow DA, Scirica BM, Sabatine MS, et al. B-type natriuretic peptide and the effect of ranolazine in patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 55: 1189, 2010.
 53. Morrow DA, Scirica BM, Chaitman BR, et al. Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. *Circulation* 119: 2032, 2009.
 54. Sabbah HN, Mishima T, Biesiadecki BJ, et al. Ranolazine improves left ventricular performance in dogs with chronic heart failure. *J Am Coll Cardiol* 34(Suppl A): 218A, 2000.
 55. CV Therapeutics, Inc. CV Therapeutics announces preclinical data evaluating ranolazine and dobutamine in a model of CHF. Available at <http://www.cvt.com>.
 56. Wenger NK, Chaitman B, Vetovec GW. Gender comparison of efficacy and safety of ranolazine for chronic angina pectoris in 4 randomized clinical trial. *Am J Cardiol* 99: 11, 2007.
 57. Rich MW, Crager M, McKay CR. Safety and efficacy of extended-release ranolazine in patients aged 70 years or older with chronic stable angina pectoris. *Am J Geriatr Cardiol* 16: 216, 2007.
 58. Reddy BM, Weintraub HS, Schwartzbard AZ. Ranolazine. A new approach to treating an old problem. *Texas Heart Inst J* 37: 641, 2010.

References for Chapter 16

Nonspecific Antihypertensive Vasodilators

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1. McVeigh GE, Bratteli, CW, Morgan DJ, et al: Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis: Aging and arterial compliance. *Hypertension* 33:1392, 1999.
2. Hoffman BB: Therapy of hypertension. In Brunton LL, Lazo JS, Parker KL (eds): *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th ed. NY: McGraw-Hill, 2006: 845.
3. Sica DA, Gehr TW: Pharmacologic treatment of hypertension. In Antman EM (ed): *Cardiovascular Therapeutics. A companion to Braunwald's Heart Disease 3rd ed.* Philadelphia, Saunders: 2007, 578.
4. Ram CVS, Fennes A: Direct arterial dilators. In Izzo JL Jr, Black HR, eds. *Hypertension Primer*, 4th ed. Dallas, American Heart Association, 2008, 469.
5. Chobanian AV, Bakris GL, Black HR, et al and the National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 289: 2560, 2003.
6. Guidelines Subcommittee: 1999 World Health Organization—International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 17:151, 1999.
7. Seedat YK: Hypertension in developing nations in Sub-Saharan Africa. *J Hum Hypertens* 14:739, 2001.
8. Frishman WH, Schlocke SJ, Awad K, Tejani N: Pathophysiology and medical management of systemic hypertension in pregnancy. *Cardiol in Rev* 13: 274, 2005.
9. Calhoun DA: Hypertensive crisis. In Oparil S, Weber MA (eds): *Hypertension: A Companion to Brenner and Rector's The Kidney*. Philadelphia: Saunders, 2000; 715.
10. Abalos E, Duley L, Steyn DW, Henderson-Smart DJ: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy (Cochrane Review). The Cochrane Library, 2007.
11. Cohn JN, Archibald DG, Ziesche S, et al: Effect of vasodilator therapy on mortality in chronic congestive heart failure: Results of a Veterans Administration Cooperative Study. *N Engl J Med* 314:1547, 1986.
12. Cohn JN, Johnson G, Ziesche S, et al: A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 325:303, 1991.
13. Carmody MS, Anderson JR: BiDil (isosorbide dinitrate and hydralazine): a new fixed-dose combination of two older medications for the treatment of heart failure in black patients. *Cardiol in Rev* 15: 46, 2007.
14. Frishman WH, Lee BY, Galandauer I, Phan AH: Potassium-channel openers and sodium/hydrogen-channel effectors. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed.* New York: McGraw Hill 2003: 481.
15. Clapham JC, Trail BK, Hamilton TC: K⁺ channel activators, acute glucose tolerance and glibenclamide-induced hypoglycemia in the hypertensive rat. *Eur J Pharmacol* 257:79, 1994.
16. Stone CK, Wellington KL, Willick A, et al: Acute hemodynamic effects of pinacidil in hypertensive patients with and without propranolol treatment. *J Clin Pharmacol* 31:333, 1991.
17. Krusell LR, Jespersen LT, Thomsen K, Pedersen OL: Proximal renal tubular pressure-natriuresis in essential hypertensives following acute vasodilation. *Blood Press* 2:40, 1993.

18. Lundeen TE, Dolan DR, Ram CV: Pericardial effusion associated with minoxidil therapy. *Postgrad Med* 70: 98, 1981.
19. Frohlich ED: Other adrenergic inhibitors and the direct-acting smooth muscle vasodilators. In Oparil S, Weber MA (eds): *Hypertension: A Companion to Brenner and Rector's The Kidney*. Philadelphia: Saunders, 2000; 637.

References for Chapter 17

Antiarrhythmic Drugs

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1. Members of the Sicilian Gambit: New approaches to antiarrhythmic therapy, Part I. Emerging therapeutic applications of the cell biology of cardiac arrhythmias. *Circulation* 104:2865, 2001.
2. Members of the Sicilian Gambit: New approaches to antiarrhythmic therapy, Part II. Emerging therapeutic applications of the cell biology of cardiac arrhythmias. *Circulation* 104:2990, 2001.
3. Lau W, Newman D, Dorian P: Can antiarrhythmic agents be selected based on mechanism of action? *Drugs* 60:1315, 2000.
4. Harrison DC: Antiarrhythmic drug classification: New science and practical applications. *Am J Cardiol* 50:185, 1985.
5. The Task Force of the Working Group on Arrhythmias of the European Society of Cardiology: The Sicilian gambit: A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. *Circulation* 84:1831, 1991.
6. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators: Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 321:406, 1989.
7. ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: *Circulation* 2006;114:e257-354.
8. Wyse D, Waldo A, DiMarco J et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-33.
9. Ellenbogen KA, Clemon HF, Stambler BS, et al: Efficacy of ibutilide for termination of atrial fibrillation and flutter. *Am J Cardiol* 78(8A):42, 1996.
10. Natale A, Newby KH, Pisano E, et al: Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter. *J Am Coll Cardiol* 35:1898, 2000.
11. Bauernfeind RA, Amat-y-Leon F, Dhingra RC, et al: Chronic nonparoxysmal sinus tachycardia in otherwise healthy persons. *Ann Intern Med* 91:702, 1979.
12. Kastor J: Multifocal atrial tachycardia. *N Engl J Med* 322(24):1713, 1990.
13. Cannom DS, Prystowsky EN: Management of ventricular arrhythmias. Detection, drugs and devices. *JAMA* 281:172, 1999.
14. Buxton AE, Lee K, Fisher JD, et al: A Randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 341:1882, 1999.
15. Kuck K-H, Cappato R, Siebels J: Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest. The Cardiac Arrest Study Hamburg (CASH). *Circulation* 102:748, 2000.
16. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators: A Comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 337:1576, 1997.
17. Pacifico A, Hohnloser SH, Williams JH, et al: Prevention of implantable-defibrillator shocks by treatment with sotalol. d, l—Sotalol Implantable Cardioverter-Defibrillator Study Group. *N Engl J Med* 340(24):1885, 1999.
18. Hoffman BF, Rosen MR, Wit AL: Electrophysiology and pharmacology of cardiac arrhythmias: VII. Cardiac effects of quinidine and procainamide. *Am Heart J* 90:117, 1975.

19. Ueda CT, Williamson BJ, Dzindzio BS: Absolute quinidine bioavailability. *Clin Pharmacol Ther* 20:260, 1976.
20. Kessler KM, Humphries WC, Black M, Spann J: Quinidine pharmacokinetics in patients with cirrhosis receiving propranolol. *Am Heart J* 96:627, 1978.
21. Drayer DE, Hughes M, Lorenzo B, Reidenberg M: Prevalence of high (S)-3-hydroxyquinidine/quinidine ratios in serum, and clearance of quinidine in cardiac patients with age. *Clin Pharmacol Ther* 27:72, 1980.
22. Kessler KM, Lowenthal DT, Warner H, et al: Quinidine elimination in patients with congestive heart failure or poor renal function. *N Engl J Med* 290:706, 1974.
23. Uematsu T, Sato R, Vozeh S, et al: Relative electrophysiological potencies of quinidine, 3-OH quinidine and quinidine-N-oxide in guinea-pig heart. *Arch Intern Pharmacodyn Ther* 297:29, 1989.
24. DiMarco JP, Garan H, Ruskin JN: Efficacy of quinidine in the treatment of ventricular arrhythmias: The role of electrophysiologic testing. *Circulation* 64(Suppl IV):38, 1981.
25. Ruskin JN, DiMarco JP, Garan H: Out-of-hospital cardiac arrest: Electrophysiologic observations and selection of long-term antiarrhythmic therapy. *N Engl J Med* 303:607, 1980.
26. Lown B, Wolf M: Approaches to sudden death from coronary heart disease. *Circulation* 44:130, 1971.
27. Farringer JA, McWay-Hess K, Clementi WA: Cimetidine-quinidine interaction. *Clin Pharm* 3:81, 1984.
28. Leahey EB, Reiffel JA, Drusin RE, et al: Interaction between quinidine and digoxin. *JAMA* 240:533, 1978.
29. Schenck-Gustafsson K, Jogestrand T, Norlander R, Dahlqvist TR: Effect of quinidine on digoxin concentration skeletal muscle and serum in patients with atrial fibrillation: Evidence for reduced binding of digoxin in muscle. *N Engl J Med* 305:209, 1981.
30. Funck-Brentano C, Turgeon J, Woosley RL, Roden DM: Effect of low dose quinidine on encainide pharmacokinetics and pharmacodynamics: Influence of genetic polymorphism. *J Pharmacol Exp Ther* 249:134, 1989.
31. Funck-Brentano C, Kroener HK, Pavlou H, et al: Genetically determined interaction between propafenone and low dose quinidine: Role of active metabolites in modulating net drug effect. *Br J Clin Pharmacol* 27:435, 1989.
32. Lau C-P, Chow MSS, Tse H-F, et al: Control of paroxysmal atrial fibrillation recurrence using combined administration of propafenone and quinidine. *Am J Cardiol* 86:1327, 2000.
33. Mark LC, Kayden HJ, Steele JM, et al: The physiological disposition and cardiac effects of procainamide. *J Pharmacol Exp Ther* 102:5, 1951.
34. Miller H, Nathanson MH, Griffith GC: The action of procainamide in cardiac arrhythmias. *JAMA* 146:1004, 1951.
35. Josephson ME, Caracta AR, Ricciutti MA, et al: Electrophysiologic properties of procainamide in man. *Am J Cardiol* 33:596, 1974.
36. Manion CV, Lalka D, Baer DT, Meyer MB: Absorption, kinetics of procainamide in humans. *J Pharm Sci* 66:981, 1977.
37. Karlsson E: Clinical pharmacokinetics of procainamide. *Clin Pharmacokinet* 3:97, 1978.
38. Singh S, Gelband H, Mehta AV, et al: Procainamide elimination kinetics in pediatric patients. *Clin Pharmacol Ther* 32:607, 1982.
39. Kluger J, Leech S, Reidenberg MM, et al: Long-term antiarrhythmic therapy with acetylprocainamide. *Am J Cardiol* 48:1124, 1981.
40. Bigger JT, Heissenbuttel RH: The use of procainamide and lidocaine in the treatment of cardiac arrhythmias. *Prog Cardiovasc Dis* 11:515, 1969.
41. Waxman HL, Buxton AE, Sadowski LM, Josephson ME: The response to procainamide during electrophysiologic study for sustained ventricular tachyarrhythmias predicts the response to other medications. *Circulation* 67:30, 1983.
42. Rae AP, Sokoloff NM, Webb CR, et al: Limitations of failure of procainamide during electrophysiological testing to predict response to other medical therapy. *J Am Coll Cardiol* 6:410, 1985.
43. Ellrodt AG, Murata GH, Riedinger MS, et al: Severe neutropenia associated with sustained-release procainamide. *Ann Intern Med* 100:197, 1984.
44. Sim E: Drug-induced immune-complex disease. *Comp Inflamm* 6:119, 1989.
45. Adams LE, Sanders CE, Budinsky RA, et al: Immunomodulatory effects of procainamide metabolites: Their implications in drug-related lupus. *J Lab Clin Med* 113:482, 1989.
46. Asherson RA, Zulman J, Hughes GR: Pulmonary thromboembolism associated with procainamide induced lupus syndrome and anticardiolipin antibodies. *Ann Rheum Dis* 48:232, 1989.
47. Li GC, Greenberg CS, Currie MS: Procainamide-induced lupus anticoagulants and thrombosis. *South Med J* 81:262, 1988.
48. Heyman MR, Flores RH, Edelman BB, Carliner NH: Procainamide-induced lupus anticoagulant. *South Med J* 81:934, 1988.
49. Kosoglou T, Rocci ML, Vlases PH: Trimethoprim

- alters the disposition of procainamide and N-acetylprocainamide. *Clin Pharmacol Ther* 44:467, 1988.
50. Lai MY, Jiang FM, Chung CH, et al: Dose dependent effect of cimetidine on procainamide disposition in man. *Int J Clin Pharmacol Ther Toxicol* 26:118, 1988.
 51. Christian CD, Meredith CG, Speeg KV: Cimetidine inhibits renal procainamide clearance. *Clin Pharmacol Ther* 36:221, 1984.
 52. Danilo P Jr, Hordoff AJ, Rosen MR: Effects of disopyramide on electrophysiologic properties of canine cardiac Purkinje fibers. *J Pharmacol Exp Ther* 201:701, 1977.
 53. Sasyniuk BI, Kus T: Cellular electrophysiologic changes induced by disopyramide in normal and infarcted hearts. *J Int Med Res* 4 (Suppl I): 20, 1976.
 54. Kidwell GA, Lima JJ, Schaal SF, Muir WW: Hemodynamic and electrophysiologic effects of disopyramide enantiomers in a canine blood superfusion model. *J Cardiovasc Pharmacol* 13:644, 1989.
 55. Birkhead JS, Vaughan Williams EM: Dual effect of disopyramide on atrial and atrioventricular conduction and refractory periods. *Br Heart J* 39:657, 1977.
 56. Morady F, Scheinman MM, Desai J: Disopyramide. *Ann Intern Med* 96:337, 1982.
 57. Bexton RS, Hellestrand KJ, Cory-Pearce R, et al: The direct electrophysiologic effects of disopyramide phosphate in the transplanted human heart. *Circulation* 67:38, 1983.
 58. Katoh T, Karagueuzian HS, Jordan J, Mandel JW: The cellular electrophysiologic mechanism of the dual actions of disopyramide on rabbit sinus node dysfunction. *Circulation* 66:1216, 1979.
 59. Dubetz DK, Brown NN, Hooper WD, et al: Disopyramide: Pharmacokinetics and bioavailability. *Br J Clin Pharmacol* 6:279, 1978.
 60. Capparelli EV, DiPersio DM, Zhao H, et al: Clinical pharmacokinetics of controlled-release disopyramide in patients with cardiac arrhythmias. *J Clin Pharmacol* 28:306, 1988.
 61. Bonde J, Jensen NM, Pedersen LE, et al: Elimination kinetics and urinary excretion of disopyramide in human healthy volunteers. *Pharmacol Toxicol* 62:298, 1988.
 62. Lima JJ, Boudoulas H, Blanford M: Concentration-dependence of disopyramide binding to plasma protein and its influence on kinetics and dynamics. *J Pharmacol Exp Ther* 219:741, 1981.
 63. Leach AJ, Brown JE, Armstrong PW: Cardiac depression by intravenous disopyramide in patients with left ventricular dysfunction. *Am J Med* 68:839, 1980.
 64. Podrid PJ, Schoeneberger A, Lown B: Congestive heart failure caused by oral disopyramide. *N Engl J Med* 302:614, 1980.
 65. Yoshida Y, Hirai M, Yamada T, et al: Antiarrhythmic efficacy of dipyridamole in treatment of reperfusion arrhythmias. Evidence for cAMP-mediated triggered activity as a mechanism responsible for reperfusion arrhythmias. *Circulation* 101:624, 2000.
 66. Jennings G, Jones MBS, Besterman EMM, et al: Oral disopyramide in prophylaxis of arrhythmias following myocardial infarction. *Lancet* 1:51, 1976.
 67. Vismara LA, Mason DT, Amsterdam EA: Disopyramide phosphate: Clinical efficacy of a new oral antiarrhythmic drug. *Am Heart J* 16:330, 1974.
 68. Jonason T, Ringqvist I, Bandh S, et al: Propafenone versus disopyramide for treatment of chronic symptomatic ventricular arrhythmias: A multicenter study. *Acta Med Scand* 223:515, 1988.
 69. Ueda CT, Dzindzio BS, Vosik WM: Serum disopyramide concentrations and suppression of ventricular premature contractions. *Clin Pharmacol Ther* 36:326, 1984.
 70. Vismara LA, Vera Z, Miller RR, Mason DT: Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. *Am J Cardiol* 39:1027, 1977.
 71. Kim SG, Mercado AD, Tam S, Fisher JD: Combination of disopyramide and mexiletine for better tolerance and additive effects for treatment of ventricular arrhythmias. *J Am Coll Cardiol* 13:659, 1989.
 72. Della-Bella P, Tondo C, Marenzi G, et al: Facilitating influence of disopyramide on atrial flutter termination by overdrive pacing. *Am J Cardiol* 61:1046, 1988.
 73. Karlson BW, Torstensson I, Jansson SO, Peterson LE: Disopyramide in the maintenance of sinus rhythm after electroconversion of atrial fibrillation: A placebo-controlled one-year follow-up study. *Eur Heart J* 9:284, 1988.
 74. Fujimura O, Klein GJ, Sharma AD, et al: Acute effect of disopyramide on atrial fibrillation in the Wolff-Parkinson-White syndrome. *J Am Coll Cardiol* 13:1133, 1989.
 75. Morillo CA, Leitch JW, Yee R, Klein GJ: A placebo-controlled trial of intravenous and oral disopyramide for prevention of neurally mediated syncope induced by head-up tilt. *J Am Coll Cardiol* 22(7):1843, 1993.
 76. Nicholson WJ, Martin CE, Gracey JG, Knoch HR: Disopyramide induced ventricular fibrillation. *Am J Cardiol* 43:1053, 1979.
 77. Nakabayashi H, Ito T, Igawa T, et al: Disopyramide induces insulin secretion and plasma glucose dimi-

- nution: Studies using the in situ canine pancreas. *Metabolism* 38:179, 1989.
78. Ragosta M, Wiehl AC, Rosenfeld LE: Potentially fatal interaction between erythromycin and disopyramide. *Am J Med* 86:465, 1989.
 79. Harrison DC, Sprouse JH, Morrow AG: The antiarrhythmic properties of lidocaine and procainamide. *Circulation* 28:486, 1963.
 80. Harrison DC, Alderman EL: The pharmacology and clinical use of lidocaine as an antiarrhythmic drug. *Modern Treatment* 9:139, 1972.
 81. Rosen KM, Lau SH, Weiss MB, Damato AN: The effect of lidocaine on atrioventricular and intraventricular conduction in man. *Am J Cardiol* 25:1, 1970.
 82. Singh BN, Vaughn Williams EM: Effect of altering potassium concentration on the action of lidocaine and di phenylhydantoin on rabbit atrial and ventricular muscle. *Circ Res* 29:286, 1971.
 83. Lichtstein E, Chadda KD, Gupta PK: Atrioventricular block with lidocaine therapy. *Am J Cardiol* 31:277, 1973.
 84. DeBoer AG, Breimer DD, Mattie H, et al: Rectal bioavailability of lidocaine in man: Partial avoidance of first-pass metabolism. *Clin Pharmacol Ther* 26:701, 1979.
 85. Drayer DE, Lorenzo B, Werns S, Reidenberg MM: Plasma levels, protein binding, and elimination data of lidocaine and active metabolites in cardiac patients of various ages. *Clin Pharmacol Ther* 34:14, 1983.
 86. Routledge PA, Barchowsky A, Bjornsson TD, et al: Lidocaine plasma protein binding. *Clin Pharmacol Ther* 27:347, 1980.
 87. Stenson RE, Constantino RT, Harrison DC: Interrelationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. *Circulation* 43:205, 1971.
 88. Rowland M, Thomson PD, Guichard A, Melmon KL: Disposition kinetics of lidocaine in normal subjects. *Ann NY Acad Sci* 179:383, 1971.
 89. Thomson PD, Melmon KL, Richardson JA, et al: Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. *Ann Intern Med* 78:499, 1973.
 90. LeLorier J, Grenon D, Latour Y, et al: Pharmacokinetics of lidocaine after prolonged intravenous infusion in uncomplicated myocardial infarction. *Ann Intern Med* 87:700, 1977.
 91. Narang PK, Crouthamel WG, Carliner NH: Lidocaine and its active metabolites. *Clin Pharmacol Ther* 24:654, 1978.
 92. Teo KK, Yusuf S, Furberg CD: Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials. *JAMA* 270(13):1589, 1993.
 93. Yusuf S, Wittes J, Friedman L: Overview of results of randomized clinical trials in heart disease: I. Treatments following myocardial infarction. *JAMA* 260:2088, 1988.
 94. Noneman JW, Jones MR: Lidocaine in drug treatment of cardiac arrhythmias. In: Goupd LA, ed. *Drug Treatment of Cardiac Arrhythmias*. Mt. Kisco, NY: Futura, 1983:193.
 95. Ochs HR, Carstens G, Greenblatt DJ: Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. *N Engl J Med* 303:373, 1980.
 96. Feely J, Wilkinson GR, McAllister CB, Wood AJJ: Increased toxicity and reduced clearance of lidocaine by cimetidine. *Ann Intern Med* 96:592, 1982.
 97. Boyce JR, Cervencko FW, Wright FJ: Effects of halothane on the pharmacokinetics of lidocaine in digitalis-toxic dogs. *Can Anaesth Soc J* 25:323, 1978.
 98. Koster RW, Dunning AJ: Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction. *N Engl J Med* 313:1105, 1985.
 99. Singh BN, Vaughn Williams EM: Investigations of the mode of action of a new antidysrhythmic drug, Ko 1173. *Br J Pharmacol* 44:1, 1972.
 100. Allen JD, Kofi Ekue JM, et al: The effect of Ko 1173, a new anticonvulsant agent, on experimental cardiac arrhythmias. *Br J Pharmacol* 45:561, 1972.
 101. Weld FM, Bigger JT, Swistel D, et al: Electrophysiologic effects of mexiletine (Ko 1173) on bovine cardiac Purkinje fibres. *J Pharmacol Exp Ther* 210:222, 1979.
 102. Arita M, Goto M, Nagamoto Y, Saikawa T: Electrophysiological actions of mexiletine (Ko 1173) on canine Purkinje fibers and ventricular muscle. *Br J Pharmacol* 67:143, 1979.
 103. Campbell NPS, Pantridge JF, Adgey AAJ: Long-term antiarrhythmic therapy with mexiletine. *Br Heart J* 40:796, 1978.
 104. Nora MO, Chandrasekaran K, Hammill SC, Reeder GS: Prolongation of ventricular depolarization: ECG manifestation of mexiletine toxicity. *Chest* 95:925, 1989.
 105. Prescott LF, Clements JA, Pottage A: Absorption, distribution and elimination of mexiletine. *Postgrad Med J* 53(Suppl I):50, 1977.
 106. Middleton D: Baseline pharmacology, electrophysiology and pharmacokinetics of mexiletine. *Acta Cardiol* 25(Suppl): 45, 1980.
 107. Horowitz JD, Anavekar SN, Morris PM, et al: Comparative trial of mexiletine and lidocaine in treat-

- ment of early ventricular tachyarrhythmias after acute myocardial infarction. *J Cardiovasc Pharmacol* 3:409, 1981.
108. Stein J, Podrid PJ, Lampert S, Hirshowitz GH: Long-term mexiletine for ventricular arrhythmia. *Am Heart J* 107:1091, 1984.
 109. Whitford EG, McGovern B, Schoenfeld MH, et al: Long-term efficacy of mexiletine alone and in combination with a class Ia antiarrhythmic drugs for refractory ventricular arrhythmias. *Am Heart J* 115:360, 1988.
 110. Duff HJ: Mexiletine-quinidine combination: Enhanced antiarrhythmic and electrophysiologic activity in the dog. *J Pharmacol Exp Ther* 249:617, 1989.
 111. Kim SG, Mercado AD, Tam S, Fisher JD: Combination of disopyramide and mexiletine for better tolerance and additive effects for treatment of ventricular arrhythmias. *J Am Coll Cardiol* 13:659, 1989.
 112. Kim SG, Felder SD, Waspe LE, Fisher JD: Electrophysiologic effects and clinical efficacy of mexiletine used alone or in combination with class Ia agents for refractory recurrent ventricular tachycardias or ventricular fibrillation. *Am J Cardiol* 58:485, 1986.
 113. Achuff SC, Campbell RWF, Pottage A, et al: Mexiletine in the prevention of ventricular arrhythmias in acute myocardial infarction. *Postgrad Med J* 53(Suppl I):163, 1977.
 114. Campbell RWF, Dolder MA, Prescott LF, et al: Comparison of procainamide and mexiletine in prevention of ventricular arrhythmias after acute myocardial infarction. *Lancet* 1:1257, 1975.
 115. Murray KT, Barbet JT, Kopelman HA, et al: Mexiletine and tocainide: A comparison of antiarrhythmic efficacy, adverse effects, and predictive value of lidocaine testing. *Clin Pharmacol Ther* 45:553, 1989.
 116. Zehender M, Geibel A, Tresse N, et al: Prediction of efficacy and tolerance of oral mexiletine by intravenous lidocaine application. *Clin Pharmacol Ther* 44:389, 1988.
 117. Banitt EH, Coyne WE, Schmid JR, Mendel A: Antiarrhythmics. N-aminoalkylene) trifluoroethoxybenzamides and N-(aminoalkylene) trifluoroethoxynaphthamides. *J Med Chem* 18:1130, 1975.
 118. Seipel L, Abendroth PR, Breithart G: Electrophysiologische Effekte des neuen Antiarrhythmikums Flecainid (R818) beim Menschen. *Z Kardiol* 70:524, 1981.
 119. Vik-Mo H, Ohm O-J, Lund-Johansen P: Electrophysiologic effects of flecainide acetate in patients with sinus node dysfunction. *Am J Cardiol* 50:1090, 1982.
 120. Hodess AB, Follanshee WT, Spear JF: Electrophysiological effects of a new antiarrhythmic agent, flecainide, in the intact canine heart. *J Cardiovasc Pharmacol* 1:427, 1979.
 121. Hellestrand KJ, Bexton RS, Nathan AW, et al: Acute electrophysiologic effects of flecainide acetate on cardiac conduction and refractoriness in man. *Br Heart J* 48:140, 1982.
 122. Conrad GJ, Ober RE: Metabolism of flecainide. *Am J Cardiol* 53:4B, 1982.
 123. Anderson JL, Stewart JR, Perry BA, et al: Oral flecainide acetate for the treatment of ventricular arrhythmias. *N Engl J Med* 305:473, 1981.
 124. Hodges M, Haugland JM, Granrud G, et al: Suppression of ventricular ectopic depolarizations by flecainide acetate, a new antiarrhythmic agent. *Circulation* 65:879, 1982.
 125. Forland SC, Cutler RE, McQuinn RL, et al: Flecainide pharmacokinetics after multiple dosing in patients with impaired renal function. *J Clin Pharmacol* 28:727, 1988.
 126. McQuinn RL, Pentikainen PJ, Chang SF, Conrad GJ: Pharmacokinetics of flecainide in patients with cirrhosis of the liver. *Clin Pharmacol Ther* 44:566, 1988.
 127. Cohen AA, Daru V, Covelli G, et al: Hemodynamic effects of intravenous flecainide in acute uncomplicated myocardial infarction. *Am Heart J* 110:1193, 1985.
 128. Webb CR, Morganroth J, Senior S, et al: Safety and efficacy of antiarrhythmic therapy with flecainide for patients with ventricular tachycardia and ventricular dysfunction. *Clin Res* 32:685A, 1984.
 129. Josephson MA, Ikeda N, Singh BN: Effects of flecainide on ventricular function: Clinical and experimental correlations. *Am J Cardiol* 53:945B, 1984.
 130. Van Wijk LM, den Heijer P, Crijns HJ, et al: Flecainide versus quinidine in the prevention of paroxysms of atrial fibrillation. *J Cardiovasc Pharmacol* 13:32, 1989.
 131. Wafa SS, Ward DE, Parker DJ, Camm AJ: Efficacy of flecainide acetate for atrial arrhythmias following coronary artery bypass grafting. *Am J Cardiol* 63:1058, 1989.
 132. Gavaghan TP, Koegh AM, Kelly RP, et al: Flecainide compared with a combination of digoxin and disopyramide for acute atrial arrhythmias after cardiopulmonary bypass. *Br Heart J* 60:497, 1988.
 133. Van Wijk LM, Crijns HJ, van Gilst WH, et al: Flecainide acetate in the treatment of supraventricular tachycardias: Value of programmed electrical

- stimulation for long-term prognosis. *Am Heart J* 117:365, 1989.
134. Zee Cheng CS, Kim SS, Ruffey R: Flecainide acetate for treatment of bypass tract mediated reentrant tachycardia. *Am J Cardiol* 62:23D, 1988.
 135. Kim SS, Smith P, Ruffey R: Treatment of atrial tachyarrhythmias and preexcitation syndrome with flecainide acetate. *Am J Cardiol* 62:29D, 1988.
 136. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators: Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: The CAPS. *Am J Cardiol* 61:501, 1988.
 137. Capparelli EV, Kluger J, Regnier JC, Chow MS: Clinical and electrophysiologic effects of flecainide in patients with refractory ventricular tachycardia. *J Clin Pharmacol* 28:268, 1988.
 138. Flecainide-Quinidine Research Group: Flecainide versus quinidine for treatment of chronic ventricular arrhythmias: A multicenter clinical trial. *Circulation* 67:1117, 1983.
 139. Morganroth J, Price B: Flecainide vs quinidine: Efficacy and tolerance in patients with chronic stable ventricular ectopy. *Am J Cardiol* 49:1015, 1982.
 140. Viswanathan PC, Bezzina CR, George AL Jr, et al: Gating-dependent mechanisms for flecainide action in SCH5A-linked arrhythmia syndromes. *Circulation* 104:1200, 2001.
 141. Lal R, Chapman PO, Naccarrelli GV, et al: Short- and long-term experience with flecainide acetate in the management of refractory life threatening ventricular arrhythmias. *J Am Coll Cardiol* 6:772, 1985.
 142. Chimienti M, Cullen MT, Casadei G: Safety of long-term flecainide and propafenone in the management of patients with symptomatic paroxysmal atrial fibrillation: Report from the Flecainide and Propafenone Italian Study Investigators. *Am J Cardiol* 77:60A, 1996.
 143. Reid PR, Griffith LSC, Platia EV, Ord SE: Evaluation of flecainide acetate in the management of patients at high risk of sudden cardiac death. *Am J Cardiol* 53:108B, 1983.
 144. Hellestand KJ, Burnett PJ, Milne JR, et al: Effect of the antiarrhythmic agent flecainide acetate on acute and chronic pacing thresholds. *PACE* 6:892, 1983.
 145. Kohlhardt M: Basic electrophysiological action of propafenone in heart muscle. In: Schlepper M, Olsen B, eds. *Cardiac Arrhythmias: Diagnosis, Prognosis and Therapy: Proceedings of 1st International Rhythmnorm Congress*. New York: Springer-Verlag, 1983:91.
 146. Zeiler RH, Grough WB, El-Sherif N: Electrophysiologic effects of propafenone on canine ischemic cardiac cells. *Am J Cardiol* 54:424, 1984.
 147. Rudolph W, Petri H, Kafka W, Hall D: Effects of propafenone on the accessory pathway in patients with WPW syndrome. *Am J Cardiol* 43:430, 1979.
 148. Dubuc M, Kus T, Campa MA, et al: Electrophysiologic effects of intravenous propafenone in Wolff-Parkinson-White syndrome. *Am Heart J* 117:370, 1989.
 149. Kroemer HK, Funck-Brentano C, Silberstein DJ, et al: Stereoselective disposition and pharmacologic activity of propafenone enantiomers. *Circulation* 79:1068, 1989.
 150. Karagueuzian HS, Katoh T, McCullen A, et al: Electrophysiologic and hemodynamic effects of propafenone, a new antiarrhythmic agent, on the anesthetized, closed-Chest dog: Comparative study with lidocaine. *Am Heart J* 107:418, 1984.
 151. Chilson DA, Heger JJ, Zipes DP, et al: Electrophysiologic effects and clinical efficacy of oral propafenone therapy in patients with ventricular tachycardia. *J Am Coll Cardiol* 5:1407, 1985.
 152. Connolly ST, Kates RE, Labsack CS, et al: Clinical efficacy and electrophysiology of oral propafenone for ventricular tachycardia. *Am J Cardiol* 52:1208, 1983.
 153. Connolly SJ, Kates RE, Lebsack CS, et al: Clinical pharmacology of propafenone. *Circulation* 68:589, 1983.
 154. Siddoway LA, Thompson KA, McAllister CB, et al: Polymorphism of propafenone metabolism and disposition in man: Clinical and pharmacokinetic consequences. *Circulation* 75:785, 1987.
 155. Baker BJ, Dinh H, Kroskey D, et al: Effect of propafenone on left ventricular ejection fraction. *Am J Cardiol* 54:20D, 1984.
 156. Podrid PJ, Cytryn R, Lown B: Propafenone: Noninvasive evaluation of efficacy. *Am J Cardiol* 54:53D, 1984.
 157. Henze E, Roth J, Haerer W, et al: Long term inotropic effects of flecainide and propafenone. *Eur J Nucl Med* 13:568, 1988.
 158. Shen EN, Sung RJ, Morady F, et al: Electrophysiologic and hemodynamic effects of intravenous propafenone in patients with recurrent ventricular tachycardia. *J Am Coll Cardiol* 3:1291, 1984.
 159. Singh BN, Kaplinsky E, Kirsten E, Guerrero J: Effects of propafenone on ventricular arrhythmias: Double-blind, parallel, randomized, placebo-controlled dose-ranging study. *Am Heart J* 116:1542, 1988.
 160. Dinh H, Baker BJ, deSoyza N, Murphy ML: Sustained therapeutic efficacy and safety of oral propafenone for treatment of chronic ventricular arrhythmias: A 2-year experience. *Am Heart J*

- 115(1Pt 1):92, 1988.
161. Prystowsky EN, Heger JJ, Chilson DA, et al: Antiarrhythmic and electrophysiologic effects of oral propafenone. *Am J Cardiol* 54:26D, 1984.
 162. Connolly SJ, Hoffert DL: Usefulness of propafenone for recurrent paroxysmal atrial fibrillation. *Am J Cardiol* 63:817, 1989.
 163. Aliot E, Denjoy I: Comparison of the safety and efficacy of flecainide versus propafenone in hospital out-patients with symptomatic paroxysmal atrial fibrillation/flutter: The Flecainide AF French Study Group. *Am J Cardiol* 77:66A, 1996.
 164. Kates RE, Yee Y-G, Kirsten EB: Interaction between warfarin and propafenone in healthy volunteer subjects. *Clin Pharmacol Ther* 42:305, 1987.
 165. Capucci A, Boriani G, Botto GL, Lenzi T, et al: Conversion of recent-onset atrial fibrillation by a single oral loading dose of propafenone or flecainide. *Am J Cardiol* 74(5):503, 1994.
 166. Wit AL, Hoffman BF, Rosen MR: Electrophysiology and pharmacology of cardiac arrhythmias: IX. Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade (Part B). *Am Heart J* 90:665, 1975.
 167. Frishman WH: Beta-adrenoreceptor antagonists: New drugs and new indications. *N Engl J Med* 305:500, 1981.
 168. Wit AL, Hoffman BF, Rosen MR: Electrophysiology and pharmacology of cardiac arrhythmias: IX. Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade (Part C). *Am Heart J* 90:795, 1975.
 169. Josephson ME, Seides SF: *Clinical Cardiac Electrophysiology*. Philadelphia: Lea & Febiger, 1979, p 68.
 170. Frishman WH, Cavusoglu E: β -Adrenergic blockers and their role in the therapy of arrhythmias. In: Podrid PJ, Kowey PR, eds. *Cardiac Arrhythmias—Mechanisms, Diagnosis and Management*. Baltimore: Williams & Wilkins, 1995:421.
 171. Huikure HV, Cox M, Interian A, et al: Efficacy of intravenous propranolol for suppression of inducibility of ventricular tachyarrhythmias with different electrophysiologic characteristics in coronary artery disease. *Am J Cardiol* 64:1305, 1989.
 172. Sactal package insert. Philadelphia: Wyeth-Ayerst, 1999.
 173. De Soyza N, Shapiro W, Chandraratra PAN, et al: Acebutolol therapy for ventricular arrhythmia: A randomized, placebo-controlled, double blind multicenter study. *Circulation* 65:1129, 1982.
 174. Boissel J-P, Leizorovicz A., Picolet H, Ducruet T, and the APSI investigators: Efficacy of acebutolol after acute myocardial infarction (the APSI trial). *Am J Cardiol* 66:24C, 1990.
 175. Greenspan AM, Spielman SR, Horowitz LN, et al: The electrophysiologic properties of esmolol, a short acting beta-blocker. *Int J Clin Pharmacol Ther Toxicol* 26:209, 1988.
 176. Gorczynski RJ: Basic pharmacology of esmolol. *Am J Cardiol* 56:3F, 1985.
 177. Frishman WH, Murthy VS, Strom JA, Hershman DL: Ultrashort-acting beta-adrenoreceptor blocking drug: Esmolol. In: Messerli FH, ed. *Cardiovascular Drug Therapy*, 2d ed. Philadelphia: Saunders, 1996.
 178. Shaffer JE, Quon CY, Gorczynski RJ: Beta-adrenoreceptor antagonist potency and pharmacodynamics of ASL-8123, the primary acid metabolite of esmolol. *J Cardiovasc Pharmacol* 11:187, 1988.
 179. Morganroth J, Horowitz LN, Anderson J, et al: Comparative efficacy and tolerance of esmolol to propranolol for control of supraventricular tachyarrhythmia. *Am J Cardiol* 56:33F, 1985.
 180. Platia EV, Michelson EL, Porterfield JK, Das G: Esmolol versus verapamil in the acute treatment of atrial fibrillation or atrial flutter. *Am J Cardiol* 63:925, 1989.
 181. Kloner RA, Kirshenbaum J, Lange R, et al: Experimental and clinical observations on the efficacy of esmolol in myocardial infarction. *Am J Cardiol* 56:40F, 1985.
 182. Singh BN, Vaughn Williams EM: The effect of amiodarone, a new antianginal drug, on cardiac muscle. *Br J Pharmacol* 39:657, 1970.
 183. Levine JH, Moore EN, Kadish AH, et al: Mechanisms of depressed conduction from long-term amiodarone therapy in canine myocardium. *Circulation* 78:684, 1988.
 184. Kamiya K, Nishiyama A, Yasui K, et al: Short- and long-term effects of amiodarone on the two components of cardiac delayed rectifier K^+ current. *Circulation* 103:1317, 2001.
 185. Rosenbaum MB, Chiale PA, Ryba D, Elizazri MV: Control of tachyarrhythmias associated with Wolff-Parkinson-White syndrome by amiodarone hydrochloride. *Am J Cardiol* 34: 215, 1974.
 186. Mitchell LB, Wyse DG, Gillis AM, Duff HJ: Electropharmacology of amiodarone therapy initiation: Time courses of onset of electrophysiologic and antiarrhythmic effects. *Circulation* 80:34, 1989.
 187. Marcus FI: Clinical pharmacology of amiodarone. *Ann NY Acad Sci* 427:112, 1984.
 188. Connolly SJ: Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 100:2025, 1999.
 189. Munoz A, Karila P, Gallay P, et al: A randomized hemodynamic comparison of intravenous amiodarone with and without Tween 80. *Eur Heart J* 9:142, 1988.

190. Cushing DJ, Adams MP, Cooper WD, et al: Evaluation of the effects of PM101, a cyclodextrin-based formulation of intravenous amiodarone, on blood pressure in healthy humans. *Am J Cardiol* 104:1152, 2009.
191. Block PJ, Winkle RA: Hemodynamic effects of antiarrhythmic drugs. *Am J Cardiol* 52:14C, 1983.
192. Roy D, Talajic M, Dorian P, et al for the Canadian Trial of Atrial Fibrillation Investigators: Amiodarone to prevent recurrence of atrial fibrillation. *N Engl J Med* 342:913, 2000.
193. Giri S, White CM, Dunn AB, et al: Oral amiodarone for prevention of atrial fibrillation after open heart surgery, the Atrial Fibrillation Suppression Trial (AFIST): A randomised, placebo-controlled trial. *Lancet* 357:830, 2001.
194. Gold RL, Haffajee CL, Charos G, et al: Amiodarone for refractory atrial fibrillation. *Am J Cardiol* 57:124, 1986.
195. Brodsky MA, Allen BJ, Walker CJ III, et al: Amiodarone for maintenance of sinus rhythm after conversion of atrial fibrillation in the setting of a dilated left atrium. *Am J Cardiol* 60:572, 1987.
196. The Canadian Trial of Atrial Fibrillation Investigators: Amiodarone to prevent recurrence of atrial fibrillation. *N Engl J Med* 342:913, 2000.
197. Heger JE, Prystowsky E, Zipes DP: Clinical efficacy of amiodarone in treatment of recurrent ventricular tachycardia and ventricular fibrillation. *Am Heart J* 106:887, 1983.
198. Greenspon AJ, Volosin KJ, Greenberg RM, et al: Amiodarone therapy: Role of early and late electrophysiologic studies. *J Am Coll Cardiol* 11:117, 1988.
199. Cairns JA, Connolly SJ, Roberts R, et al: Canadian amiodarone myocardial infarction arrhythmia trial (CAMIAT): Rationale and protocol. *Am J Cardiol* 72:87F, 1993.
200. Camm AJ, Julian D, Munoz A, et al: The European myocardial infarct amiodarone trial (EMIAT). *Am J Cardiol* 72:95F, 1993.
201. Singh SN, Fletcher RD, Fisher S, et al: Veterans affairs congestive heart failure antiarrhythmic trial: CHF STAT investigators. *Am J Cardiol* 72:99F, 1993.
202. Kowey PR, Levine JH, Herre JM, et al: Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. *Circulation* 92:3255, 1995.
203. Scheinman MM, Levine JH, Cannom DS, et al: Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. *Circulation* 92:3264, 1995.
204. Levine JH, Massumi A, Scheinman MM, et al: Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias: Intravenous Amiodarone Multicenter Trial Group. *J Am Coll Cardiol* 27:67, 1996.
205. Kerin NZ, Fattel K, Naini M: The efficacy of intravenous amiodarone for the conversion of chronic atrial fibrillation: Amiodarone vs. quinidine for conversion of atrial fibrillation. *Arch Intern Med* 156:49, 1996.
206. Bogazzi F, Bartalena L, Gasperi M, et al: The various effects of amiodarone on thyroid function. *Thyroid* 11:511, 2001.
207. Singh BN: Antiarrhythmic actions of amiodarone: A profile of a paradoxical agent. *Am J Cardiol* 78(4A):41, 1996.
208. Kudenchuk PJ, Cob LA, Copass MK, et al: Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 341(12):871, 1999.
209. Dorian P, Cass D, Schwartz B, et al: Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 346:884, 2002.
210. Section 5: Pharmacology I: Agents for arrhythmias. *Circulation* 102(Suppl 1):I-112, 2000.
211. Strauss HC, Bigger JT Jr, Hoffman BF: Electrophysiological and beta-receptor blocking effects of MJ 1999 on dog and rabbit cardiac tissue. *Circ Res* 26:661, 1970.
212. Rowland E, Perrins EJ, Donaldson RM, Rickards AF: D-sotalol: The clinical electrophysiological effects of a new class III antiarrhythmic agent. *Br Heart J* 53:87, 1985.
213. Nathan AW, Hellestrand KJ, Bexton RS, et al: Electrophysiological effects of sotalol—just another beta blocker? *Br Heart J* 47:515, 1982.
214. Rizos I, Senges J, Jauernig R, et al: Differential effects of sotalol and metoprolol on induction of paroxysmal supraventricular tachycardia. *Am J Cardiol* 53:1022, 1984.
215. Sundquist H: Basic review and comparison of beta-blocker pharmacokinetics. *Curr Ther Res* 28:388, 1980.
216. Parmley WW, Rabinowitz B, Chuck L, et al: Comparative effects of sotalol and propranolol on contractility of papillary muscles and adenylyl cyclase activity of myocardial extracts of cat. *J Clin Pharmacol* 12:127, 1972.
217. Simon A, Berman E: Long-term sotalol therapy in patients with atrial arrhythmias. *J Clin Pharmacol* 19:547, 1979.
218. Cavusoglu E, Frishman WH: Sotalol: A new β -adrenergic blocker for ventricular arrhythmias. *Prog Cardiovasc Dis* 37(6):423, 1995.

219. Gonzalez R, Scheinman MM, Herre JM, et al: Usefulness of sotalol for drug-refractory malignant ventricular arrhythmias. *J Am Coll Cardiol* 12:1568, 1988.
220. Singh SN, Cohen A, Chen YW, et al: Sotalol for refractory sustained ventricular tachycardia and nonfatal cardiac arrest. *Am J Cardiol* 62:399, 1988.
221. Kienzle MG, Martins JB, Wendt DJ, et al: Enhanced efficacy of oral sotalol for sustained ventricular tachycardia refractory to type I antiarrhythmic drugs. *Am J Cardiol* 61:1012, 1988.
222. Nademanee K, Feld G, Hendrickson JA, et al: Electrophysiologic and antiarrhythmic effects of sotalol in patients with life-threatening ventricular tachyarrhythmias. *Circulation* 72:555, 1985.
223. Dorian P, Newman D: Effect of sotalol on ventricular fibrillation and defibrillation in humans. *Am J Cardiol* 72(4):72A, 1993.
224. Pacifico A, Hohnloser SH, Williams JH, et al: Prevention of implantable-defibrillator shocks by treatment with sotalol. d, l-Sotalol Implantable Cardioverter-Defibrillator Study Group. *N Engl J Med* 340(24):1885, 1999.
- 224a. Somberg JC, Preston RA, Ranade V, Molnar J: Developing a safe intravenous sotalol dosing regimen. *Am J Therap* 17: 365, 2010.
225. Waldo AL, Camm AJ, deRuyter H, et al: Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. *Lancet* 10:348:416, 1996.
226. DiMarco JP, VanderLugt JT, Lee KS, et al: Ibutilide. In: Singh BN, Wellens HJJ, Hiroka M, eds. *Electropharmacological Control of Arrhythmias*. Mount Kisco, NY: Futura, 1994:589.
227. Wesley RC, Farkhani F, Bautista J: Ibutilide-induced reduction in defibrillation threshold: Enhanced countershock efficacy via slow inward sodium current activation. *PACE* 14:716, 1991.
228. Glatter K, Yang Y, Chatterjee K, et al: Chemical cardioversion of atrial fibrillation or flutter with ibutilide in patients receiving amiodarone therapy. *Circulation* 103:253, 2001.
229. Zaqa M, Afshar H, Rasekh A, et al: Predictors of conversion to sinus rhythm using ibutilide for atrial fibrillation or flutter. *Am J Cardiol* 85:112, 2000.
230. Kumar Das M, Cheriparambil K, Bedi A, et al: Cardioversion of atrial fibrillation with ibutilide: When is it most effective? *Clin Cardiol* 25:411, 2002.
231. Glatter KA, Dorostkar PC, Yang Y, et al: Electrophysiological effects of ibutilide in patients with accessory pathways. *Circulation* 104:1933, 2001.
232. Dofetilide. Package insert and prescribing information. New York: Pfizer, 1999.
233. Torp-Pedersen C, Møller M, Bloch-Thomsen PE, et al for the Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group: Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med* 341:857, 1999.
234. Brendorp B, Elming H, Jun L, et al for the DIAMOND Study Group: QTc interval as a guide to select those patients with congestive heart failure and reduced left ventricular systolic function who will benefit from antiarrhythmic treatment with dofetilide. *Circulation* 103:1422, 2001.
235. Pedersen OD, Bagger H, Keller N, et al for the Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group: Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function. A the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) substudy. *Circulation* 104:292, 2001.
236. Køber L, Bloch Thomsen PE, Møller M, et al for the the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) Study Group: Effect of dofetilide in patients with recent myocardial infarction and left ventricular dysfunction: a randomised trial. *Lancet* 356:2052, 2000.
237. Nørgaard BJ, Wachtell K, Christensen PD, et al and the Danish Dofetilide in Atrial Fibrillation and Flutter Study Group: Efficacy and safety of intravenously administered dofetilide in acute termination of atrial fibrillation and flutter: A multicenter, randomized, double-blind, placebo-controlled trial. *Am Heart J* 137:1062, 1999.
238. Singh S, Zoble RG, Yellen L, et al: Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation and atrial flutter. The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) Study. *Circulation* 102:2385, 2000.
239. Mounsey JP, DiMarco JP: Dofetilide. *Circulation* 102:2665, 2000.
240. Falk RH, Polak A, Singh SN, Friedrich T: Intravenous dofetilide, a class III antiarrhythmic agent for the termination of sustained atrial fibrillation or flutter. Intravenous Dofetilide Investigators. *J Am Coll Cardiol* 29(2):385, 1997.
241. Zimetbaum PJ: Dronedarone for atrial fibrillation—an odyssey. *N Engl J Med* 360: 1811, 2009.
242. Patel C, Yan G-X, Kowey PR: Dronedarone. *Circulation* 120: 636, 2009.
- 242a. Singh D, Cingolani E, Diamond GA, Kaul S: Dronedarone for atrial fibrillation. Have we expanded the antiarrhythmic armamentarium? *J Am Coll Cardiol* 55: 1569, 2010.
- 242b. Garcia D, Cheng-Lai A: Dronedarone: a new anti-

- arrhythmic drug for the treatment of atrial fibrillation. *Cardiol in Rev* 17: 230, 2009.
243. Manning AS, Thisse V, Hodeige D, et al: SR33589, a new amiodarone-like antiarrhythmic agent: Electrophysiological effects in anesthetized dogs. *J Cardiovasc Pharmacol* 25:252, 1995.
 244. Sun W, Wei S, Jonnalagedda S, Singh B: Electrophysiological effects of dronedarone (sr33589), a noniodinated benzofuran derivative, in the rabbit heart. *Circulation* 100(22):2276, 1999.
 245. Singh B, Connolly S, Crijns H, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;357:987-99.
 246. Djandjighian L, Planchenault J, Finance O, Pastor G: Hemodynamic and antiadrenergic effects of dronedarone and amiodarone in animals with a healed myocardial infarction. *J Cardiovasc Pharmacol* 36(3):376, 2001.
 247. Le Heuzey JY, De Ferrari GM, Radzik D, et al: A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. *J Cardiovasc Electrophysiol* 21: 606, 2010.
 248. Kober L, Torp-Pederson C, McMurray J, et al: Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 358:2678, 2008.
 249. Hohnloser S, Crijns H, Van Eickels M, et al: Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 360:668, 2009.
 250. Connolly SJ, Crijns HJGM, Torp-Pedersen C, et al for the ATHENA Investigators: Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *Circulation* 120: 1174, 2009.
 251. Davey J, Herold M, Hognlund C, et al. Dronedarone for the control of ventricular rate in permanent atrial fibrillation. The Efficacy and safety of dronedarone for the control of ventricular rate during atrial fibrillation study. *Am Heart J* 156:527, 2008.
 252. Gautier P, Guillemare E, Dhandhigian L, et al. In vivo and in vitro characterization of the novel antiarrhythmic agent SSR 149744C: electrophysiological, anti-adrenergic and anti-angiotensin 2 effects. *J Cardiovasc Pharmacol.* 44:244, 2004.
 253. Kowey P, Aliot E, Capucci , et al. Placebo-controlled double-blind dose ranging study of the efficacy and safety of SSR 149744C in patients with recent atrial fibrillation/ flutter. *Heart Rhythm* 4:572, 2007.
 254. Arya A, Silberbauer J, Teichman SL, et al: A preliminary assessment of the effects of ATI-2042 in subjects with paroxysmal atrial fibrillation using implanted pacemaker methodology. *Europace* 11: 458, 2009.
 255. Tian D, Frishman WH: Vernakalant: a new drug to treat patients with acute onset atrial fibrillation. *Cardiol in Rev* 19: 41, 2011.
 256. Dorian P, Pintner A, Mangat I et al. The effect of vernakalant (RSD 1235), an investigational antiarrhythmic agent, on atrial electrophysiology in humans. *J Cardiovasc Pharmacol.* 50:35, 2007.
 257. Roy D, Pratt C, Juul-Moller S, et al. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: A phase 3, randomized, placebo-controlled trial. *Circulation* 117:1518, 2008.
 258. Kowey PR, Dorian P, Mitchell LB, et al: Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2: 652, 2009.
 259. Wit AL, Cranefield PF: Verapamil inhibition of the slow response: A mechanism for its effectiveness against reentrant AV nodal tachycardia. *Circulation* 50(III):146, 1974.
 260. Sung RJ, Shapiro WA, Shen EN, et al: Effects of verapamil on ventricular tachycardias possibly caused by reentry, automaticity, and triggered activity. *J Clin Invest* 72:350, 1983.
 261. Hoon TJ, Bauman JL, Rodvold KA, et al: The pharmacodynamic and pharmacokinetic differences of the d and l isomers of verapamil: Implications in the treatment of paroxysmal supraventricular tachycardia. *Am Heart J* 112:396, 1986.
 262. Abernethy DR, Schwartz JB, Todd EL, et al: Verapamil pharmacodynamics and disposition in young and elderly hypertensive patients: Altered electrocardiographic and hypotensive response. *Ann Intern Med* 105:329, 1986.
 263. Waxman HL, Meyerburg RJ, Appel R, Sung: Verapamil for control of ventricular rate in paroxysmal supraventricular tachycardia and atrial fibrillation or flutter. *Ann Intern Med* 94:1, 1981.
 264. Haft JL, Habbab MA: Treatment of atrial arrhythmias, effectiveness of verapamil when preceded by calcium infusion. *Arch Intern Med* 146:1085, 1986.
 265. Klein HO, Kaplinsky E: Verapamil and digoxin: their respective effects on atrial fibrillation and their interaction. *Am J Cardiol* 50:894, 1982.
 266. Keech AC, Harper RW, Harrison PM, et al: Pharmacokinetic interaction between oral metoprolol and verapamil for angina pectoris. *Am J Cardiol* 58:551, 1986.
 267. Stark G, Schulze-Bauer C, Stark U, et al: Comparison of the frequency-dependent effects on

- the atrioventricular node of verapamil, amiodarone, digoxin, and diltiazem in isolated guinea pig hearts. *J Cardiovasc Pharmacol* 25:330, 1995.
268. Talajic M, Lemery R, Roy D, et al: Rate-dependent effects of diltiazem on human atrioventricular nodal properties. *Circulation* 86:870, 1992.
 269. Dougherty AH, Jackman WM, Naccarelli GV, et al: Acute conversion of paroxysmal supraventricular tachycardia with intravenous diltiazem. *Am J Cardiol* 70:587, 1992.
 270. Clair WK, Wilkinson WE, McCarthy EA, et al: Treatment of paroxysmal supraventricular tachycardia with oral diltiazem. *Clin Pharmacol Ther* 51:562, 1992.
 271. Roy D: Efficacy of diltiazem in recurrent supraventricular tachyarrhythmias. *Can J Cardiol* 11:538, 1995.
 272. Pelleg A: Cardiac cellular electrophysiologic actions of adenosine and adenosine triphosphate. *Am Heart J* 110:688, 1985.
 273. Belhassen B, Glick A, Laniado S: Comparative clinical and electrophysiologic effects of adenosine triphosphate and verapamil on paroxysmal reciprocating junctional tachycardia. *Circulation* 77:795, 1988.
 274. Garratt C, Linker N, Griffith M, et al: Comparison of adenosine and verapamil for termination of paroxysmal junctional tachycardia. *Am J Cardiol* 64:1310, 1989.
 275. DiMarco JP, Sellers TD, Lerman BB, et al: Diagnostic and therapeutic use of adenosine in patients with supraventricular tachyarrhythmias. *J Am Coll Cardiol* 6:417, 1985.
 276. Lerman BB, Belardinelli L, West GA, et al: Adenosine sensitive ventricular tachycardia: Evidence suggesting cyclic AMP-mediated triggered activity. *Circulation* 74:270, 1986.
 277. Withering W: An account of the foxglove and some of its medical uses, with practical remarks on dropsy and other diseases. In: Willis FA, Keys TE, eds. *Classics of Cardiology*. New York: Henry Schuman, 1941:231.
 278. Sellers TD, Bashore TM, Gallagher JJ: Digitalis in the preexcitation syndrome—analysis during atrial fibrillation. *Circulation* 56:260, 1977.
 279. Cotten M de V, Stopp PE: Action of digitalis on the nonfailing heart of the dog. *Am J Physiol* 192:114, 1958.
 280. Sonnenblick EH, Williams JF Jr, Glick G, et al: Studies on digitalis: XV. Effects of cardiac glycosides on myocardial force velocity relations in the nonfailing human heart. *Circulation* 34:532, 1966.
 281. Mason DT, Braunwald E: Studies on digitalis: X. Effects of ouabain on forearm vascular resistance and venous tone in normal subjects and in patients in heart failure. *J Clin Invest* 43:532, 1964.
 282. DeMots H, Rahimtoola SH, McAnulty JH, Porter GA: Effects of ouabain on coronary and systemic vascular resistance and myocardial oxygen consumption in patients without heart failure. *Am J Cardiol* 41:88, 1978.
 283. Shanbour LL, Jacobson ED: Digitalis and the mesenteric circulation. *Am J Dig Dis* 17:826, 1972.
 284. Murgatroyd FD, Gibson SM, Baiyan X, et al: Double-blind placebo-controlled trial of digoxin in symptomatic paroxysmal atrial fibrillation. *Circulation* 99:2765, 1999.
 285. Smith TW, Butler VP, Haber E, et al: Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. *N Engl J Med* 307:1357, 1982.
 286. Nordrehaug JE, Johannessen K, Von der Lippe G: Serum potassium concentration as a risk factor of ventricular arrhythmias early in acute myocardial infarction. *Circulation* 71:645, 1985.
 287. Zwillinger L: Uber die Magnesiumwirkung auf das Hertz. *Klin Wochenschr* 14:1429, 1935.
 288. Watanabe Y, Dreifus LS: Electrophysiological effects of magnesium and its interactions with potassium. *Cardiovasc Res* 6:79, 1972.
 289. Chen H, Bando S, Nakaya Y: Alterations of cardiac conduction and refractoriness in humans following intravenous administration of magnesium sulfate. *Tokushima J Exp Med* 35:13, 1988.
 290. Iseri LT, French JH: Magnesium: nature's physiologic calcium blocker. *Am Heart J* 108:188, 1984.
 291. Reinhart RA: Magnesium metabolism: A review with special reference to the relationship between intracellular content and serum levels. *Arch Intern Med* 148:2415, 1988.
 292. Specter MJ, Schweizer E, Goldman RH: Studies on magnesium's mechanism of action in digitalis-induced arrhythmias. *Circulation* 52:1001, 1975.
 293. Tzivoni D, Banai S, Schuger C, et al: Treatment of torsades de pointes with magnesium sulfate. *Circulation* 77:392, 1988.
 294. Scheinman MM, Sullivan RW, Hyatt KH: Magnesium metabolism in patients undergoing cardiopulmonary bypass. *Circulation* 39:1235, 1969.
 295. Billman GE, Hoskins RS: Prevention of ventricular fibrillation with magnesium sulfate. *Eur J Pharm* 158:167, 1988.
 296. Allen BJ, Brodsky MA, Capparelli EV, et al: Magnesium sulfate therapy for sustained monomorphic ventricular tachycardia. *Am J Cardiol* 64:1202, 1989.
 297. Dyckner T, Wester PO: Ventricular extrasystoles and intracellular electrolytes before and after po-

- tassium and magnesium infusions in patients on diuretic treatment. *Am Heart J* 97:12, 1979.
298. Smith LF, Heagerty RF, Bing RF, Barnett DB: Intravenous infusion of magnesium sulphate after acute myocardial infarction: Effects on arrhythmias and mortality. *Int J Cardiol* 12:175, 1986.
 299. Healy J, Baranchuk A, Crystal E. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 45:1832, 2005.
 300. Zhang Y, Zhang P, Mu Y, et al: The role of renin-angiotensin system blockade therapy in the prevention of atrial fibrillation: a meta-analysis of randomized controlled trials. *Clin Pharmacol Ther-*
ap 88: 521, 2010.
 301. Disertori M, Latini R, Barlera S. Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med* 360:1606, 2009.
 302. Kulik A, Singh JP, Levin R, et al: Association between statin use and the incidence of atrial fibrillation following hospitalization for coronary artery disease. *Am J Cardiol* 105: 1655, 2010.
 303. Adabag AS, Mithani S, Al Aloul B, et al for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group: Efficacy of gemfibrozil in the primary prevention of atrial fibrillation in a large randomized controlled trial. *Am Heart J* 157: 913, 2009.

References for Chapter 18

Antiplatelet and Other Antithrombotic Drugs

William H. Frishman, MD

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1. Furie B, Furie BC: Mechanisms of thrombus formation. *N Engl J Med* 359: 938, 2008.
2. Bennett JS: Mechanisms of platelet adhesion and aggregation: An update. *Hosp Prac* 15:70, 1992.
3. Detwiler TC, Charo IP, Feinman RD: Evidence that calcium regulates platelet function. *Thromb Haemost* 40:207, 1978.
4. Smyth SS, Woulfe DS, Weitz JI, et al for the 2008 Platelet Colloquium Participants. G-protein-coupled receptors as signaling targets for antiplatelet therapy. *Arterioscler Thromb Vasc Biol* 29: 449, 2009.
- 4a. Coller BS: Blood elements at surfaces: Platelets. *Ann N Y Acad Sci* 516:362, 1987.
- 4b. Ma YQ, Qin J, Plow EF: Platelet integrin alpha(IIb) beta(3): activation mechanisms. *J Thromb Haemost* 5: 1345, 2007.
5. Hirsh J, Salzman EW, Marder VJ, Colman RW: Overview of the thrombotic process and its therapy. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. 3d ed. Philadelphia: Lippincott, 1994: 1151.
6. Virmani R, Kolodgie FD, Burke AP, et al: Lessons from sudden coronary death. A comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 20: 1262, 2000.
7. Faggiotto A, Ross R, Harker L: Studies of hypercholesterolemia in the nonhuman primate. I. Changes that lead to fatty streak formation. *Arteriosclerosis* 4:323, 1984.
8. Mann JM, Davies MJ: Vulnerable plaque: Relation of characteristics to degree of stenosis in human coronary arteries. *Circulation* 94:928, 1996.
9. Richardson PD, Davies MJ, Born GBR: Influence of plaque configuration and stress distribution of fissuring of coronary atherosclerotic plaques. *Lancet* 2:941, 1989.
- 9a. Gurbel PA, Tantry US: Acceptance of high platelet reactivity as a risk factor (editorial comment). *J Am Coll Cardiol Cardiovasc Interv* 3: 1008, 2010.
- 9b. Frishman WH, Weksler B, Christodoulou JP, et al: Reversal of abnormal platelet aggregability and change in exercise tolerance in patients with angina pectoris following oral propranolol. *Circulation* 50: 887, 1974.
10. Steering Committee of the Physician's Health Study Research Group: Final Report on the Aspirin Component of the Ongoing Physician's Health Study. *N Engl J Med* 321:129, 1989.
11. Lee G, Garcia JM, Corso PJ, et al: Correlation of coronary angioscopic to angiographic findings in coronary artery disease. *Am J Cardiol* 58:238, 1986.
12. Virmani R, Burke AP, Kolodgie FD: Histopathology of atherosclerosis. In: Colman RW, Marder VJ, Clowes AW, et al (eds). *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. 5th ed. Philadelphia: Lippincott, 2006: 813.
13. Ault KA, Cannon CP, Mitchell J, et al: Platelet activation in patients after an acute coronary syndrome: Results from the TIMI-12 trial. *J Am Coll Cardiol* 33:634, 1999.
14. Miner J, Hoffhines A: The discovery of aspirin's antithrombotic effects. *Texas Heart Inst J* 34: 179, 2007.
15. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C: Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 353: 2373, 2005.
16. Frishman WH, Cheng-Lai A, Nawarskas J, eds: *Current Cardiovascular Drugs*. 4th ed. Philadelphia: Current Medicine, 2005:98.

17. Antiplatelet Trialists' Collaboration: Secondary prevention of vascular disease by prolonged antiplatelet treatment. *BMJ* 296:320, 1988.
18. Gross PL, Weitz JI: New antithrombotic drugs. *Clin Pharmacol Ther* 86: 139, 2009.
19. Awtry EH, Loscalzo J: Aspirin. *Circulation* 101:1206, 2000.
20. Miller, KP, Frishman WH: Platelets and anti-platelet therapy in ischemic heart disease. *Med Clin North Am* 72:117, 1988.
21. Patrono C, Collier B, Dalen JE, et al: Platelet-active drugs: The relationships among dose, effectiveness, and side effects. *Chest* 126(Suppl 1):243S, 2004.
22. Moncada S, Vane JR: The role of prostacyclin in vascular tissue. *Fed Proc* 38:66, 1979.
23. Preston FE, Whipples S, Jackson CA, et al: Inhibition of prostacyclin and platelet thromboxane A₂ after low-dose aspirin. *N Engl J Med* 304:76, 1981.
24. Clarke RJ, Mayo G, Price P, et al: Suppression of thromboxane A₂ but not of systemic prostacyclin by controlled-release aspirin. *N Engl J Med* 324:1137, 1991.
25. Taylor DW, Barnett HJ, Haynes RB, et al: Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: A randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. *Lancet* 353:2179, 1999.
- 25a. Rothwell PM, Wilson M, Elwin CE, et al: Long-term effect of aspirin on colorectal cancer incidence and mortality: 20 year follow-up of five randomised trials. *Lancet* 376: 1741, 2010.
26. Cipollone F, Rocca B, Patrono C: Cyclooxygenase 2 expression and inhibition in atherothrombosis. *Arterioscler Thromb Vasc Biol* 24: 246, 2004.
27. Berger JS, Brown DL, Becker RC: Low-dose aspirin in patients with stable cardio-vascular disease: a meta-analysis. *Am J Med* 121: 43, 2008.
28. Ridker PM, Manson JE, Graziano M, et al: Low-dose aspirin therapy for chronic stable angina: A randomized, placebo-controlled clinical trial. *Ann Intern Med* 114:835, 1991.
29. Chesebro JH, Webster MWI, Smith HC, et al: Antiplatelet therapy in coronary disease progression: Reduced infarction and new lesion formation. *Circulation* 80 (Suppl 11):266, 1989.
30. Juul-Moller S, Edvardsson N, Jahnmatz B, et al: Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. *Lancet* 340:1421, 1992.
- 30a. O'Connor RE, Brady W, Brooks SC, et al: Part 10: acute coronary syndromes. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 122 Suppl 3: S787, 2010.
31. Lewis HD, Davis JW, Archibald DG, et al: Protective effects of aspirin against myocardial infarction and death in men with unstable angina. *N Engl J Med* 309:396, 1983.
32. Cairns JA, Gent M, Singer J, et al: Aspirin, sulfinpyrazone, or both in unstable angina. *N Engl J Med* 313:1369, 1985.
33. Theroux P, Quimet H, McCans J, et al: Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 320:1014, 1989.
34. The RISC Group: Risk of myocardial infarction and death during treatment with low-dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 336:827, 1990.
35. Manson JE, Grobbee DE, Stampfer MJ, et al: Aspirin in the primary prevention of angina pectoris in a randomized trial of United States physicians. *Am J Med* 89:772, 1990.
36. Steering Committee of the Physicians' Health Study Research Group: Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 321:129, 1989.
37. Peto R, Gray R, Collins R, et al: Randomized trial of prophylactic daily aspirin in British male doctors. *BMJ* 296:313, 1988.
38. Fowkes FGR, Price JF, Stewart MCW, et al for the Aspirin for Asymptomatic Atherosclerosis Trialists: Aspirin for the prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA* 303: 841, 2010.
39. Manson JE, Stampfer MJ, Colditz GA, et al: A prospective study of aspirin use and primary prevention of cardiovascular disease in women. *JAMA* 266:521, 1991.
40. Ridker PM, Cook NR, Lee IM, et al: A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 352: 1293, 2005.
41. Wolff T, Miller T, Ko S: Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 150: 405, 2009.
42. U.S. Preventive Services Task Force: Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 150: 396, 2009.
43. Greving JP, Buskens E, Koffjberg H, Algra A: Cost-effectiveness of aspirin treatment in the primary prevention of cardiovascular disease events in subgroups based on age, gender and varying cardiovascular risk. *Circulation* 117: 2875, 2008.

44. Berger JS, Roncaglioni MC, Avanzini F, et al: Aspirin for the primary prevention of cardiovascular events in women and men. A sex-specific meta-analysis of randomized controlled trials. *JAMA* 295: 306, 2006.
45. de Gaetano G: Collaborative Group of the Primary Prevention Project (PPP): Low-dose aspirin and vitamin E in people at cardiovascular risk: A randomised trial in general practice. *Lancet* 357:89, 2001.
46. Antithrombotic Trialists' (ATT) Collaboration: Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. *Lancet* 373: 1849, 2009.
47. Berger JS: Aspirin for preventive therapy in patients with asymptomatic vascular disease (editorial). *JAMA* 303: 880, 2010.
48. Jackson EA, Sivasubramian R, Spencer FA, et al: Changes over time in the use of aspirin in patients hospitalized with acute myocardial infarction (1975-1977): A population-based prospective. *Am Heart J* 144:259, 2002.
49. The Persantine-Aspirin Reinfarction Study Research Group: Persantine and aspirin in coronary artery disease. *Circulation* 62:449, 1980.
50. The Aspirin Myocardial Infarction Study Research Group: The aspirin myocardial infarction study: final results. *Circulation* 62 (Suppl V):V79, 1980.
51. Breddin K, Loew D, Lechner K, et al: The German-Austrian Aspirin Trial: A comparison of acetylsalicylic acid, placebo and phenprocoumon in secondary prevention of myocardial infarction. *Circulation* 62(Suppl V):V63, 1980.
52. Elwood PC, Cochrane AL, Burr ML, et al: A randomized controlled trial of acetylsalicylic acid in the secondary prevention of mortality from myocardial infarction. *Br Med J* 1:436, 1974.
53. Elwood PC, Sweetnam PM: Aspirin and secondary mortality after myocardial infarction. *Circulation* 62(Suppl V):V53, 1980.
54. The Coronary Drug Project Research Group: Aspirin in coronary heart disease. *Circulation* 62(Suppl V):V59, 1980.
55. Climt CR, Knatterud GL, Stamler J: Persantine-Aspirin Reinfarction Study II. Secondary coronary prevention with persantine and aspirin. *J Am Coll Cardiol* 7:251, 1986.
56. Aspirin after myocardial infarction. *Lancet* 1:1172, 1980.
57. Goldstein RE, Andrews M, Hall W, et al: Marked reduction in long-term cardiac deaths with aspirin after a coronary event. *J Am Coll Cardiol* 28:326, 1996.
58. ACC/AHA Guidelines for the Management of Patients with ST Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 110:3-82, 2004.
59. Hart RG, Halperin JL, McBride R, et al: Aspirin for the primary prevention of stroke and other major vascular events: Meta-analysis and hypotheses. *Arch Neurol* 57:306, 2000.
60. De Wood MA, Spores J, Notske R, et al: Prevalence of total coronary occlusion during the early hours of transmural infarction. *N Engl J Med* 303:897, 1980.
61. Fitzgerald DJ, Catella R, Roy L, et al: Marked platelet activation in vivo after intravenous streptokinase in patients with acute myocardial infarction. *Circulation* 77:142, 1988.
62. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 2:349, 1988.
63. Patrono C, Baigent C, Hirsh J, Roth G: Antiplatelet drugs. ACCP evidence-based clinical practice guidelines 8th ed. *Chest* 133 (Suppl): 199S, 2008.
64. Frishman WH, Chiu R, Landzberg BR, Weiss M: Medical therapies for the prevention of restenosis after percutaneous coronary interventions. *Curr Probl Cardiol* 23:533, 1998.
65. Lam JYT, Chesebro JH, Steel PM, et al: Is vasopressin related to platelet deposition? Relationship in a porcine preparation of arterial injury in vivo. *Circulation* 75:243, 1987.
66. White CW, Chaitman B, Ticlopidine Study Group: Antiplatelet agents are effective in reducing the immediate complications of PTCA: Results from the ticlopidine multicenter trial (abstr.). *Circulation* 76(Suppl IV):IV-400, 1987.
67. Schwartz L, Bourassa MG, Lesperance J, et al: Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med* 318:1714, 1988.
68. Barnathan ES, Schwartz JS, Taylor L, et al: Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. *Circulation* 76:125, 1987.
69. Muller C, Buttner HJ, Petersen J, Roskamm H: A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation* 101(6):590, 2000.

70. Lytle W, Loop FD, Cosgrove DM, et al: Long-term (5 to 12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts. *J Thorac Cardiovasc Surg* 89:248, 1985.
71. Spray TL, Roberts WC: Changes in saphenous veins used as aortocoronary bypass grafts. *Am Heart J* 94:500, 1977.
72. Brown BG, Cukingnan RA, DeRouen T, et al: Improved graft patency in patients treated with platelet-inhibiting therapy after coronary bypass surgery. *Circulation* 72:138, 1985.
73. Chesebro JH, Fuster V, Elveback LR, et al: Effect of dipyridamole and aspirin on late vein-graft patency after coronary artery bypass operations. *N Engl J Med* 310:209, 1984.
74. Goldman S, Copeland J, Moritz T, et al: Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: Results of a Veterans Administration Cooperative study. *Circulation* 77:1324, 1988.
75. Goldman S, Copeland J, Moritz T, et al: Saphenous vein graft patency 1 year after coronary artery bypass surgery and effects of antiplatelet therapy: Results of a Veterans Administration Cooperative study. *Circulation* 80:1190, 1989.
76. Goldman S, Zadina K, Krasnicka B, et al: Predictors of graft patency 3 years after coronary artery bypass graft surgery. Department of Veterans Affairs Cooperative Study Group No. 297. *J Am Coll Cardiol* 29:1563, 1997.
77. Yli-Mayry S, Huikuri HV, Korhonen UR, et al: Efficacy and safety of anticoagulant therapy started pre-operatively in preventing coronary vein graft occlusion. *Eur Heart J* 14(5):723, 1993.
78. Gavaghan TP, GebSKI V, Baron DW: Immediate postoperative aspirin improves vein graft patency early and late after coronary artery bypass graft surgery. A placebo-controlled, randomized study. *Circulation* 83(5):1526, 1991.
79. Antiplatelet Trialists' Collaboration: Collaborative overview of randomized trials of antiplatelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 308:81, 1994.
80. The UK-TIA Study Group: United Kingdom Transient Ischemic Attack aspirin trial: Final results. *J Neurol Neurosurg Psychiatry* 54:1044, 1991.
81. *Fed Reg* 63:56802, 66015, 1998.
82. CAPRIE Steering Committee: A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 348:1329, 1996.
83. Diener HC, Cunha L, Forbes C, et al: European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 143(1-2):1, 1996.
84. Wahl DG, Bounameaux H, de Moerloose P, Sarasin FP: Prophylactic antithrombotic therapy for patients with systemic lupus erythematosus with or without antiphospholipid antibodies. Do the benefits outweigh the risks? A decision analysis. *Arch Intern Med* 160:2042, 2000.
85. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group: Prevention of pulmonary embolism and deep venous thrombosis with low-dose aspirin: Pulmonary Embolism Prevention (PEP) Trial. *Lancet* 355:1295, 2000.
86. Peterson P, Boysen G, Godfredsen J, et al: Placebo-controlled randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: The Copenhagen AFASAK Study. *Lancet* 1:175, 1989.
87. The Stroke Prevention in Atrial Fibrillation Investigators: A comparison of warfarin with aspirin for prevention of thromboembolism in atrial fibrillation: Results of the SPAFII Study. *Lancet* 343:687, 1994.
88. Golzari H, Cebul RD, Bahler RC: Atrial fibrillation restoration and maintenance of sinus rhythm and indications for anticoagulation therapy. *Ann Intern Med* 125:311, 1996.
89. Yasaka M, Yamaguchi T: Secondary prevention of stroke in patients with nonvalvular atrial fibrillation: optimal intensity of anticoagulation. *CNS Drugs* 15: 623, 2001.
90. Warfarin Antiplatelet Vascular Evaluation Trial Investigators: Oral anticoagulant and anti-platelet therapy and peripheral arterial disease. *N Engl J Med* 357: 217, 2007.
91. Mohler ER III: Atherothrombosis – wave goodbye to combined anticoagulation and anti-platelet therapy? *N Engl J Med* 357: 293, 2007.
92. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR: Aspirin for the prevention of cardio-vascular events in patients with peripheral artery disease. A meta-analysis of randomized trials. *JAMA* 301: 1909, 2009.
93. Catella-Lawson F, Crofford LJ: Cyclooxygenase inhibition and thrombogenicity. *Am J Med* 110(Suppl 3A):28S, 2001.
- 93a. Fosslie E: Cardiovascular complications of non-steroidal anti-inflammatory drugs. *Ann Clin Lab Sci* 35: 347, 2005.
94. Jhund PS, Davie AP, McMurray JJV: Aspirin inhibits the acute venodilator response to furosemide in patients with chronic heart failure. *J Am Coll Cardiol* 37:1234, 2001.
95. Hanjic C, Frishman WH, Lerner RG: Aspirin resis-

- tance. Mechanisms and clinical implications. *Cardiol in Rev* 14: 18, 2006.
96. Gurbel PA, Bliden KP, DiChiara J, et al: Evaluation of dose-related effects of aspirin on platelet function. Results from the Aspirin-Induced Platelet Effect (ASPECT) study. *Circulation* 115: 3156, 2007.
 97. Cuisset T, Frere C, Quilici J, et al: Aspirin noncompliance is the major cause of "aspirin resistance" in patients undergoing coronary stenting. *Am Heart J* 157: 889, 2009.
 98. Braunwald E, Angiolillo D, Bates E, et al: Investigating the mechanisms of hyporesponse to antiplatelet approaches. *Clin Cardiol* 31 (suppl 1): I-21, 2008.
 99. Gladding P, Webster M, Ormiston J, et al: Antiplatelet drug nonresponsiveness. *Am Heart J* 155: 591, 2008.
 100. Braunwald E, Angiolillo D, Bates E, et al: Assessing the current role of platelet function testing. *Clin Cardiol* 31 (Suppl 1): I-10, 2008.
 101. Gurbel PA, Becker RC, Mann KG, et al: Platelet function monitoring in patients with coronary artery disease. *J Am Coll Cardiol* 50: 1822, 2007.
 102. Fusitani RM, Merdestgaard AG, Marcus CS, et al: Perioperative suppression of platelet adherence to small diameter polytetrafluoroethylene grafts. *J Surg Res* 44:455, 1998.
 103. Best LC, McGuire MB, Jones PBB, et al: Mode of action of dipyridamole on human platelets. *Thromb Res* 16:367, 1979.
 104. Mehta J, Mehta P, Pepine CJ, et al: Platelet function studies in coronary artery disease. Effect of dipyridamole. *Am J Cardiol* 47:1111, 1981.
 105. Cructhley DJ, Ryan JW: Effects of aspirin and dipyridamole on the degradation of adenosine diphosphate by cultured cells derived from bovine pulmonary artery. *J Clin Invest* 66:29, 1989.
 106. Salem DN, O'Gara PT, Madias C, Pauker SG: Valvular and structural heart disease. ACCP evidence-based clinical practice guidelines 8th ed. *Chest* 133(Suppl):593S, 2008.
 107. Pumphrey CW, Chesebro JH, Dewanjee MK: In vivo quantitation of platelet deposition on human peripheral arterial bypass grafts using indium-111-labeled platelets. *Am J Cardiol* 51:796, 1983.
 108. Dixon BS, Beck GJ, Vazquez MA, et al for the DAC study group: Effect of dipyridamole plus aspirin on hemodialysis graft patency. *N Engl J Med* 360: 2191, 2009.
 109. Diener HC, Cunha L, Forbes C, et al: European Stroke Prevention Study. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 143: 1, 1996.
 110. Schwartz L, Bourassa MG, Lesperance J, et al: Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med* 318:1714, 1988.
 111. DiMinno G, Cerbone Am, Mattioli PM, et al: Functionally thromboasthenic state in normal platelets following the administration of ticlopidine. *J Clin Invest* 75:328, 1985.
 112. Gent M, Blakely JA, Easton JD, et al: The Canadian American Ticlopidine Study in thromboembolic stroke. *Lancet* I:1215, 1989.
 113. Hass WK, Easton JD, Adams HP, et al: A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high risk patients. *N Engl J Med* 321:501, 1989.
 114. Janzon L, Bergqvist D, Boberg J, et al: Prevention of myocardial infarction and stroke in patients with intermittent claudication: Effects of ticlopidine: Results from STIMS, the Swedish Ticlopidine Multicenter Study. *J Intern Med* 227:301, 1990.
 115. Limet R, David JL, Magotteau P, et al: Prevention of aorta-coronary bypass graft occlusion. Beneficial effect of ticlopidine on early and late patency rates of venous coronary bypass surgery grafts: A double-blind study. *J Thorac Cardiovasc Surg* 94:773, 1987.
 116. Balsano F, Rizzon P, Violi F, et al: Antiplatelet treatment with ticlopidine in unstable angina: a controlled multicenter trial. *Circulation* 82:17, 1990.
 117. Schomig A, Neumann FJ, Kastrati A, et al: A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary artery stents. *N Engl J Med* 334:1084, 1996.
 118. Steinhubl SR, Ellis SG, Wolski K, et al, for the EPISTENT Investigators: Ticlopidine pretreatment before coronary stenting is associated with sustained decrease in adverse cardiac events. Data from the Evaluation of Platelet IIb/IIIa inhibitor for Stenting (EPISTENT) Trial. *Circulation* 103:1403, 2001.
 119. Scrutinio D, Cimminiello C, Marubini E, et al, on behalf of the STAMI Group: Ticlopidine versus aspirin after myocardial infarction (STAMI) trial. *J Am Coll Cardiol* 37:1259, 2001.
 120. Marco J, Ariens RAS, Fajadet J, et al: Effect of aspirin and ticlopidine on plasma tissue factor levels in stable and unstable angina pectoris. *Am J Cardiol* 85:527, 2000.
 121. Steinhubl SR, Tan WA, Foody JM, Topol EJ: Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *JAMA* 281:806, 1999.
 122. Taniuchi M, Kurz HI, Lasala JM: Randomized

- comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation* 104:539, 2001.
123. Jarvis B, Simpson K: Clopidogrel. A review of its use in the prevention of atherosclerosis. *Drugs* 60:347, 2000.
 124. Lerner RG, Frishman WH, Mohan KT: Clopidogrel. A new antiplatelet drug. *Heart Dis* 2:168, 2000.
 125. Saw J, Madsen EH, Chan S, Maurer-Spurej E: The ELAPSE (Evaluation of Long-Term Clopidogrel Antiplatelet and Systemic Anti-Inflammatory Effects) study. *J Am Coll Cardiol* 52: 1826, 2008.
 126. Moshfegh K, Redondo M, Julmy F, et al: Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: Enhanced inhibitory effects of combination therapy. *J Am Coll Cardiol* 36:699, 2000.
 127. Mehta SR, Yusuf S, Peters RJG, et al, for the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. *Lancet* 358:527, 2001.
 128. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 345:494, 2001.
 129. Sabatine MS, Cannon CP, Gibson CM, et al for the CLARITY-TIMI 28 Investigators: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 352: 1179, 2005.
 130. Hughes S: COMMIT trial confirms clopidogrel benefit in MI. Available at <http://www.theheart.org/printarticle.do?primarykey-401761>. Accessed March 10, 2005.
 131. Berger PB, Bell MR, Rihal CS, et al: Clopidogrel versus ticlopidine after intracoronary stent placement. *J Am Coll Cardiol* 34:1891, 1999.
 132. Bertrand ME, Rupprecht H-J, Urban P, et al, for the CLASSICS Investigators: Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting. The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 102:624, 2000.
 133. Banerjee S, Varghese C, Samuel J, et al: Comparison of the impact of short (<1 year) and long-term (\geq 1 year) clopidogrel use following percutaneous coronary intervention on mortality. *Am J Cardiol* 102: 1159, 2008.
 - 133a. Park SJ, Park DW, Kim YH, et al: Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *N Engl J Med* 362: 1374, 2010.
 - 133b. Berger PB: Optimal duration of clopidogrel use after implantation of drug-eluting stents – still in doubt. *N Engl J Med* 362: 1441, 2010.
 134. Ho PM, Peterson ED, Wang L, et al: Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA* 299: 532, 2008.
 135. Patel JH, Stoner JA, Owora A, et al: Evidence for using clopidogrel alone or in addition to aspirin in post coronary artery bypass surgery patients. *Am J Cardiol* 103: 1687, 2009.
 136. The ACUITY Trial: Outcomes following pre-operative clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery. *J Am Coll Cardiol* 53: 1965, 2009.
 137. Bhatt DL, Fox KAA, Werner-Hacke ChB, et al for the CHARISMA Investigators: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 354: 1706, 2006.
 138. Sacco RL, Diener H-C, Yusuf S, et al for the PROFESS Study Group: Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 359: 1238, 2008.
 139. The ACTIVE Investigators: Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 360: 2066, 2009.
 140. The ACTIVE Writing Group on behalf of the ACTIVE Investigators: Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 367: 1903, 2006.
 - 140a. Paikin JS, Wright DS, Crowther MA, et al: Triple antithrombotic therapy in patients with atrial fibrillation and coronary artery stents. *Circulation* 121: 2067, 2010.
 141. Nguyen T, Frishman WH, Nawarskas J, Lerner RG: Variability of response to clopidogrel. Possible mechanisms and clinical implications. *Cardiol in Rev* 14: 136, 2006.
 142. Yong G, Rankin J, Ferguson L, et al: Randomized trial comparing 600 with 300 mg loading dose of clopidogrel in patients with non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention: results of the Platelet Responsiveness to Aspirin and Clopidogrel and Troponin Increment after Coronary Intervention in Acute Coronary Lesions (PRACTICAL) trial. *Am Heart*

- J 157: e1, 2009.
143. Bonello L, Camoin-Jau L, Armero S, et al: Tailored clopidogrel loading dose according to platelet reactivity monitoring to prevent acute and subacute stent thrombosis. *Am J Cardiol* 103; 5, 2009.
 144. Bonello L, Lemesle G, De Labriolle A, et al: Impact of a 600 mg loading dose of clopidogrel on 30 day outcome in unselected patients undergoing percutaneous coronary intervention. *Am J Cardiol* 102: 1318, 2008.
 145. Gladding P, Webster M, Zeng I, et al: The antiplatelet effect of higher loading and maintenance dose regimens of clopidogrel. The PRINC (Plavix Response in Coronary Intervention) trial. *J Am Coll Cardiol Intervent* 1: 612, 2008.
 146. Aleil B, Jacquemin L, DePoli F, et al: Clopidogrel 150 mg/day to overcome low responsiveness in patients undergoing elective percutaneous coronary intervention. *J Am Coll Cardiol Intervent* 1: 631, 2008.
 147. von Beckerath N, Kastrati A, Wiecek A, et al: A double-blind, randomized study on platelet aggregation in patients treated with a daily dose of 150 or 75 mg of clopidogrel for 30 days. *Eur Heart J* 28: 1814, 2007.
 148. Cuisset T, Frere C, Quilici J: Benefit of a 600 mg loading dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non-ST segment elevation acute coronary syndrome undergoing coronary stenting. *J Am Coll Cardiol* 48: 1339, 2006.
 149. Patti G, Colonna G, Pasceri V, et al: Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention. Results from the ARMYDA-2 (Antiplatelet therapy for reduction of myocardial damage during angioplasty) study. *Circulation* 111: 2099, 2005.
 150. Dangas G, Mehran R, Guagliumi G, et al for the HORIZONS-AMI Trial Investigators: role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty. *J Am Coll Cardiol* 54: 1438, 2009.
 - 150a. Mehta SR, Bassand JP, Chrolavicius S, et al: Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 363: 930, 2010.
 - 150b. Mehta SR, Tanguay J-F, Eikelboom JW, et al: Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS7): a randomised factorial trial. *Lancet* 376: 1233, 2010.
 151. Saw J, Steinhubl SR, Berger PB, et al: Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. *Circulation* 108: 921, 2003.
 152. Gilard M, Arnaud B, Cornily J-C, et al: Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin. *J Am Coll Cardiol* 51: 256, 2008.
 153. PPI interactions with clopidogrel revisited. *The Medical Letter* 51: 13, 2009.
 154. Khalique SC, Cheng-Lai A: Drug interaction between clopidogrel and proton pump inhibitors. *Cardiol in Rev* 17: 198, 2009.
 - 154a. Gaglia MA, Waksman R: Proton pump inhibitors and clopidogrel. *Cardiovasc Therap* epub March 25, 2010.
 - 154b. Ray WA, Murray KT, Griffin MR, et al: Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Ann Intern Med* 152: 337, 2010.
 155. O'Donoghue ML, Braunwald E, Antman EM, et al: Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton pump inhibitor: an analysis of two randomised trials. *Lancet* 374: 989, 2009.
 - 155a. Bhatt DP, Cryer BL, Contant CF, et al: Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 363: 1909, 2010.
 - 155b. Rassen JA, Choudhry NK, Avorn J, Schneeweiss S: Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. *Circulation* 120: 2322, 2009.
 156. Simon T, Verstuyft C, Mary-Krause M, et al: Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 360: 363, 2009.
 157. Mega JL, Close SL, Wiviott SD, et al: Cytochrome P450 polymorphisms and response to clopidogrel. *N Engl J Med* 360: 354, 2009.
 158. Shuldiner AR, O'Connell JR, Bliden KP, et al: Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 302: 849, 2009.
 159. Roden DM, Stein CM: Clopidogrel and the concept of high-risk pharmacokinetics. *Circulation* 119: 2127, 2009.
 160. Freedman JE, Hylek EM: Clopidogrel, genetics and drug responsiveness. *N Engl J Med*; 360: 411, 2009.
 - 160a. Mega JL, Close SL, Wiviott SD, et al: Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI38 trial: a pharmacogenetic analysis. *Lancet* 376: 1312, 2010.
 - 160b. Wiviott SD, Mega JL: Another step on the road to

- tailored antiplatelet therapy (editorial comment): *J Am Coll Cardiol* 56: 1637, 2010.
- 160c. Mega JL, Simon T, Collet J-P, et al: Reduced function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI. *JAMA* 304: 1821, 2010.
 161. Duggan ST, Keating GM: Prasugrel: a review of its use in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *Drugs* 69: 1707, 2009.
 162. Koo MH, Nawarskas JJ, Frishman WH: Prasugrel. A new antiplatelet drug for the prevention and treatment of cardiovascular disease. *Cardiol in Rev* 16: 314, 2008.
 - 162a. Wiviott SD, Antman EM, Braunwald E: Prasugrel. *Circulation* 122: 394, 2010.
 163. Jakubowski J, Payne C, Brandt J, et al. The platelet inhibitory effects and pharmacokinetics of prasugrel after administration of loading and maintenance doses in healthy subjects. *J Cardiovasc Pharmacol* 47:377, 2006.
 164. Farid NA, Payne CD, Ernest II CS, et al: Prasugrel, a new thienopyridine antiplatelet drug, weakly inhibits cytochrome P450 2B6 in humans. *J Clin Pharmacol* 48: 53. 2008.
 165. Weerakkody GJ, Jakubowski JA, Brandt JT, et al. Comparison of speed of onset of platelet inhibition after loading doses of clopidogrel versus prasugrel in healthy volunteers and correlation with responder status. *Am J Cardiol* 100: 331, 2007.
 166. Jernberg T, Payne CD, Winters KJ, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. *Eur Heart J* 27:1166, 2006.
 167. Brandt JT, Payne CD, Wiviott SD, et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J* 153:66-e9, 2007.
 168. Payne CD, Li YG, Small DS, et al: Increased active metabolite formation explains the greater platelet inhibition with prasugrel compared to high-dose clopidogrel. *J Cardiovasc Pharmacol* 50: 555, 2007.
 169. Wiviott SD, Antman EM, Winters KJ, et al. Randomized comparison of prasugrel, a novel thienopyridine P2Y₁₂ antagonist, with clopidogrel in percutaneous coronary intervention. Results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO) TIMI-26 trial. *Circulation* 111:3366, 2005.
 170. Wiviott SD, Antman EM, Gibson M, et al. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel- Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). *Am Heart J* 152:627, 2006.
 171. Wiviott SD, Braunwald E, McCabe, CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357: 2001, 2007.
 172. Wiviott SD, Braunwald E, Angiolillo DJ, et al for the TRITON-TIMI 38 Investigators: Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38. *Circulation* 118: 1626, 2008.
 173. Montalescot G, Wiviott SD, Braunwald E, et al for the TRITON-TIMI 38 Investigators: Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction TRITON-TIMI 38): double-blind randomised controlled trial. *Lancet* 373: 723, 2009.
 174. Wiviott SD, Braunwald E, McCabe C, et al for the TRITON-TIMI 38 Investigators: Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet* 372: 1353, 2008.
 175. Unger EF: Weighing benefits and risks – the FDA’s review of prasugrel. *N Engl J Med* 361: 942, 2009.
 176. Wiviott SD, Trenk D, Frelinger AL, et al for the PRINCIPLE-TIMI 44 Investigators: Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention. The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 Trial. *Circulation* 116: 2923, 2007.
 177. Gurbel PA, Becker RC, Mann KG, et al: Platelet function monitoring in patients with coronary artery disease. *J Am Coll Cardiol* 50: 1822, 2007.
 178. Bhatt DL: Prasugrel in clinical practice. *N Engl J Med* 361, 940, 2009.
 179. Antman EM, Wiviott SD, Murphy SA, et al: Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 51: 2028, 2008.
 180. O’Donoghue M, Antman EM, Braunwald E, et al: The efficacy and safety of prasugrel with and with-

- out a glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndromes undergoing percutaneous intervention. *J Am Coll Cardiol* 54: 678, 2009.
181. Mega JL, Close SL, Wiviott SD, et al: Cytochrome P450 genetic polymorphisms and the response to prasugrel. *Circulation* 119: 2553, 2009.
 182. Phillips DR, Charo IF, Scarborough RM: GPIIb-IIIa: The responsive integrin. *Cell* 65:359, 1991.
 183. Collier BS: Platelets and thrombolytic therapy. *N Engl J Med* 322:33, 1990.
 184. D'Souza SE, Ginsberg MH, Burke TA, Plow EF: Localization of an arg-gly-asp recognition site within an integrin adhesion receptor. *Science* 242:91, 1988.
 185. Frishman WH, Burns B, Atac B, et al: Novel antiplatelet therapies for treatment of patients with ischemic heart disease: Inhibitors of the platelet glycoprotein IIb/IIIa integrin receptor *Am Heart J* 130:877, 1995.
 186. Lefkowitz J, Plow EF, Topol EJ: Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N Engl J Med* 332:1553, 1995.
 187. Shebuski RJ, Stabilito IJ, Sitko GR, Polokoff MH: Acceleration of a recombinant tissue-type plasminogen activator-induced thrombolysis and prevention of reocclusion by the combination of heparin and the arg-gly-asp-containing peptide bitistatin in a canine model of coronary thrombosis. *Circulation* 82:169, 1990.
 188. Yasuda T, Gold HF, Leinbach RC, Y et al: Kistrin, a polypeptide GPIIb/IIIa receptor antagonist, enhances and sustains coronary arterial thrombolysis with recombinant tissue-type plasminogen activator in a canine preparation. *Circulation* 83:1038, 1991.
 189. Scarborough RM, Rose JW, Hsu MA, et al: Barbourin: A GPIIb/IIIa-specific integrin antagonist from the venom of *Sistrurus M. barbouri*. *J Biol Chem* 266:9359, 1991.
 190. Collier BS, Peerschke EI, Scudder LE, Sullivan CA: A murine monoclonal antibody that completely blocks the binding of fibrinogen to platelets produces a thrombasthenic-like state in normal platelets and binds to glycoproteins IIb and/or IIIa. *J Clin Invest* 72:325, 1983.
 191. Collier BS: A new murine monoclonal antibody reports an activation dependent change in the conformation and/or microenvironment of the glycoprotein IIb/IIIa complex. *J Clin Invest* 76:101, 1985.
 192. Collier BS, Anderson K, Weisman HF: New antiplatelet agents: platelet GPIIb/IIIa antagonists. *Thromb Haemost* 74(1):302, 1995.
 193. Kohler G, Milstein C: Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 256:495, 1975.
 194. Faulds D, Sorkin EM. Abciximab (c7E3 Fab): A review of its pharmacology and therapeutic potential in ischemic heart disease. *Drugs* 48:583, 1994.
 195. Hanson SR, Pareti FI, Ruggeri ZM, et al: Effects of monoclonal antibodies against the platelet glycoprotein IIb/IIIa complex on thrombosis and hemostasis in the baboon. *J Clin Invest* 81:149, 1988.
 196. Gold HK, Gimple LW, Yasuda T, Collier BS: Pharmacodynamic study of F(ab')₂ fragments of murine monoclonal antibody 7E3 directed against human platelet glycoprotein IIb/IIIa in patients with unstable angina pectoris. *J Clin Invest* 86:651, 1990.
 197. Bhattacharya S, Jordan R, Machin S, et al: Blockade of human platelet GP IIb/IIIa receptor by a murine monoclonal antibody Fab fragment (7E3): Potent dose-dependent inhibition of platelet function. *Cardiovasc Drug Ther* 9:665, 1995.
 198. Christopoulos C, Mackie I, Lahiri A, et al: Flow cytometric observations on the in vivo use of Fab fragments of a chimeric monoclonal antibody to platelet glycoprotein IIb-IIIa. *Blood Coag Fibrinolysis* 4:729, 1993.
 199. Sweeney J, Holme S, Heaton A, et al: Infusion of a chimeric monoclonal Fab fragment (c7E3) against platelet glycoprotein IIb-IIIa potently inhibits platelet aggregation but does not affect in vivo platelet survival (abstr). *J Am Coll Cardiol* 21:253A, 1993.
 200. Simoons ML, deBoer MJ, van den Brand MJB, et al, and the European Cooperative Study Group: Randomized trial of GPIIb/IIIa platelet receptor blocker in refractory unstable angina. *Circulation* 89:596, 1994.
 201. Kaplan AV, Leung LL-K, Leung W-H, et al: Roles of thrombin and platelet membrane glycoprotein IIb/IIIa in platelet-subendothelial deposition after angioplasty in an ex vivo whole artery model. *Circulation* 84:1279, 1991.
 202. Tchong JE, Ellis SG, George BS, et al: Pharmacodynamics of chimeric glycoprotein IIb/IIIa integrin antiplatelet antibody Fab 7E3 in high-risk coronary angioplasty. *Circulation* 90:1757, 1994.
 203. EPIC Investigators: Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 330:956, 1994.
 204. Topol EJ, Califf RM, Weissman HF, et al, on behalf of EPIC Investigators. Randomized trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis; results at six months. *Lancet* 343:881, 1994.

205. Collier BS: Anti-GPIIb/IIIa drugs: Current strategies and future directions. *Thromb Haemost* 86:427, 2000.
206. Dasgupta H, Blankenship JC, Wood GC, et al: Thrombocytopenia complicating treatment with intravenous glycoprotein IIb/IIIa receptor inhibitors: a pooled analysis. *Am Heart J* 140:206, 2000.
207. Fredrickson BJ, Turner NA, Kleiman NS, et al: Effects of abciximab, ticlopidine, and combined abciximab/ticlopidine therapy on platelet and leukocyte function in patients undergoing coronary angioplasty. *Circulation* 101:1122, 2000.
208. Lincoff AM: Results of the interim analysis of the EPILOG Trial. *J Am Coll Cardiol* 27(Suppl A):XXI, 1996.
209. Ferguson JJ: EPILOG and CAPTURE trials halted because of positive interim results. *Circulation* 93:637, 1996.
210. GUSTO IV-ACS Investigators: Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation. *Lancet* 357:1915, 2001.
211. Stone GW, Grines CL, Cox DA, et al: Comparison of angioplasty with stenting, with or without abciximab in acute myocardial infarction. *N Engl J Med* 346:957, 2002.
212. Gibson CM, deLemos J, Murphy SA et al, for the TIMI Study Group: Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction. A TIMI 14 substudy. *Circulation* 103:2550, 2001.
213. The GUSTO V Investigators: Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: The GUSTO V randomised trial. *Lancet* 357:1905, 2001.
214. Cantor WJ, Kaplan AL, Velianou JL, et al: Effectiveness and safety of abciximab after failed thrombolytic therapy. *Am J Cardiol* 87:439, 2001.
215. Montalescot G, Barragan P, Wittenberg O, et al, ADMIRAL Investigators: Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 344(25):1895, 2001.
216. Boden WE, McKay RG: Optimal treatment of acute coronary syndromes--an evolving strategy. *N Engl J Med* 344(25):1939, 2001.
217. Throckmorton DC: Future trials of antiplatelet agents in cardiac ischemia. *N Engl J Med* 344:1937, 2001.
218. Kastrati A, Mehilli J, Neumann F-J, et al: Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment. The ISAR-REACT 2 randomized trial. *JAMA* 295: 1531, 2006.
219. Kastrati MJ, Schulz S, Früangel S, et al for the BRAVE-3 Study Investigators: Abciximab in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 119: 1933, 2009.
220. Kouns WC, Kirchhofer D, Hadvary P, et al: Reversible conformational changes induced in glycoprotein IIb/IIIa by a potent and selective peptidomimetic inhibitor. *Blood* 80:2539, 1992.
221. Nichols AJ, Ruffolo RR, Huffman WF, et al: Development of GP IIb/IIIa antagonists as antithrombotic drugs. *Trends Pharmacol Sci* 13:413, 1992.
222. Goa KL, Noble S: Eptifibatide. A review of its use in patients with acute coronary syndromes and/or undergoing percutaneous coronary intervention. *Drugs* 57:439, 1999.
- 222a. Akerblom A, James SK, Koutouzis M, et al: Eptifibatide is noninferior to abciximab in primary percutaneous coronary intervention. *J Am Coll Cardiol* 56: 470, 2010.
- 222b. Zeymer U, Margenet A, Haude M, et al: Randomized comparison of eptifibatide versus abciximab in primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. Results of the EVA-AMI Trial. *J Am Coll Cardiol* 56: 463, 2010.
223. Schulman SP, Goldschmidt-Clermont PJ, Topol EJ, et al: Effects of integrilin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina. A randomized multicenter trial. *Circulation* 94(9):2083, 1996.
224. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet* 349(9063):1422, 1997.
225. The ESPRIT Investigators: Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): A randomised, placebo-controlled trial. *Lancet* 356(9247):2037, 2000.
226. O'Shea JC, Hafley GE, Greenberg S, et al, ESPRIT Investigators: Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: The ESPRIT trial: A randomized controlled trial. *JAMA* 285(19):2468, 2001.
227. Kirtane AJ, Piazza G, Murphy SA, et al: Correlates of bleeding events among moderate-to high-risk patients undergoing percutaneous coronary intervention and treated with eptifibatide. Observations

- from the PROTECT-TIMI-30 trial. *J Am Coll Cardiol* 57: 2374, 2006.
228. Fung AY, Saw J, Starovoytov A, et al: Abbreviated infusion of eptifibatide after successful coronary intervention. The BRIEF-PCI (Brief Infusion of Eptifibatide Following Percutaneous Coronary Intervention) randomized trial. *J Am Coll Cardiol* 53: 837, 2009.
 229. Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. A report of the ACC/AHA Task Force on Practice Guidelines, developed in collaboration with the American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and Society for Academic Emergency Medicine. *J Am Coll Cardiol* 50: e1, 2007.
 230. Montalescot G, Borentain M, Payot L, et al: Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction. A meta-analysis. *JAMA* 292: 362, 2004.
 231. Giugliano RP, White JA, Bode C, et al for the EARLY ACS Investigators: Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 360: 2176, 2009.
 232. Stone GW, Bertrand ME, Moses JW, et al for the ACUITY Investigators: Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. The ACUITY Timing trial. *JAMA* 297: 591, 2007.
 233. Gurm HS, Smith DE, Collins JS, et al: The relative safety and efficacy of abciximab and eptifibatide in patients undergoing primary percutaneous coronary intervention. *J Am Coll Cardiol* 51: 529, 2008.
 234. The RESTORE Investigators: Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 96(5):1445, 1997.
 235. PRISM-PLUS Study Investigators: Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms. *N Engl J Med* 339(16):1163, 1998.
 236. van't Hof AWJ, Valgimigli M: Defining the role of platelet glycoprotein receptor inhibitors in STEMI. Focus on tirofiban. *Drugs* 69: 85, 2009.
 237. Cannon CP, Weintraub WS, Demopoulos LA, et al for the TACTICS--Thrombolysis in Myocardial Infarction 18 Investigators: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 344:1879, 2001.
 238. Topol EJ, Moliterno DJ, Herrmann HC, et al: Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 344(25):1888, 2001.
 239. Valgimigli M, Camp G, Percoco G, et al: Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction. The MULTISTRATEGY randomized trial. *JAMA* 299: 1788, 2008.
 240. Kereiakes DJ, Runyon JP, Kleinman NS, et al: Differential dose response to oral xemilofiban after antecedent intravenous abciximab. *Circulation* 94: 906, 1996.
 241. O'Neill WW, Serruys P, Knudtson M, et al: Long-term treatment with a platelet glycoprotein-receptor antagonist after percutaneous coronary revascularization. EXCITE Trial Investigators. Evaluation of Oral Xemilofiban in Controlling Thrombotic Events. *N Engl J Med* 342(18):1316, 2000.
 242. Cannon CP, McCabe CH, Wilcox RG, et al: Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 102(2):149, 2000.
 243. The SYMPHONY Investigators: Comparison of sibrafin with aspirin for prevention of cardiovascular events after acute coronary syndromes: A randomised trial. *Lancet* 355(9201):337, 2000.
 244. Second SYMPHONY Investigators: Randomized trial of aspirin, sibrafin, or both for secondary prevention after acute coronary syndromes. *Circulation* 103(13):1727, 2001.
 245. Sorelle R: SmithKline Beecham halts tests of Lotrafiban, an oral glycoprotein IIb/IIIa inhibitor. *Circulation* 103:e9001, 2001.
 246. Chew DP, Bhatt DL, Sapp S, Topol EJ: Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists: A meta-analysis of phase III multicenter randomized trials. *Circulation* 103(2):201, 2001.
 247. Rosenberg RD, Bauer KA: The heparin-antithrombin system: A natural anticoagulant mechanism. In: Coleman RW, Hirsh J, Marder VJ, et al, eds. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. 3rd ed. Philadelphia: JB Lippincott, 2001.

- cott, 1992:837.
248. Bjork I, Lindahl U: Mechanism of the anticoagulant action of heparin. *Mol Cell Biochem* 48:161, 1982.
 249. Hirsh J, Raschke R: Heparin and low-molecular-weight heparin. *Chest* 126(Suppl):188S, 2004.
 250. Loscalzo J: Thrombin inhibitors in fibrinolysis: A Hobson's choice of alternatives. *Circulation* 94:863, 1996.
 251. Hull RD, Raskob GE, Hirsh J, et al: Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 315:1098, 1996.
 - 251a. Uprichard J, Manning RA, Laffan MA: Monitoring heparin anticoagulation in the acute phase response. *Br J Haematol* March 11, 2010 epub ahead of print.
 252. Levine M, Hirsh J, Gent M, et al: A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. *Arch Intern Med* 154:49, 1994.
 253. Geerts WH, Bergqvist D, Pineo GF, et al: Prevention of venous thromboembolism. *Chest* 133(Suppl):381S, 2008.
 254. Nurmohamed Mt, Rosendaal FR, Buller HR, et al: Low-molecular-weight heparin versus standard heparin in general and orthopedic surgery: A meta-analysis. *Lancet* 340:152, 1992.
 255. Iorio A, Agnelli G: Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery. A meta-analysis. *Arch Intern Med* 160:2327, 2000.
 256. Liem A, Zijlstra F, Ottervanger JP, et al: High-dose heparin as pretreatment for primary angioplasty in acute myocardial infarction: The Heparin in Early Patency (HEAP) Randomized Trial. *J Am Coll Cardiol* 35:600, 2000.
 257. Mahaffey KW, Granger CB, Collins R, et al: Overview of randomized trials of intravenous heparin in patients with acute myocardial infarction treated with thrombolytic therapy. *Am J Cardiol* 77:551, 1996.
 258. Eisenberg PR, Sherman LA, Jaffe AS: Paradoxical elevation of fibrinopeptide A after streptokinase: Evidence for continued thrombosis despite intense thrombolysis. *J Am Coll Cardiol* 10:527, 1987.
 259. Eisenberg PR, Sobel BE, Jaffe AS: Activation of prothrombin accompanying thrombolysis with recombinant tissue-type plasminogen activator. *J Am Coll Cardiol* 19:1065, 1992.
 260. The SCATI (Studio sulla Caliparina nell'Angina e nella Trombosi Ventricolare nell'Infarto) Group: Randomized controlled trial of subcutaneous calcium-heparin in acute myocardial infarction. *Lancet* 2:182, 1989.
 261. Gruppo Italiano per lo Studio della Streptochinase Nell'Infarcto Miocardico: GISSI 2: A factor randomized trial of alteplase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 336:65, 1990.
 262. The International Study Group: In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomized between alteplase and streptokinase with or without heparin. *Lancet* 336:71, 1990.
 263. ISIS-3 Collaborative Group. ISIS-3: A randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 339:753, 1991.
 264. Yusuf S, Collins R, Peto R, et al: Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: Overview of results on mortality, reinfarction and side effects from 33 randomized controlled trials. *Eur Heart J* 6:556, 1985.
 265. Hsia J, Hamilton WP, Kleiman N, et al: A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction: Heparin-Aspirin Reperfusion Trial (HART) Investigators. *N Engl J Med* 323: 1433, 1990.
 266. Topol EJ, George BS, Kereiakes DJ, et al: A randomized controlled trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. *Circulation* 79:281, 1989.
 267. The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 329:673, 1993.
 268. Harjai KJ, Stone GW, Grines CL, et al: Usefulness of routine unfractionated heparin infusion following primary percutaneous coronary intervention for acute myocardial infarction in patients not receiving glycoprotein IIb/IIIa inhibitors. *Am J Cardiol* 99: 202, 2007.
 269. Antman EM for the TIMI 9B Investigators: Heparin in acute myocardial infarction. Thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9B trial. *Circulation* 94:911, 1996.
 270. Mungall DR, Anbe D, Forrester PL, et al: A prospective randomized comparison of the accuracy of computer-assisted versus GUSTO nomogram-directed heparin therapy. *Clin Pharmacol Ther* 55:591, 1994.
 271. Braunwald E, Antman EM, Beasley JW, et al: ACC/

- AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *Circulation* 102:1193, 2000.
272. Zidane M, Schram MT, Planken EW, et al: Frequency of major hemorrhage in patients treated with unfractionated intravenous heparin for deep venous thrombosis or pulmonary embolism. A study in routine clinical practice. *Arch Intern Med* 160:2369, 2000.
273. Engelberg H: Actions of heparin in the atherosclerotic process. *Pharmacol Rev* 48:327, 1996.
274. Nelson JC, Lerner RG, Goldstein R, Cagin NA: Heparin-induced thrombocytopenia. *Arch Intern Med* 138: 548, 1978.
- 274a. Napolitano LM, Warkentin TE, AlMahameed A, Nasraway SA: Heparin-induced thrombocytopenia in the critical care setting: diagnosis and management. *Crit Care Med* 34: 2898, 2006.
275. Das P, Ziada K, Steinhubl SR, et al: Heparin-induced thrombocytopenia and cardio-vascular diseases. *Am Heart J* 152: 19, 2006.
276. Crespo EM, Oliveira GBF, Honeycutt EF, et al: Evaluation and management of thrombocytopenia and suspected heparin-induced thrombocytopenia in hospitalized patients: The Complications After Thrombocytopenia Caused by Heparin (CATCH) registry. *Am Heart J* 157: 651, 2009.
277. Oliveira GBF, Crespo EM, Becker RC, et al: Incidence and prognostic significance of thrombocytopenia in patients treated with prolonged heparin therapy. *Arch Intern Med* 168: 94, 2008.
278. Warkentin TE, Kelton JG: Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 344:1286, 2001.
279. Warkentin TE, Levine MN, Hirsh J, et al: Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin. *N Engl J Med* 332:1330, 1995.
- 279a. FDA drug safety communication: update: follow up to the Public Health Alert about changes to the heparin sodium USP monography, April 7, 2010. <http://www.fda.gov/drugs/drugsafety/postmarket-drugsafetyinformationforpatientsandproviders/ucm207506.htm>.
280. Hirsh J: Heparin. *N Engl J Med* 324:1565, 1991.
281. Hogg PJ, Jackson CM: Fibrin monomer protects thrombin from inactivation by heparin-antithrombin III: Implications for heparin efficacy. *Proc Natl Acad Sci USA* 86:3619, 1989.
282. Weitz JI, Huboda M, Massel D, et al: Clot-bound thrombin is protected from inhibition by heparin-antithrombin but is susceptible to inactivation by antithrombin III-independent inhibitors. *J Clin Invest* 86:385, 1990.
283. Loscalzo J, Melnick B, Handin R: The interaction of platelet factor 4 and glycosaminoglycans. *Arch Biochem Biophys* 240:446, 1985.
284. Hirsh J, Levine MN: Low-molecular-weight heparin. *Blood* 79:1, 1992.
285. Lane DA, Denton J, Flynn AM, et al: Anticoagulant activities of heparin oligosaccharides and their neutralization by platelet factor IV. *Biochem J* 218:725, 1984.
286. Andersson LO, Barrowcliffe TW, Holmer E, et al: Molecular weight dependency of the heparin potentiated inhibition of thrombin and activated factor X: Effect of heparin neutralization in plasma. *Thromb Res* 115:531, 1979.
287. Kakkar VV: Effectiveness and safety of low-molecular-weight heparins (LMWH) in the prevention of venous thromboembolism. *Thromb Haemost* 74:364, 1995.
288. Hirsh J, Siragusa S, Ginsberg JS: Low-molecular-weight heparins (LMWH) in the treatment of patients with acute venous thromboembolism. *Thromb Haemost* 74:360, 1995.
289. Kakkar VV, Cohen AT, Edmundson RA, et al: Low-molecular-weight heparins versus standard heparin for patients of venous thromboembolism after major abdominal surgery. *Lancet* 341:259, 1993.
290. Albers GW, Amarenco P, Easton JD, et al: Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest* 119:300s, 2001.
291. International Stroke Trial Collaborative Group: The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet* 349(9065):1569, 1997.
292. Kay R, Wong KS, Yu YL, et al: Low-molecular-weight heparin for the treatment of acute ischemic stroke. *N Engl J Med* 333:1588, 1995.
293. Carter NJ, McCormack PL, Plosker GL: Enoxaparin. A review of its use in ST-segment elevation myocardial infarction. *Drugs* 68: 691, 2008.
294. The Assessment of the Safety and Efficacy of a new Thrombolytic Regimen (ASSENT)-3 Investigators: Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin in acute myocardial infarction: ASSENT-3. *Lancet* 358:605, 2001.
295. Llevadot J, Giugliano RP, Antman EM: Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA* 286:442, 2001.

296. Antman EM, Morrow DA, McCabe CH, et al for the EXTRACT-TIMI 25 Investigators: Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 354: 1477, 2006.
297. Gibson CM, Murphy SA, Montalescot G, et al for the EXTRACT-TIMI 25 Investigators: Percutaneous coronary intervention in patients receiving enoxaparin or unfractionated heparin after fibrinolytic therapy for ST-segment elevation myocardial infarction in the ExTRACT-TIMI 25 trial. *J Am Coll Cardiol* 49: 2238, 2007.
298. Eikelboom JW, Quinlan DJ, Mehta SR, et al: Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction. A meta-analysis of the randomized trials. *Circulation* 112: 3855, 2005.
299. Gurfinkel EP, Manos EJ, Mejail RI, et al: Low-molecular-weight heparin versus regular heparin or aspirin in treatment of unstable angina and silent ischemia. *J Am Coll Cardiol* 26:313, 1995.
300. Low-molecular-weight heparin during instability in coronary artery disease, Fragmin during Instability in Coronary Artery Disease (FRISC) study group. *Lancet* 347:561, 1996.
301. Cohen M, Demers C, Gurfinkel EP, et al: A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 337(7):447, 1997.
302. Goodman SG, Cohen M, Bigonzi F, et al: Randomized trial of low-molecular-weight heparin (enoxaparin) versus unfractionated heparin for unstable coronary artery disease: One-year results of the ESSENCE Study. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events. *J Am Coll Cardiol* 36:693, 2000.
303. Eikelboom JW, Anand SS, Malmberg K, et al: Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: A meta-analysis. *Lancet* 355:1936, 2000.
304. Becker RC, Meade TW, Berger PB: The primary and secondary prevention of coronary artery disease. ACCP evidence based clinical practice guidelines 8th ed.. *Chest* 133(Suppl): 776s, 2008.
305. The SYNERGY Trial Investigators: Enoxaparin vs unfractionated heparin in high-risk patients with non-ST segment elevation acute coronary syndromes managed with an intended early invasive strategy. Primary results of the SYNERGY randomized trial. *JAMA* 292: 45, 2004.
306. Mahaffey KW, Cohen M, Garg J, et al for the SYNERGY Trial Investigators: High-risk patients with acute coronary syndromes treated with low molecular weight or unfractionated heparin. Outcomes at 6 months and 1 year in the SYNERGY trial. *JAMA* 294: 2594, 2005.
307. Levine M, Gent M, Hirsh J, et al: Ardeparin (low-molecular-weight heparin) vs. graduated compression stockings for the prevention of venous thromboembolism. *Arch Intern Med* 156:851, 1996.
308. Leclerc JR, Goerts WH, Desjardins L, et al: Prevention of venous thromboembolism after knee arthroplasty--a randomized, double-blind trial comparing enoxaparin with warfarin. *Ann Intern Med* 124:619, 1996.
309. Hull R, Raskob G, Pineo G, et al: A comparison of subcutaneous low-molecular-weight heparin with Warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med* 329:1370, 1993.
310. Heit JA, Berkowitz SD, Bona R, et al: Efficacy and safety of low-molecular-weight heparin (ardeparin sodium) compared to warfarin for the prevention of VTE after total knee replacement surgery: A double-blind, dose-ranging study. *Thromb Haemost* 77:32, 1997.
311. Hull RD, Raskob GE, Pineo GF, et al: Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 326:975, 1992.
312. Levine M, Gent M, Hirsh J, et al: A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin. Administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 334:677, 1996.
313. Koopman M, Prandoni P, Piovella F, et al: Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med* 334:682, 1996.
314. Gould MK, Dembitzer AD, Doyle RL, et al: Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 130:800, 1999.
315. Faxon DP, Spiro TE, Minor S, et al: Low-molecular-weight heparin in prevention of restenosis after angioplasty. Results of Enoxaparin Restenosis Trial (ERA). *Circulation*; 90:908, 1994.
316. Cairns JA, Gill J, Morton B, et al: Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coro-

- nary angioplasty. The EMPAR Study. *Circulation* 94:1553, 1996.
317. Lablanche JM, McFadden EP, Meneveau N, et al: Effect of nadroparin, a low-molecular-weight heparin, on clinical and angiographic restenosis after coronary balloon angioplasty: The FACT study. Fraxiparine Angioplastic Coronaire Transluminate. *Circulation* 96:3396, 1997.
 318. Kiesz RS, Buszman P, Martin JL, et al: Local delivery of enoxaparin to decrease restenosis after stenting: Results of initial multicenter trial: Polish-American Local Lovenox NIR Assessment study (The POLONIA study). *Circulation* 103:26, 2001.
 319. Montalescot G, White HD, Gallo R, et al for the STEEPLE Investigators: Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N Engl J Med* 355: 1006, 2006.
 320. White HD, Gallo R, Cohen M, et al: The use of intravenous enoxaparin in elective percutaneous coronary intervention in patients with renal impairment: results from the Safety and Efficacy of Enoxaparin in PCI patients, an international randomized evaluation (STEEPLE) trial. *Am Heart J* 157: 125: 2009.
 321. Belch JFF: Pharmacotherapy of Raynaud's phenomenon. *Drugs* 52:682, 1996.
 322. Mannarino E, Pasqualini L, Innocente S, et al: Efficacy of low-molecular-weight heparin in the management of intermittent claudication. *Angiology* 42:1, 1991.
 323. Calabro A, Piarulli F, Milan D, et al: Clinical assessment of low-molecular-weight heparin effects in peripheral vascular disease. *Angiology* 44:188, 1993.
 324. Edmondson RA, Cohen AT, Das SK, et al: Low-molecular-weight heparin versus aspirin and dipyridamole after femoropopliteal bypass grafting. *Lancet* 344:914, 1994.
 325. Boston Area Anticoagulation Trial: The effect of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation: The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med* 323:1505, 1990.
 326. Harenberg J, Weuster B, Pfitzer M, et al: Prophylaxis of embolic events in patients with atrial fibrillation using low-molecular-weight heparin. *Semin Thromb Hemost* 19(Suppl 1):116, 1993.
 327. Berge E, Abdelnoor M, Nakstad PH, et al: Low-molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: A double-blind randomised study. *Lancet* 355:1205, 2000.
 328. Murray RD, Deitcher SR, Shah A, et al: Potential clinical efficacy and cost benefit of a transesophageal echocardiography-guided low-molecular-weight heparin (enoxaparin) approach to antithrombotic therapy in patients undergoing immediate cardioversion from atrial fibrillation. *J Am Soc Echocardiogr* 14:200, 2001.
 329. Jeffrey RF, Khan AA, Douglas, JT, et al: Anticoagulation with low-molecular-weight heparin (Fragmin) during continuous hemodialysis in the intensive care unit. *Artif Organs* 17(8):717, 1993.
 330. Schmitt Y, Schneider H: Low-molecular-weight heparin (LMWH): Influence on blood lipids in patients on chronic hemodialysis. *Nephrol Dial Transplant* 8(5):438, 1993.
 331. Saltissi D, Morgan C, Westhuyzen J, Healy H: Comparison of low-molecular-weight heparin (enoxaparin sodium) and standard unfractionated heparin for haemodialysis anticoagulation. *Nephrol Dial Transplant* 11:2698, 1999.
 332. Melandri G, Semprini F, Cervi V, et al: Benefit of adding low-molecular-weight heparin to the conventional treatment of stable angina pectoris. A double-blind, randomized, placebo-controlled trial. *Circulation* 88(6):2517, 1993.
 333. Lee AY, Levine MN, Baker RI, et al: Low-molecular-weight-heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 349: 146, 2003.
 334. Estrada CA, Mansfield CJ, Heudebert GR: Cost-effectiveness of low-molecular-weight heparin in the treatment of proximal deep vein thrombosis. *J Gen Intern Med* 15:108, 2000.
 335. Marcoff L, Zhang Z, Zhang W, et al: Cost effectiveness of enoxaparin in acute ST-segment elevation myocardial infarction. The ExTRACT-TIMI 25 study. *J Am Coll Cardiol* 54: 1271, 2009.
 336. Hull RD, Raskob GE, Rosenbloom D, et al: Treatment of proximal vein thrombosis with subcutaneous low-molecular-weight heparin vs intravenous heparin. An economic perspective. *Arch Intern Med* 157:289, 1997.
 337. Wilde MI, Markham A: Danaparoid: A review of its pharmacology and clinical use in the management of heparin induced thrombocytopenia. *Drugs* 54:903, 1997.
 338. Chesebro J, Fuster V: Thrombosis in unstable angina. *N Engl J Med* 327:192, 1992.
 - 338a. Rupperecht HJ, Blank R: Clinical pharmacology of direct and indirect factor Xa inhibitors. *Drugs* 70: 2153, 2010.
 339. Graham DJ, Alexander JJ: The effect of thrombin on bovine aortic endothelial and smooth muscle cells. *J Vasc Surg* 11:307, 1990.
 340. Jones A, Geczy CL: Thrombin and factor Xa enhance the production of interleukin-1. *Immunol-*

- ogy 71:236, 1990.
- 340a. Greinacher A, Lubenow N: Recombinant hirudin in clinical practice. *Circulation* 103:1479, 2001.
 341. Rydel TJ, Ravichandran KG, Tulinsky A, et al: The structure of a complex of recombinant hirudin and human alpha-thrombin. *Science* 249:277, 1990.
 342. Greinacher A, VÖlpel H, Janssens U, et al: Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with the immunologic type of heparin-induced thrombocytopenia: A prospective study. *Circulation* 99:73, 1999.
 343. Greinacher A, Janssens U, Berg G, et al: Lepirudin (recombinant hirudin) for parenteral anticoagulation in patients with heparin-induced thrombocytopenia. *Circulation* 100:587, 1999.
 - 343a. Desirudin (Iprivask) for DVT prevention. *The Medical Ltr* 52: 85, 2010.
 - 343b. Eriksson BI, Ekman S, Lindbratt S, et al: Prevention of thromboembolism with use of recombinant hirudin. Results of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. *J Bone Joint Surg Am* 79: 326, 1997.
 344. Cannon CP, McCabe CH, Henry TD, et al: A pilot trial of recombinant desulfatohirudin compared with heparin in conjunction with tissue-type plasminogen activator and aspirin for acute myocardial infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) 5 Trial. *J Am Coll Cardiol* 23:993, 1994.
 345. Neuhaus KL, Niederer W, Wagner J, et al: HIT (Hirudin for the Improvement of Thrombolysis) results of a dose escalation study (abstr.). *Circulation* 88:I-292, 1993.
 346. Lee LV, for the TIMI 6 Investigators: Initial experience with hirudin and streptokinase in acute myocardial infarction: Results of the TIMI 6 trial. *Am J Cardiol* 75:7, 1995.
 347. Antman EM, for the TIMI 9A Investigators: Hirudin in acute myocardial infarction: Safety report from the Thrombolysis and Thrombin Inhibition in Myocardial (TIMI) 9A trial. *Circulation* 90:1624, 1994.
 348. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators: A randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 90:1631, 1994.
 349. Antman EM for the TIMI 9B Investigators: Hirudin in acute myocardial infarction: thrombolysis and thrombin inhibition in myocardial infarction: Thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9B trial. *Circulation* 94:911, 1996.
 350. van den Boss AA, Deckers JW, Heyndricks GR, et al: Safety and efficacy of recombinant hirudin (CGP 39393) versus heparin in patients with stable angina undergoing coronary angioplasty. *Circulation* 88:2058, 1993.
 351. OASIS-2 Investigators: Effects of recombinant hirudin (Lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation in patients with acute myocardial ischaemia without ST elevation. A randomised trial. *Lancet* 353: 429, 1999.
 352. Serruys PW, Deckers JW, Close P, on behalf of the HELVETICA study group: A double-blind, randomized heparin controlled trial evaluating acute and long-term efficacy of r-hirudin (CGP 39393) in patients undergoing coronary angioplasty (abstr). *Circulation* 90(Suppl I) [pt 2]:I-394, 1994.
 353. Bittl JA, Strony J, Brinker JA, et al: Treatment with bivalirudin (hirulog) as compared with heparin during coronary angioplasty for unstable and post-infarction angina. Hirulog Angioplasty Study Investigators. *N Engl J Med* 333:764, 1995.
 354. Zoldhelyi P, Webster MWI, Fuster V, et al: Recombinant hirudin in patients with chronic, stable coronary artery disease: Safety, half-life, and effect on coagulation parameters. *Circulation* 88:2015, 1993.
 355. Walenga JM, Hoppensteadt D, Koza MM, et al: Comparative studies on various assays for the laboratory evaluation of hirudin. *Semin Thromb Hemost* 17:103, 1991.
 356. Lefkovits J, Topol EJ: Direct thrombin inhibitors in cardiovascular medicine. *Circulation* 90:1522, 1994.
 357. Porta R, Pescador M, Mantovani M, Prino G: Quantitative comparison of recombinant hirudin's antithrombotic and anticoagulant activities with those of heparin. *Thromb Res* 57:639, 1990.
 358. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators: A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndrome. *N Engl J Med* 335:775, 1996.
 - 358a. Gajra A, Husain J, Smith A: Lepirudin in the management of heparin-induced thrombocytopenia. *Expert Opin Drug Metab Toxicol* 4: 1131, 2008.
 - 358b. Petros S: Lepirudin in the management of patients with heparin-induced thrombocytopenia. *Biologics* 2: 481, 2008.
 359. Fareed J, Walenga J, Hoppensteadt D, et al: Neutralization of recombinant hirudin: Some practical considerations. *Semin Thromb Hemost* 17:137, 1991.
 360. Theroux P, Perez-Villa F, Waters D, et al: A ran-

- domized double-blind comparison of two doses of Hirulog or heparin as adjunctive therapy to streptokinase to promote early patency of the infarct-related artery in acute myocardial infarction. *Circulation* 91:2132, 1995.
361. Maraganore JM, Bourdon P, Jablonski J, et al: Design and characterization of Hirulog: A novel class of bivalent peptide inhibitors of thrombin. *Biochemistry* 29:7095, 1990.
362. Fuchs J, Cannon CP: Hirulog in the treatment of unstable angina: Results of the Thrombin Inhibition in Myocardial Ischemia (TIMI) 7 trial. *Circulation* 92:727, 1995.
363. Nawarskas JJ, Anderson JR: Bivalirudin: A new approach to anticoagulation. *Heart Dis* 3:131, 2001.
364. Dogne JM, de Leval X, Delarge J, et al: New trends in thromboxane and prostacyclin modulators. *Curr Med Chem* 7(6):609, 2000.
365. Lincoff AM, Bittl JA, Kleiman NS, et al for the REPLACE-1 Investigators: Comparison of bivalirudin versus heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE]-1 Trial). *Am J Cardiol* 93: 1092, 2004.
366. Lincoff AM, Bittl JA, Harrington RA, et al for the REPLACE-2 Investigators: Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention. REPLACE-2 randomized trial. *JAMA* 289: 853, 2003.
367. Chew DP, Lincoff AM, Gurm H, et al for the REPLACE-2 Investigators: Bivalirudin versus heparin and glycoprotein IIb/IIIa inhibition among patients with renal impairment undergoing percutaneous coronary intervention (a subanalysis of the REPLACE-2 trial). *Am J Cardiol* 95: 581, 2005.
368. Gibson CM, Morrow DA, Murphy SA, for the TIMI study group: A randomized trial to evaluate the relative protection against post-percutaneous coronary intervention microvascular dysfunction, ischemia and inflammation among antiplatelet and anti-thrombotic agents. The PROTECT-TIMI 30 trial. *J Am Coll Cardiol* 47: 2364, 2006.
369. Stone GW, McLaurin BT, Cox DA, et al for the ACUITY Investigators: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 355: 2203, 2006.
370. Stone GW, White HD, Ohman EM, et al: Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. *Lancet* 369: 907, 2007.
371. Kastrati A, Neumann FJ, Mehilli J, et al for the ISAR-REACT 3 trial investigators: Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med* 359: 688, 2008.
372. Stone GW, Witzenbichler B, Guagliumi G, et al for the HORIZONS-AMI Trial Investigators: Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 358: 2218, 2008.
373. Mehran R, Lansky AJ, Witzenbichler B, et al for the HORIZONS-AMI Trial Investigators: Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1 year results of a randomised controlled trial. *Lancet* 374: 1149, 2009.
374. Feldman DN, Wong SC, Gade CL, et al: Impact of bivalirudin on outcomes after percutaneous coronary revascularization with drug-eluting stents. *Am Heart J* 154: 695, 2007.
- 374a. Parodi G, Antoniucci D, Nikolsky E, et al: Impact of bivalirudin therapy in high-risk patients with acute myocardial infarction. 1-year results from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial. *J Am Coll Cardiol Interv* 3: 796, 2010.
- 374b. Grubb KJ, Salehi P, Chedrawy EG: Bivalirudin: alternative anticoagulation during cardiopulmonary bypass in patients with heparin-induced thrombocytopenia. *Recent Pat Cardiovasc Drug Discov* 5: 20, 2010.
375. Yeh RW, Jang IK: Argatroban: update. *Am Heart J* 151: 1131, 2006.
376. Lewis BE, Wallis DE, Berkowitz SD, et al for the ARG-911 Study Investigators: Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. *Circulation* 103: 1838, 2001.
377. Hursting MJ, Verme-Gibboney CN: Risk factors for major bleeding in patients with heparin-induced thrombocytopenia treated with argatroban: a retrospective study. *J Cardiovasc Pharmacol* 52: 561, 2008.
378. Lewis BE, Wallis DE, Hursting MJ, et al: Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. *Chest* 129: 407, 2006.
379. Cruz-Gonzalez I, Sanchez-Ledesma M, Osakabe M, et al: What is the optimal anti-coagulation level with argatroban during percutaneous coronary intervention? *Blood Coagul Fibrinolysis* 19: 401, 2008.
380. SPORTIF Executive Steering Committee for the SPORTIF V Investigators: Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. A randomized trial. *JAMA*

- 293: 690, 2005.
381. Colwell C, Mouret P: Ximelagatran for the prevention of venous thromboembolism following elective hip or knee replacement surgery. *Semin Vasc Med* 5: 266, 2005.
 382. Francis CW, Berkowitz SD, Comp PC, et al for the EXULT A Study Group: Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med* 349: 1703, 2003.
 383. Turpie AGG, Bauer KA, Eriksson BI, et al: Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery. A meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 162: 1833, 2002.
 384. Cohen AT, Davidson BL, Gallus AS, et al: Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ* 332: 325, 2006.
 385. Buller HR, Davidson BL, Decousus H, et al: Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis. A randomized trial. *Ann Intern Med* 140: 867, 2004.
 - 385a. Decousus H, Prandoni P, Mismetti P, et al for the CALISTO Study Group: Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med* 363: 1222, 2010.
 386. The Matisse Investigators: Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 349: 1695, 2003.
 387. Mehta SR, Steg PG, Granger CB, et al for the ASPIRE Investigators: Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention. Arixtra Study in Percutaneous Coronary Intervention: A randomized evaluated (ASPIRE) pilot trial. *Circulation* 111: 1390, 2005.
 - 387a. FUTURA-OASIS 8 Trial Group, Steg PG, Jolly SS, Mehta SR, et al: Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux: the FUTURA-OASIS 8 randomized trial. *JAMA* 304: 1339, 2010.
 388. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 354: 1464, 2006.
 389. Mehta SR, Granger CB, Eikelboom JW, et al: Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention. Results from the OASIS-5 Trial. *J Am Coll Cardiol* 50: 1742, 2007.
 390. Sculpher MJ, Lozano-Ortega G, Sambrook J, et al: Fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndromes: short-term cost and long-term cost-effectiveness using data from the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) Trial. *Am Heart J* 157: 845, 2009.
 391. Jolly SS, Faxon DP, Fox KAA, et al: Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes treated with glycoprotein IIb/IIIa inhibitors or thienopyridines. Results from the OASIS-5 Trial. *J Am Coll Cardiol* 54: 468, 2009.
 392. The OASIS-6 Trial Group: Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction. The OASIS-6 Randomized Trial. *JAMA* 295: 1519, 2006.
 393. Turpie AGG: Fondaparinux in the management of patients with ST-elevation acute myocardial infarction. *Vasc Health Risk Mgmt* 2: 371, 2006.
 394. Mehta SR, Boden WE, Eikelboom JW, et al: Anti-thrombotic therapy with fondaparinux in relation to interventional management strategy in patients with ST-segment and non-ST-segment elevation acute coronary syndromes. An individual patient-level combined analysis of the Fifth and Sixth Organization to Assess Strategies in Ischemic Syndromes (OASIS 5 & 6) Randomized Trials. *Circulation* 118: 2038, 2008.
 395. The van Gogh Investigators: Idraparinix versus standard therapy for venous thrombo-embolic disease. *N Engl J Med* 357: 1084, 2007.
 - 395a. Harenberg J: Development of idraparinix and idrabiotaparinix for anticoagulant therapy. *Thromb Haemost* 102: 811, 2009.
 396. Hirsh J: Oral anticoagulant drugs. *N Engl J Med* 324:1865, 1991.
 - 396a. Ansell J, Hirsh J, Hylek E, et al: Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th ed). *Chest* 133: 160S, 2008.
 397. Koch-Weser J, Sellers EM: Drug interactions with coumarin anticoagulants. *N Engl J Med* 285:487-498, 547, 1971.
 398. Wells PS, Holbrook AM, Crowther NR, et al: Interactions of warfarin with drugs and food. *Ann Intern Med* 121:676, 1994.
 - 398a. Ozer N, Cam N, Tangurek B, et al: The impact of CYP2C9 and VKORC1 genetic poly-morphism and patient characteristics upon warfarin dose re-

- quirements in an adult Turkish population. *Heart Vessels* 25: 155, 2010.
399. Raskob GE, Pineo GE, Hull RD: The technique of administering oral anticoagulant therapy. *J Crit Illness* 6:923, 1991.
 400. Hirsh J: Substandard monitoring of warfarin in North America. Time for change. *Arch Intern Med* 152:257, 1992.
 401. Guyatt GH, Cook DJ, Jaeschke R, et al: Grades of recommendation for antithrombotic agents. ACCP evidence-based practice guidelines 8th ed. *Chest* 133:123S, 2008.
 402. Hirsh J, Dalen JE, Deykin D, et al: Oral anticoagulants. Mechanism of action, clinical effectiveness and optimal therapeutic range. *Chest* 108:231S, 1995.
 403. Warkentin TE: Venous thromboembolism in heparin-induced thrombocytopenia. *Curr Opin Pulm Med* 6:343, 2000.
 404. Moriarty HT, Lam-PO-Tang PR, Anastas N: Comparison of the thromboplastins using the ISI and INR system. *Pathology* 22:71, 1990.
 405. Van den Besselaar AMHP, Lewis SM, Mannucci PM: Status of present and candidate international reference preparations (IRP) of thromboplastins for the prothrombin time: A report of the subcommittee for the control of anticoagulation. *Thromb Haemost* 69:85, 1993.
 406. Cannegieter SC, Rosendaal FR: Optimal oral anticoagulation for patients with mechanical heart valves. *N Engl J Med* 333:11, 1995.
 407. Cortelazzo S, Finazzi G, Viero P, et al: Thrombotic and hemorrhagic complications in patients with mechanical heart valve prosthesis attending an anticoagulation clinic. *Thromb Haemost* 69:316, 1993.
 408. Rosendaal FR: The Scylla and Charybdis of oral anticoagulant treatment. *N Engl J Med* 335:587, 1996.
 409. Turpie AG, Gent M, Laupacis A, et al: Comparison of aspirin with placebo in patients treated with warfarin after heart valve replacement. *N Engl J Med* 329:524, 1993.
 410. Fihn SD: Aiming for safe anticoagulation. *N Engl J Med* 333:54, 1995.
 411. Stein PD, Alpert JS, Bussey HI, et al: Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. *Chest* 119(Suppl 1):220S, 2001.
 412. Salem DN, Daudelin HD, Levine HJ, et al: Antithrombotic therapy in valvular heart disease. *Chest* 119(Suppl 1):207S, 2001.
 413. Singer DE, Albers GW, Dalen JE, et al: Antithrombotic therapy in atrial fibrillation. *Chest* 133(Suppl 1):546S, 2008.
 414. Hylek EM, Skates SJ, Sheehan MA, et al: An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with non-rheumatic atrial fibrillation. *N Engl J Med* 335:540, 1996.
 415. The European Atrial Fibrillation Trial Study Group: Optimal oral anticoagulant therapy in patients with non-rheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med* 333:5, 1995.
 416. Yamaguchi T, for Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group: Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation. A multicenter, prospective, randomized trial. *Stroke* 31:817, 2000.
 417. Veterans Administration Cooperative Study: Anticoagulants in acute myocardial infarction: results of a cooperative clinical trial. *JAMA* 225:724, 1973.
 418. International Anticoagulant Review Group: Collaborative analysis of long-term anticoagulant administration after acute myocardial infarction. *Lancet* 1:203, 1970.
 419. ASPECT Research Group: Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. *Lancet* 343:400, 1994.
 420. Smith P, Arnesen H, Holme I: The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med* 323:147, 1990.
 421. Azar AJ, Cannegieter SC, Deckers JW, et al: Optimal intensity of oral anticoagulant therapy after myocardial infarction. *J Am Coll Cardiol* 27:1349, 1996.
 422. Cohen M, Adams PC, Parry G, et al, and the Antithrombotic Therapy in Acute Coronary Syndromes Research Group: Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. *Circulation* 89:81, 1994.
 423. Cannegieter SC, Rosendaal FR, Wintzen AR, et al: Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 333:11, 1995.
 424. Chesebro JH, Fuster V: Optimal antithrombotic therapy for mechanical prosthetic heart valves. *Circulation* 94:2055, 1996.
 425. Altman R, Rouvier J, Gurfinkel E, et al: Comparison of high-dose with low-dose aspirin in patients with mechanical heart valve replacement treated with oral anticoagulant. *Circulation* 94:2113, 1996.
 426. Massel D, Little SH: Risks and benefits of adding anti-platelet therapy to warfarin among patients with prosthetic heart valves: A meta-analysis. *J Am Coll Cardiol* 37:569, 2001.

427. Collaborative Group of the Primary Prevention Project (PPP): Low-dose aspirin and vitamin E in people at cardiovascular risk: A randomised trial in general practice. *Lancet* 357:89, 2001.
428. Ezekowitz MD, Bridgers SL, James KE, et al, for the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators: Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med* 327:1406, 1992.
429. Atrial Fibrillation Investigators: Risk factors for stroke and efficacy of anti-thrombotic therapy in atrial fibrillation: Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 154:1449, 1994.
430. The Stroke Prevention in Atrial Fibrillation Investigators: Predictors of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk. *Ann Intern Med* 116:1, 1992.
431. Singer DE, Chang Y, Fang MC, et al: The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med* 151: 297, 2009.
432. Mant J, Hobbs R, Fletcher K, et al: Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 370: 493, 2007.
433. Mungall D, White R: Aging and warfarin therapy. *Ann Intern Med* 117:878, 1992.
434. Choudhry NK, Soumerai SB, Normand SLT, et al: Warfarin prescribing in atrial fibrillation: the impact of physician, patient, and hospital characteristics. *Am J Med* 119: 607, 2006.
435. Verheugt FWA: Good old warfarin for stroke prevention in atrial fibrillation (commentary). *Lancet* 367: 1877, 2006.
- 435a. Hansen ML, Sorensen R, Clausen MT, et al: Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 170: 1433, 2010.
436. Presti CF, Hart RG: Thyrotoxicosis, atrial fibrillation and embolism revisited. *Am Heart J* 117:976, 1989.
437. ten Berg JM, Kelder JC, Suttrop MJ, et al: Effect of coumarins started before coronary angioplasty on acute complications and long-term follow up. A randomized trial. *Circulation* 102:386, 2000.
438. Aguilar MI, Hart RG, Kase CS, et al: Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. *Mayo Clin Proc* 82: 82, 2007.
439. Garcia DA, Regan S, Crowther M, Hylek EM: The risk of hemorrhage among patients with warfarin-associated coagulopathy. *J Am Coll Cardiol* 47: 804, 2006.
440. DeZee KJ, Shimeall WT, Douglas KM, et al: Treatment of excessive anticoagulation with phytonadione (vitamin K). *Arch Intern Med* 166: 391, 2006.
441. Sun DK, Frishman WH, Grossman M: Adverse dermatologic effects of cardiovascular drug therapy. In Frishman WH, Sonnenblick EH (eds): *Cardiovascular Pharmacotherapeutics*. NY: McGraw Hill 1997; 1005.
442. Gage BF, Birman-Deych E, Radford MJ, et al: Risk of osteoporotic fracture in elderly patients taking warfarin. *Arch Intern Med* 166: 241, 2006.
443. Lerner RG, Aronow WS, Sekhri A, et al: Warfarin use and the risk of valvular calcification. *J Thromb Haemost* 7: 2023, 2009.
444. Hall JAG, Pauli RM, Wilson KM: Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 68:122, 1980.
445. Anderson JL, Horne BD, Stevens SM, et al: Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation* 116: 2563, 2007.
446. Rosove MH, Grody WW: Should we be applying warfarin pharmacogenetics to clinical practice? No, not now. *Ann Intern Med* 151: 270, 2009.
447. Smith WL: Prostanoid biosynthesis and mechanisms of action. *Am J Physiol* 263:F181, 1992.
448. Gresele P, Deckmyn H, Giuseppe G, et al: Thromboxane synthase inhibitors, thromboxane receptor antagonists and dual blockers in thrombotic disorders. *Trends Pharmacol Sci* 12:158, 1991.
449. Zeidner JF, Frishman WH, Lerner RG: Investigational antiplatelet drugs for the treatment and prevention of coronary artery disease. *Cardiol in Rev* 16: 250, 2008.
450. Fiddler GI, Lumley P: Preliminary studies with thromboxane synthase inhibitors and thromboxane receptor blockers: A review. *Circulation* 81(Suppl I):I69, 1990.
451. Reilly, IA, Doran JB, Smith B, Fitzgerald GA: Increased thromboxane biosynthesis in a human preparation of platelet activation. Biochemical and functional consequences of selective inhibition of thromboxane synthase. *Circulation* 73:1300, 1986.
452. Terres W, Kupper W, Hamm CW: Resting myocardial ischemia after intravenous infusion of BM 13.177, a thromboxane receptor antagonist. *Thromb Res* 48:577, 1987.
453. Lane IF, Irwin JTC, Jennings SA, et al: A specific thromboxane receptor antagonist evaluated in vascular graft patients. *Br J Surg* 71:903, 1984.
454. Meadows TA, Bhatt DL: Clinical aspects of platelet inhibitors and thrombus formation. *Circ Res* 100:

- 1261, 2007.
455. Gresele P, Deckmyn H, Arnout J, et al: Characterization of N,N'-bis(3-picolyl)-4-Methoxy-Isophtalamide (picotamide) as a dual thromboxane synthase inhibitor/thromboxane A₂ receptor antagonist in human platelets. *Thromb Haemost* 61(3):479, 1989.
456. DeClerk F, Beetens J, deChaffoy D, et al: R 68070: Thromboxane A₂/prostaglandin endoperoxide receptor blockade combined in one molecule. Biochemical profile in vitro. *Thromb Haemost* 61(1):35, 1989.
457. Hoet B, Falcon C, De Reys S, et al: R68070, a combined thromboxane/endoperoxide receptor antagonist and thromboxane synthase inhibitor, inhibits human platelet activation in vitro and in vivo: A comparison with aspirin. *Blood* 75(3):646, 1990.
458. Timmermans C, Vrolix M, VanHaecke J, et al: Ridogrel in the setting of percutaneous transluminal coronary angioplasty. *Am J Cardiol* 68:463, 1991.
459. The RAPT Investigators: The Ridogrel vs. Aspirin Patency Trial. Randomized trial of ridogrel, a combined thromboxane A₂ synthase inhibitor and thromboxane A₂/prostaglandin endoperoxide receptor antagonist vs. aspirin as adjunct to thrombolysis in patients with acute myocardial infarction. *Circulation* 89:588, 1994.
460. Hirsh J, Salzman EW, Harker L, et al: Aspirin and other platelet active drugs: Relationship among dose, effectiveness and side effects. *Chest* 95(2):12S, 1989.
461. Tranchesi B, Pileggi F, Vercammen E, et al: Ridogrel does not increase the speed and rate of coronary recanalization in patients with myocardial infarction treated with alteplase and heparin. *Eur Heart J* 15(5):660, 1994.
462. Ritter JM, Barrow SE, Doktor HS, et al: Thromboxane A₂ receptor antagonism and synthase inhibition in essential hypertension. *Hypertension* 22:197, 1993.
463. Kudo K, Abe K, Chiba S, et al: Role of thromboxane A₂ in the hypotensive effect of captopril in essential hypertension. *Hypertension* 11:147, 1988.
464. Patel JP, Beck LD, Briglia FA, et al: Beneficial effects of combined thromboxane and leukotriene receptor antagonism in hemorrhagic shock. *Crit Care Med* 23:231, 1995.
465. Berndt MC, Shen Y, Dopheide SM, et al: The vascular biology of the glycoprotein Ib-IX-V complex. *Thromb Haemost* 86(1):178, 2001.
466. Krupski WC, Bass A, Cadroy Y, et al: Antihemostatic and antithrombotic effects of monoclonal antibodies against von Willebrand factor in non-human primates. *Surgery* 112:433, 1992.
467. Furie B, Furie BC, Flaumenhaft R: A journey with platelet P-selectin: The molecular basis of granule secretion, signalling and cell adhesion. *Thromb Haemost* 86(1):214, 2001.
468. Ray KK, Morrow DA, Gibson CM, et al: Predictors of the rise in vWF after ST elevation myocardial infarction: implications for treatment strategies and clinical outcome: an ENTIRE-TIMI 23 substudy. *Eur Heart J* 26: 440,2005.
469. Montalescot G, Philippe F, Ankri A, et al: Early increase of von Willebrand factor predicts adverse outcome in unstable coronary artery disease: beneficial effects of enoxaparin. French Investigators of the ESSENCE trial. *Circulation* 98: 294, 1998.
470. Spiel AO, Gilbert JC, Jilma B: von Willebrand factor in cardiovascular disease. Focus on acute coronary syndromes. *Circulation* 117: 1449, 2008.
471. Becker RC: The investigation of biomarkers in cardiovascular disease: time for a coordinated, international effort. *Eur Heart J* 26: 421, 2005.
- 471a. Kiefer TL, Becker RC: Inhibitors of platelet adhesion. *Circulation* 120: 2488, 2009.
472. Lee JF, Stovall GM, Ellington AD: Aptamer therapeutics advance. *Curr Opin Chem Biol* 10: 282, 2006.
473. Gilbert JC, DeFeo-Fraulini T, Hutabarat RM, et al: First-in-human evaluation of anti-von Willebrand factor therapeutic aptamer ARC1779 in healthy volunteers. *Circulation* 116: 2678, 2007.
474. Blann AD: Plasma von Willebrand factor, thrombosis, and the endothelium: the first 30 years. *Thromb Haemost* 95: 49, 2006.
475. Reininger AJ, Heijnen HF, Schumann H, et al: Mechanism of platelet adhesion to von Willebrand factor and microparticle formation under high shear stress. *Blood* 107: 3537, 2006.
476. Husted S, Emanuelsson H, Heptinstall S, et al: Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y₁₂ antagonist AZD6140 with aspirin in patients with atherosclerosis: A double-blind comparison to clopidogrel with aspirin. *Eur Heart J* 27:1038, 2006.
- 476a. Gaglia MA Jr, Manoukian SV, Waksman R: Novel antiplatelet therapy. *Am Heart J* 160: 595, 2010.
- 476b. Nawarskas JJ, Clark SM: Ticagrelor: a novel reversible oral antiplatelet agent. *Cardiol in Rev* 19: 2011 in press.
477. Schömig A: Ticagrelor – is there need for a new player in the antiplatelet-therapy field? (editorial). *New Engl J Med* 361: 1108, 2009.
- 477a. Storey RF, Angiolillo DJ, Patil SB, et al: Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary

- syndromes. The PLATO (PLATElet inhibition and patient Outcomes) PLATELET Substudy. *J Am Coll Cardiol* 56: 1456, 2010.
478. Cannon CP, Husted S, Harrington RA, et al for the DISPERSE-2 Investigators: Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST segment elevation acute coronary syndromes. Primary results of the DISPERSE-2 Trial. *J Am Coll Cardiol* 50: 1844, 2007.
 479. Storey RF, Husted S, Harrington RA, et al: Inhibition of platelet aggregation by AZD6140, a reversible oral P2N₁₂ receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol* 50: 1852, 2007.
 480. Wallentin L, Becker RC, Budaj A, et al for the PLATO Investigators: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 361: 1045, 2009.
 481. James S, Akerblom A, Cannon CP, et al: Comparison of ticagrelor, the first reversible oral P2Y₁₂ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design and baseline characteristics of the PLATElet inhibition and patient Outcomes (PLATO) trial. *Am Heart J* 157: 599, 2009.
 - 481a. Wallentin L, James S, Storey RF, et al for the PLATO Investigators: Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet* August 27, 2010 (epub ahead of print).
 - 481b. Gurbel PA, Bliden KP, Butler K, et al: Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies. The RESPOND study. *Circulation* 121: 1188, 2010.
 482. Antoniadis C, Tousoulis D, Stefanadis C. Nitric oxide-releasing aspirin: Will it say NO to atherothrombosis? *Intl J Cardiol* 118:170, 2007.
 483. Fiorucci S, Mencarelli A, Mannucci R, et al. NCX-4016, a nitric oxide-releasing aspirin, protects endothelial cells against apoptosis by modulating mitochondrial function. *FASEB J* 16:1645, 2002.
 484. Gresele P, Momi S. Pharmacologic profile and therapeutic potential of NCX 4016, a nitric oxide-releasing aspirin, for cardiovascular disorders. *Cardiovasc Drug Rev* 24:148, 2006.
 485. Fu Y, Wang Z, Chen W, et al. Cardioprotective effects of nitric oxide-aspirin in myocardial ischemia-reperfused rats. *Am J Physiol Heart Circ Physiol* 293: H1545, 2007.
 486. Napoli C, Aldini G, Wallace JL, et al. Efficacy and age-related effects of nitric oxide-releasing aspirin on experimental restenosis. *Proc Natl Acad Sci USA* 99:1689, 2002.
 487. Muscara MN, Lovren F, McKnight W, et al. Vaso-relaxant effects of a nitric oxide-releasing aspirin derivative in normotensive and hypertensive rats. *Br J Pharmacol* 133:1314, 2001.
 488. Lorusso R, De Cicco G, Beghi C, et al. Functional effects of nitric oxide-releasing aspirin on vein conduits of diabetic patients undergoing CABG. *Intl J Cardiol* 118: 164, 2007.
 489. Jayet PY, Thalmann S, Sartori C, et al. Nitro-Aspirin improves insulin sensitivity in obese subjects (abst). *Circulation* 110 Suppl III: III-820, 2004.
 490. Gresele P, Migliacci R, Bonizzoni E, et al. Nitroaspirin prevents effort-induced endothelial dysfunction in intermittent claudication (abst). *Circulation* 110(Suppl III): III-520, 2004.
 491. Wu CC, Teng CM. Comparison of the effects of PAR1 antagonists, PAR4 antagonists, and their combinations of thrombin-induced human platelet activation. *Eur J Pharmacol* 546: 142, 2006.
 - 491a. Leonardi S, Tricoci P, Becker RC: Thrombin receptor antagonists for the treatment of atherothrombosis. Therapeutic potential of vorapaxar and E-5555. *Drugs* 70: 1771, 2010.
 492. Kahn ML, Nakanishi-Matsui M, Shapiro MJ, et al. Protease-activated receptors 1 and 4 mediate activation of human platelets by thrombin. *J Clin Invest* 103:879, 1999.
 493. Xu Y, Huo Y, Toufektsian MC. Activated platelets contribute importantly to myocardial reperfusion injury. *Am J Physiol Heart Circ Physiol* 290:H692, 2006.
 494. Becker RC, Moliterno DJ, Jennings LK, et al for the TRA-PCI Investigators: Safety and tolerability of SCH530348 in patients undergoing non-urgent percutaneous coronary intervention: a randomised, double-blind, placebo-controlled phase II study. *Lancet* 373: 919, 2009.
 495. Tanigawa T, Nishikawa M, Kitai T, et al: Increased platelet aggregability in response to shear stress in acute myocardial infarction and its inhibition by combined therapy with aspirin and cilostazol after coronary intervention. *Am J Cardiol* 85:1054, 2000.
 496. Park S-W, Lee CW, Kim H-S, et al: Comparison of cilostazol versus ticlopidine therapy after stent implantation. *Am J Cardiol* 84:511, 1999.
 497. Han Y, Li Y, Wang S, et al: Cilostazol in addition to aspirin and clopidogrel improves long-term outcomes after percutaneous coronary intervention in patients with acute coronary syndromes: a randomized, controlled study. *Am Heart J* 157: 733, 2009.

498. Jeong YH, Lee SW, Choi BR, et al: Randomized comparison of adjunctive cilostazol versus high maintenance dose clopidogrel in patients with high post-treatment platelet reactivity. Results of the ACCEL-RESISTANCE (Adjunctive Cilostazol vs High Maintenance Dose Clopidogrel in Patients with Clopidogrel Resistance) randomized study. *J Am Coll Cardiol* 53: 1101, 2009.
499. Yasue H, Ogawa H, Tanaka H, et al, on behalf of the Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators: Effects of aspirin and trapi-dil on cardiovascular events after acute myocardial infarction. *Am J Cardiol* 83:1308, 1999.
500. Cruz-Fernandez JM, Lopez-Bescos L, Garcia-Dorado D, et al, and Triflusal in Myocardial Infarction (TIM) Investigators: Randomized comparative trial of Triflusal and aspirin following acute myocardial infarction. *Eur Heart J* 21:457, 2000.
501. Hirsh J, O'Donnell M, Eikelboom JW: Beyond unfractionated heparin and warfarin. Current and future advances. *Circulation* 116: 552, 2007.
502. Turpie AGG: New oral anticoagulants in atrial fibrillation. *Eur Heart J* 29: 155, 2007.
503. Lohrmann J, Becker RC: New anticoagulants – the path from discovery to clinical practice. *N Engl J Med* 358: 2827, 2008.
504. Fiessiner JN, Huisman MV, Davidson BL, et al for the THRIVE Treatment Study Investigators: Ximelagatran vs low molecular weight heparin and warfarin for the treatment of deep vein thrombosis. A randomized trial. *JAMA* 293: 681, 2005.
505. Executive Steering Committee on behalf of the SPORTIF III Investigators: Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 362: 1691, 2003.
506. Ford GA, Choy AM, Deedwania P, et al: Direct thrombin inhibition and stroke prevention in elderly patients with atrial fibrillation. Experience from SPORTIF III and V Trials. *Stroke* 38: 2965, 2007.
507. Wallentin L, Wilcox RG, Weaver WD, et al for the ESTEEM Investigators: Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. *Lancet* 362: 789, 2003.
508. Sanford M, Plosker GL: Dabigatran etexilate. *Drugs* 68: 1699, 2008.
509. Eriksson BI, Dahl OE, Rosencher N, et al for the RE-NOVATE Study Group: Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 370: 949, 2007.
510. Eriksson BI, Dahl OE, Rosencher N, et al: Oral dabigatran etexilate vs subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 5: 2178, 2007.
511. Eriksson BI, Dahl OE, Buller R, et al: A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement. The BISTRO II randomized trial. *J Thromb Haemost* 3: 103, 2005.
512. Connolly SJ, Ezekowitz MD, Yusuf S, et al for the RE-LY Steering Committee and Investigators: Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361: 1139, 2009.
- 512a. Wallentin L, Yusuf S, Ezekowitz MD, et al: Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 376: 975, 2010.
513. Lip GYH, Rasmussen LH, Olsson SB, et al: Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized dose-guiding, safety and tolerability study of four doses of AZD0837 vs vitamin K antagonists. *Eur Heart J* 30: 2897, 2009.
514. Toomey JR, Abboud MA, Valocik RE, et al: A comparison of B-D-xyloside, odiparcil, to warfarin in a rate model of venous thrombosis. *J Thromb Haemost* 4: 1989, 2006.
515. Chen T, Lam S: Rivaroxaban. An oral direct factor Xa inhibitor for the prevention of thromboembolism. *Cardiol in Rev* 17: 192, 2009.
516. Duggan ST, Scott LJ, Plosker GL: Rivaroxaban: a review of its use for the prevention of venous thromboembolism after total hip or knee replacement surgery. *Drugs* 69: 1829, 2009.
- 516a. Morell J, Sullivan B, Khalabuda M, McBride BF: Role of orally available antagonists of factor Xa in the treatment and prevention of thromboembolic disease: focus on rivaroxaban. *J Clin Pharmacol* 50: 986, 2010.
517. Eriksson BI, Borris LC, Friedman RJ, et al for the RECORD1 Study Group: Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 358: 2765, 2008.
518. Kakkar AK, Brenner B, Dahl OE, et al for the RECORD2 Investigators: Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thrombo-embolism after total hip arthroplasty: a double-blind, ran-

- domised controlled trial. *Lancet* 372: 32, 2008.
519. Lassen MR, Ageno W, Borris LC, et al for the RECORD3 Investigators: Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 358: 2776, 2008.
 520. Turpie AGG, Lassen MR, Davidson BL, et al for the RECORD4 Investigators: Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 373: 1673, 2009.
 521. Buller HR, Lensing AWA, Prins MH, et al on behalf of the Einstein-DVT Dose Ranging Study Investigators: A dose-ranging study evaluating once daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT dose ranging study. *Blood* 112: 2242, 2008.
 522. Agnelli G, Gallus A, Goldhaber SZ, et al for the ODIXa-DVT Study Investigators: Treatment of proximal deep vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY59-7939): the ODIXa-DVT (oral direct factor Xa inhibitor BAY59-7939 in patients with acute symptomatic deep vein thrombosis) study. *Circulation* 116: 180, 2007.
 - 522a. The Executive Steering Committee on behalf of the ROCKET AF Study Investigators: Rivaroxaban – once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: rationale and design of the ROCKET AF study. *Am Heart J* 159: 340, 2010.
 - 522b. Patel MR, Mahaffey KW, Garg J, Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* August 10, 2011 epub.
 523. Mega JL, Braunwald E, Mohanavelu S, et al on behalf of the ATLAS ACS-TIMI 46 study group: Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. *Lancet* 374: 29, 2009.
 - 523a. The EINSTEIN Investigators: Oral rivaroxaban for symptomatic venous thrombo-embolism. *N Engl J Med* 363: 2499, 2010.
 - 523b. Cohen AT, Spiro TE, Büller HR, et al: Extended-duration rivaroxaban thromboprophylaxis in acutely ill medical patients: MAGELLAN study protocol. *J Thromb Thrombolysis* 31: 407, 2011
 524. Tyberg A, Dias S, Lerner RG, Frishman WH: Oral anticoagulant medications in clinical development. *Cardiol in Rev* in press.
 525. Lassen MR, Raskob GE, Gallus A, et al: Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 361: 594, 2009.
 526. Lassen MR, Raskob GE, Gallus A, et al for the ADVANCE-2 Investigators: Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 375: 807, 2010.
 - 526a. Lassen MR, Gallus A, Raskob GE, et al: Apixaban versus enoxaparin for thrombo-prophylaxis after hip replacement. *N Engl J Med* 363: 2487, 2010.
 527. APPRAISE Steering Committee and Investigators: Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome. Results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. *Circulation* 119: 2877, 2009.
 - 527a. Granger CB, Alexander JH, McMurray JJV, et al for the ARISTOTLE Committee and Investigators: Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* August 28, 2011 epub.
 - 527b. Eikelboom JW, O'Donnell M, Yusuf S, et al: Rationale and design of AVERROES: Apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. *Am Heart J* 159: 348, 2010.
 - 527c. Connolly SJ, Eikelboom J, Joyner C, et al for the AVERROES Steering Committee and Investigators: Apixaban in patients with atrial fibrillation. *N Engl J Med* 364: 806, 2011.
 - 527d. APPRAISE-2 study with investigational compound apixaban in acute coronary syndrome discontinued. BusinessWire November 18, 2010. www.businesswire.com/news/bms/20101118007161/en/APPRAISE-2-study-investigational-compound-apixaban-acute-coronary.
 528. Agnelli G, Haas G, Ginsberg JS, et al: A phase II study of the oral factor Xa inhibitor LY517717 for the prevention of venous thromboembolism after hip or knee replacement. *J Thromb Haemost* 5: 746, 2007.
 - 528a. Ogata K, Mendell-Harary J, Tachibana M, et al: Clinical safety, tolerability, pharm-acokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol* 50: 743, 2010.
 - 528b. Schirmer SH, Baumhake M, Neuberger H-R, et al: Novel anticoagulants for stroke prevention in atrial fibrillation: current clinical evidence and future development. *J Am Coll Cardiol* 56: 2067, 2010.
 529. Turpie AGG, Bauer KA, Davidson BL, et al for the EXPERT Study Group: A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). *Thromb Haemost* 101: 68, 2009.

530. Konishi N, Hiroe K, Sinozawa E, et al: Antithrombotic profiles of TAK-442, a novel oral factor Xa inhibitor, in venous and arterial thrombosis models. *J Thromb Haemost* 7 Suppl 2: PP-WE-400 abstract, 2009.
- 530a. Hylek EM: Therapeutic potential of oral factor Xa inhibitors. *N Engl J Med* 363: 2559, 2010.
531. Baughman RA, Kapoor SC, Agarwal RK, et al: Oral delivery of anticoagulant doses of heparin. A randomized, double-blind, controlled study in humans. *Circulation* 98:1610, 1998.
532. Eriksson BI, Dahl OE, Lassen DP, et al: Partial factor IXa inhibition with TTP889 for prevention of venous thromboembolism: an exploratory study. *J Thromb Haemost* 6: 457, 2008.
- 532a. Cohen MG, Purdy DA, Rossi JS, et al: First clinical application of an actively reversible direct factor IXa inhibitor as an anticoagulation strategy in patients undergoing percutaneous coronary intervention. *Circulation* 122: 614, 2010.
533. Steffel J, Luscher TF: Novel anticoagulants in clinical development: focus on factor Xa and direct thrombin inhibitors. *J Cardiovasc Med* 10: 616, 2009.
534. Hinder M, Frick A, Jordaan P, et al: Direct and rapid inhibition of factor Xa by otamixaban: a pharmacokinetic and pharmacodynamic investigation in patients with coronary artery disease. *Clin Pharmacol Ther* 80: 691, 2006.
535. Sabatine MS, Antman EM, Widimsky P, et al: Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): a randomised, double-blind, active-controlled, phase 2 trial. *Lancet* 374:787, 2009.
536. Cohen M, Bhatt DL, Alexander JH, et al on behalf of the SEPIA-PCI Trial Investigators: Randomized, double-blind, dose-ranging study of otamixaban, a novel, parenteral, short-acting direct factor Xa inhibitor, in percutaneous coronary intervention. The SEPIA-PCI trial. *Circulation* 115: 2642, 2007.
537. Hirsh J, O'Donnell M, Weitz JI: New anticoagulants. *Blood* 105: 453, 2005.
538. Chesebro JH, Rauch U, Fuster V, Badimon JJ: Pathogenesis of thrombosis in coronary artery disease. *Haemostasis* 27(Suppl 1):12, 1997.
539. Toschi V, Gallo R, Lettino M, et al: Tissue factor modulates the thrombogenicity of human atherosclerotic plaques. *Circulation* 95:594, 1997.
540. Banai S, Gertz SD: Tissue factor as a therapeutic target in coronary syndromes. *Am J Cardiol* 763:87, 2001.
541. Friederich PW, Levi M, Bauer KA, et al: Ability of recombinant factor VIIa to generate thrombin during inhibition of tissue factor in human subjects. *Circulation* 103:2555, 2001.
542. Giugliano RP, Wiviott SD, Stone PH, et al for the ANTHEM-TIMI-32 Investigators: Recombinant nematode anticoagulant protein c2 in patients with non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 49: 2398, 2007.
543. Shibata M, Kumar SR, Amar A, et al: Anti-inflammatory, antithrombotic, and neuroprotective effects of activated protein C in a murine model of focal ischemic stroke. *Circulation* 103:1799, 2001.
544. Dalh ack B: Protein S and C4b-binding protein: Components involved in the regulation of the protein C anticoagulant system. *Thromb Haemost* 66:49, 1991.
545. Arljots B, Bergqvist D, Dalh ack B: Inhibition of microarterial thrombosis by activated protein C in a rabbit model. *Thromb Haemost* 72:415, 1994.
546. Esmon CT: Inflammation and thrombosis: Mutual regulation by protein C. *Immunologist* 6:84, 1998.
547. Bernard GR, Vincent JL, Laterre PF, et al: Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 344(10):699, 2001.
548. Esmon CT: The roles of protein C and thrombomodulin in the regulation of blood coagulation. *J Biol Chem* 258:12238, 1983.
549. Ireland H, Kunz G, Kyriakoulis K, et al: Thrombomodulin gene mutations associated with myocardial infarction. *Circulation* 96:15, 1997.
550. Nakashima M, Uematsu T, Umemura K et al: A novel recombinant soluble human thrombomodulin, ART-123, activates the protein C pathway in healthy male volunteers. *J Clin Pharmacol* 38:540, 1998.
551. Eikelboom JW, Weitz JI: update on antithrombotic therapy. New anticoagulants. *Circulation* 121: 1523, 2010.
552. RD Heparin Arthroplasty Group: RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty. *J Bone Joint Surg* 76: 1174, 1994.
553. Spiro TE, Fitzgerald RH, Trowbridge AA, et al: Enoxaparin low molecular weight heparin for the prevention of venous thromboembolic disease after knee replacement surgery. *Blood* 83: 246a, 1994.
554. Heit JA, Berkowitz Sd, Bona R, et al: Efficacy and safety of low molecular weight heparin (ardeparin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement: a double-blind, dose-ranging study: Ardeparin Arthroplasty Study Group: *Thromb Haemost* 77: 32, 1997.

References for Chapter 19

Thrombolytic Agents

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1. Collen D: Fibrin-selective thrombolytic therapy for acute myocardial infarction. *Circulation* 93:857, 1996.
2. Robbins KC, Summaira L., Hsieh B, Shah RJ: The peptide chains of human plasmin. Mechanism of activation of human plasminogen to plasmin. *J Biol Chem* 242:2333, 1967.
3. Granger CB, Califf RM, Topol EJ: Thrombolytic therapy for acute myocardial infarction. *Drugs* 44:293, 1992.
4. Collen D, Verstrate M: Pharmacology of thrombolytic drugs. In: Schlant RC, Alexander RW, eds. *Hurst's The Heart*, 8th ed. New York: McGraw Hill, 1994:1327.
5. Kamat SG, Michelson AD, Benoit SE, et al: Fibrinolysis inhibits shear stress-induced platelet aggregation. *Circulation* 92:1399, 1995.
6. Collen D: On the regulation of control of fibrinolysis. *Thromb Haemost* 43:77, 1980.
7. Anderson HV, Willerson JT: Thrombolysis in acute myocardial infarction. *N Engl J Med* 329:703, 1993.
8. Modi NB, Fox NL, Clow F-W, et al: Pharmacokinetics and pharmacodynamics of tenecteplase: Results from a phase II study in patients with acute myocardial infarction. *J Clin Pharmacol* 40:508, 2000.
9. van de Werf F, Cannon CP, Luyten A, et al for the ASSENT-1 investigators: Safety assessment of single-bolus administration of TNK tissue-plasminogen activator in acute myocardial infarction: The ASSENT-1 trial. *Am Heart J* 137:786, 1999.
10. Torr SR, Nachowiak DA, Fujui S, Sobel BE: Plasminogen steal and clot lysis. *J Am Coll Cardiol* 19:1085, 1992.
11. Davies, MJ, Thomas, AC: Plaque fissuring—the cause of acute myocardial infarction, sudden ischemic death and crescendo angina. *Br Heart J* 53:363, 1985.
12. DeWood MA, Spokes J, Notske R, et al: Prevalence of total coronary occlusion during early hours of transmural myocardial infarction. *N Engl J Med* 303:897, 1980.
13. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB: The wake-front phenomenon of ischemic cell death I. Myocardial infarct size versus duration of coronary occlusion in dogs. *Circulation* 56:786, 1977.
14. Rentrop P, Blanke H, Karsch KR, et al: Acute myocardial infarction. Intracoronary application of nitroglycerin and streptokinase. *Clin Cardiol* 2:354, 1979.
15. Rentrop P, Blanke H, Karsch KR, et al: Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina. *Circulation* 63:307, 1981.
16. Kennedy JW, Ritchie JL, Davis KB, et al: The Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. *N Engl J Med* 309:1477, 1983.
17. Kennedy JW, Ritchie JL, Davis KB, et al: The Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. *N Engl J Med* 312:1073, 1985.
18. van Domburg RT, Sonnenschein K, Nieuwlaat R, et al: Sustained benefit 20 years after reperfusion therapy in acute myocardial infarction. *J Am Coll Cardiol* 46: 15, 2005.
19. Gruppo Italiano per lo Studio della streptochinasi nell'infarto miocardico (GISSI): Effective intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1:1397, 1986.
20. ISIS-2 (Second International Study of Infarct Sur-

- vival) Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 2:349, 1988.
21. The ISAM Study Group: A prospective trial of intravenous streptokinase in acute myocardial infarction (ISAM) mortality, morbidity, and infarct size at 21 days. *N Engl J Med* 314:1465, 1986.
 22. AIMS Trial Study Group: Effect of intravenous APSAC on mortality after acute myocardial infarction: Preliminary report of a placebo-controlled clinical trial. *Lancet* 1:842, 1988.
 23. AIMS Trial Study Group: Long-term effects of intravenous anistreplase in acute myocardial infarction: Final report of the AIMS study. *Lancet* 335:427, 1990.
 24. Wilcox RG, Von der Lippe G., Olson G, et al: Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet* 2:525, 1988.
 25. Gruppo Italiano per lo Studio Della sopravvivenza nell'infarcto miocardico. GISSI-2: A factorial randomized trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 336:65, 1990.
 26. Third International Study of Infarct Survival Collaborative Group. ISIS-3: A randomized comparison of streptokinase versus tissue plasminogen activator versus anistreplase and of aspirin plus heparin nobreak versus aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 339:753, 1992.
 27. The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 329:673, 1993.
 28. Califf RM, White HD, Van de Werf F, et al: One-year results from the Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO-1) trial. *Circulation* 94:1233, 1996.
 29. Mueller HS, Rao AK, Forman SA: The TIMI Investigators thrombolysis in myocardial infarction (TIMI): Comparative studies of coronary reperfusion and systemic fibrinogenolysis with two forms of recombinant tissue-type plasminogen activator. *J Am Coll Cardiol* 10:479, 1987.
 30. The Continuous Infusion versus Double-Bolus Administration of Alteplase (COBOLT) Investigators: A comparison of continuous infusion of alteplase with double-bolus administration for acute myocardial infarction. *N Engl J Med* 337:1124, 1997.
 31. Bode C, Smalling RW, Berg G, et al for RAPID II Investigators; Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activators) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. *Circulation* 94:891, 1996.
 32. International Joint Efficacy Comparison of thrombolytics: Randomized, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): Trial to investigate equivalence *Lancet* 346:329, 1995.
 33. Global Use of Strategies to Open Coronary Arteries (GUSTO III) Investigation: Comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 337:1118, 1997.
 34. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators: Single bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind trial. *Lancet* 354:716, 1999.
 35. EMERAS (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) Collaborative Group: Randomized trial of late thrombolysis in patients with suspected acute myocardial infarction. *Lancet* 342:767, 1993.
 36. LATE Study Group: Late assessment of thrombolysis efficacy (LATE). Study with alteplase after onset of acute myocardial infarction. *Lancet* 342:759, 1993.
 - 36a. Lambert L, Brown K, Segal I, et al: Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. *JAMA* 303: 2148, 2010.
 37. Morrison LJ, Verbeek PR, McDonald AC, et al. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis - *JAMA* 283:2686, 2000.
 38. Steg PG, Bonnefoy E, Chbaud S et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from CAPTIM randomized clinical trial. *Circulation* 108: 2851, 2003.
 39. Bottiger BW, Arntz H-R, Chamberlain DA, et al for the TROICA Trial Investigators and the European Resuscitation Council Study Group: Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med* 359: 2651, 2008.
 40. Stadlbauer KH, Krismer AC, Arntz HR, et al: Effects of thrombolysis during out-of-hospital cardiopulmonary resuscitation. *Am J Cardiol* 97: 305, 2006.
 41. Stenestrand U, Lindback J, Wallentin L for the RIKS-HIA Registry: Long-term outcome of pri-

- mary percutaneous coronary intervention vs pre-hospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. *JAMA* 296:1749, 2006.
42. Chesboro JH, Knatterud G, Roberts R, et al: Thrombolysis in myocardial infarction (TIMI) trial, phase 1: A comparison between intravenous and tissue plasminogen activator and intravenous streptokinase. *Circulation* 76:142, 1987.
 43. Dalen JE: Six and twelve month follow-up of phase 1 thrombolysis in myocardial infarction (TIMI) trial. *Am J Cardiol* 62:179, 1988.
 44. The GUSTO angiographic investigators: The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ventricular function and survival after acute myocardial infarction. *N Engl J Med* 329:1615, 1993.
 45. Gillis JC, Wagstaff AJ, Goa KL: Alteplase. Reappraisal of its pharmacologic properties and therapeutic uses in acute myocardial infarction. *Drugs* 50:101, 1995.
 46. Rurors JA, McNeil AJ, Siddiqui RT, et al: Efficacy of 100-mg of double-bolus alteplase in achieving complete perfusion in the treatment of acute myocardial infarction. *J Am Coll Cardiol* 23:6, 1994.
 47. Smalling RW, Bode C, Kalbfleisch J, et al and RAPID investigators: More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. *Circulation* 91:2725, 1995.
 48. Cannon CP, McCabe CH, Gibson CM, et al and TIMI 10A investigators. TNK-tissue plasminogen activator in acute myocardial infarction. Results of thrombolysis in myocardial infarction (TIMI) 10A dose ranging trial. *Circulation* 95:351, 1997.
 49. Cannon CP, Gibson CM, McCabe CH, et al for TIMI 10B investigators. TNK-tissue plasminogen activator compared with front loaded alteplase in acute myocardial infarction. *Circulation* 98:2805, 1998.
 50. Gibson CM, Murphy SA, Kirtane AJ et al. Association of duration of symptoms at presentation with angiographic and clinical outcomes after fibrinolytic therapy in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 44:980, 2004.
 51. Goldman LE, Eisenberg MJ: Identification and management of patients with failed thrombolysis after acute myocardial infarction. *Ann Intern Med* 132:556, 2000.
 52. Ohman EM, Califf RM, Topol EJ, et al: Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. *Circulation* 82:781, 1990.
 53. Pilote L, Miller DP, Califf RM, et al: Determinants of the use of coronary angiography and revascularization after thrombolysis for acute myocardial infarction. *N Engl J Med* 335:1198, 1996.
 54. Barbarsh GI, Birnbaum Y, Bogaerts K, et al: Treatment of reinfarction after thrombolytic therapy for acute myocardial infarction. An analysis of outcome and treatment choices in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO I) and Assessment of the Safety of a New Thrombolytic (ASSENT 2) studies. *Circulation* 103:954, 2001.
 55. White HD: Thrombolytic treatment for recurrent myocardial infarction. Avoid repeating streptokinase or anistreplase. *BMJ* 302:429, 1991.
 56. Barbash GI, Hod H, Roth A. et al: Repeat infusions of recombinant tissue-type plasminogen activator in patients with acute myocardial infarction and recurrent myocardial ischemia. *J Am Coll Cardiol* 16:779, 1990.
 57. Wijeyesundera HC, Vijayraghavan R, Brahamjee K et al. Rescue angioplasty or repeat fibrinolysis after failed therapy for ST-segment myocardial infarction. A meta-analysis of randomized trials. *J Am Coll Cardiol* 49:422, 2007.
 58. Anderson JL, Karagounis LA, Becker LC, et al: TIMI perfusion grade 3 but not grade 2 results improve outcome after thrombolysis for myocardial infarction. Ventriculographic enzymatic, and electrocardiographic evidence from the TEAM-3 study. *Circulation* 87:1829, 1993.
 59. Simes RJ, Topol EJ, Holmes DR: Link between angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. *Circulation* 91:1923, 1995.
 60. Gibson CM, Murphy SA, Rizzo MJ et al: Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. *Circulation* 99:1945, 1999.
 61. Grines CL, DeMaria AN: Optimal utilization of thrombolytic therapy for acute myocardial infarction: Concepts and controversies. *J Am Coll Cardiol* 16:223, 1990.
 62. Fibrinolytic Therapy Trialists (FTT) Collaborative Group: Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity in results from all randomized trials of more than 1000 patients. *Lancet* 343:311, 1994.
 63. The TIMI IIIB Investigators: Effects of tissue plasminogen activator and comparison of early invasive and conservative strategies in unstable angina

- and non-Q wave myocardial infarction. Results of the TIMI IIIB trial. *Circulation* 89:1545, 1994.
64. Braunwald E, Cannon PC: Non Q wave and ST segment depression myocardial infarction: Is there a role for thrombolytic therapy? *J Am Coll Cardiol* 27:1333, 1996.
 65. Langes A, Goodman SG, Topol EJ, et al: Late assessment of thrombolytic efficacy (LATE) Study: Prognosis in patients with non-Q wave myocardial infarcts. *J Am Coll Cardiol* 27:1327, 1996.
 66. Sgarbossa EB, Pinski SL, Barbagelata A, et al for GUSTO-1 investigators. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle branch block. *N Eng J Med* 344:481, 1996.
 67. Holmes DR, Bates ER, Kleinman NS, et al: Contemporary reperfusion therapy for cardiogenic shock: The GUSTO-1 trial experience. *J Am Coll Cardiol* 26:668, 1995.
 68. Hochman JS, Sleeper LA, Webb JG, et al: Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Eng J Med* 341:625, 1999.
 69. Berger AK, Radford MJ, Wang Y, Krumholz HM: Thrombolytic therapy in older patients. *J Am Coll Cardiol* 36:366, 2000.
 70. Ayanian JZ, Braunwald E: Thrombolytic therapy for patients with myocardial infarction who are older than 75 years. Do the risks outweigh the benefits? *Circulation* 101:2224, 2000.
 71. Mateen FJ, Nasser M, Spencer BR, et al: Outcomes of intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 90 years or older. *Mayo Clin Proc* 84: 334, 2009.
 72. Lenefsky EJ, Lundergan CF, Hodgson JMcB, et al: Increased left ventricular dysfunction in elderly patients despite successful thrombolysis. The GUSTO-1 angiographic experience. *J Am Coll Cardiol* 28:331, 1996.
 73. Thiemann DZR, Coresh J, Schulman SP, et al: Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation* 101:2239, 2000.
 74. White HD: Thrombolytic therapy in the elderly (editorial). *Lancet* 356:2028, 2000.
 75. Ridker PM, Hennekens CH: Age and thrombolytic therapy. *Circulation* 94:1807, 1996.
 76. Antman EM, Giugliano RP, Gibson C.M., et al: Abciximab facilitates the rate and extent of thrombolysis. Results of the Thrombolysis in Myocardial Infarction (TIMI) 14 trial. *Circulation* 99:2720, 1999.
 77. Neumann F-J, Zohnhofer D, Fakhoury D, et al: Effect of glycoprotein IIb/IIIa. Receptor blockade on platelet/leukocyte interaction and surface expression of the leukocyte integrin Mac-1 in acute myocardial infarction. *J Am Coll Cardiol* 34:1420, 1999.
 78. Ohman EM, Kleiman NS, Gacioch G, et al for IMPACT-AMI Investigators: Combined accelerated tissue plasminogen activator and platelet glycoproteins IIb/IIIa. Integrin receptor blockade with integrelin in acute myocardial infarction. Results of a randomized, placebo-controlled dose-ranging trial. *Circulation* 95:846, 1997.
 79. Strategies for Patency Enhancement in the Emergency Department (SPEED) Group Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. *Circulation* 101:2788, 2000.
 80. Gibson CM., deLemos JA, Murphy SA, et al: Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction. A TIMI 14 Sub-study. *Circulation* 103:2550, 2001.
 81. The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: The GUSTO V randomized Trial. *Lancet* 357:1905, 2001.
 82. Assessment of the Safety and Efficacy of a New Thrombolytic regimen (ASSENT-3) investigators: Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab or unfractionated heparin: The ASSENT-3 randomized trial in acute myocardial infarction. *Lancet* 358:605, 2001.
 83. Eisenberg PR, Sherman LA, Jaffe AS: Paradoxical elevation of fibrinopeptide A: Evidence for continued thrombosis despite intensive fibrinolysis. *J Am Coll Cardiol* 10:527, 1987.
 84. Aronson DL, Chang P, Kessler CM: Platelet-dependent thrombin generation after in vitro-fibrinolytic treatment. *Circulation* 85:1706, 1992.
 85. Fitzgerald DJ, Catella F, Roy L, et al: Marked platelet activation in vivo after intravenous streptokinase in patients with acute myocardial infarction. *Circulation* 77:142, 1988.
 86. Keller NM, Feit F: Thrombolytic therapy in acute MI, Part 2: Update on adjuvants. *J Crit Illness* 13:646, 1998.
 87. Handin, R.I.: Platelets and coronary artery disease. *N Engl J Med* 334:1126, 1996.
 88. Sabatine MC, Cannon CP, Gibson CM et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Eng J Med* 352:1179, 2005.
 89. Granger CB, Becker R, Tracy RP, et al for the GUSTO-I Hemostasis Substudy Group: Thrombin generation, inhibition and clinical outcomes in pa-

- tients with acute myocardial infarction treated with thrombolytic therapy and heparin: Results from the GUSTO-I trial. *J Am Coll Cardiol* 31:497, 1998.
90. Topol EJ, George BS, Kareiakes DJ, et al: A randomized trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. *Circulation* 79:281, 1989.
 91. Hsia JA, Hamilton WP, Kleinman N, et al: A comparison between heparin and low dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 323:1433, 1990.
 92. DeBono DP, Simoons ML, Tijssen J: Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase. Thrombolysis: Results of a randomized double-blind European Cooperative Study Group Trial. *Br Heart J* 67:122, 1992.
 93. Hirsh J, Fuster V: Guide to anticoagulant therapy, part 1: Heparin. *Circulation* 89:1449, 1994.
 94. International Study Group: In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomized between alteplase and streptokinase. *Lancet* 336:71, 1990.
 95. The SCATI (Studio sulla Calciparina nell'Angina e nella Trombosi Ventricolare nell' Infarto) Group: Randomized controlled trial of subcutaneous calcium heparin in acute myocardial infarction. *Lancet* 2:182, 1989.
 96. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIA Investigators: Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 90:1631, 1994.
 97. Antman EM for TIMI9A Investigators: Hirudin in acute myocardial infarction safety report from the thrombolysis and thrombin inhibitors in myocardial infarction (TIMI) 9A trial. *Circulation* 90:1624, 1994.
 98. Nehaus KL, Essen R, Tebbe U, et al: Safety observations from the pilot phase of randomized versus hirudin for improvement of thrombolysis (HIT-III) study. *Circulation* 90:1638, 1994.
 99. Jang I-K, Brown DFM, Giugliano RP, et al for the MINT Investigators: A multicenter, randomized study of argatroban versus heparin as adjunct to tissue plasminogen activator (TPA) in acute myocardial infarction: Myocardial Infarction with Novastan and TPA (MINT) Study. *J Am Col Cardiol* 33:1879, 1999.
 100. American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 1999 Update: ACC/AHA guidelines for management of patients with acute myocardial infarction: Executive summary and recommendations *Circulation* 100:1016, 1999.
 101. Antman EM, Morrow DA, McCabe CH et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Eng J Med* 1477:354 2006.
 102. Collet JP, Montalescot G, Le May M et al Percutaneous coronary intervention after fibrinolysis: a multiple meta-analysis approach according to the type of strategy. *J Am Coll Cardiol.* 48:1326, 2006.
 103. Assessment of safety and efficiency of a new treatment strategy with percutaneous coronary intervention (ASSENT-4PCI) investigators. Primary versus tenecteplase- facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomized trial, *Lancet* 367:569, 2006.
 104. Cantor WJ, Fitchett D, Borgundvaag B et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Eng J Med* 360-2705, 2009.
 105. Khawaja FJ and Ting H. Quality dimensions of primary percutaneous coronary intervention. Timeliness, access, and availability. *Circulation* 120:2411, 2009.
 106. Aguirre FA, Varghese JJ, Kelly MP et al. Rural inter-hospital transfer of ST-elevation myocardial infarction patients for revascularization. The stat heart program. *Circulation.* 117:1145, 2008.
 107. Keely EC, Boura JA, and Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials. *Lancet* 361:12, 2003.
 108. Patel SC, Mody A: Cerebral hemorrhage complications of thrombolytic therapy. *Prog Cardiovasc Dis* 42:217, 1999.
 109. Berkowitz SD, Granger CB, Pieper KS, et al for the GUSTO I Investigators: Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. *Circulation* 95:2508, 1997.
 110. Sloan MA, Gore JM: Ischemic stroke and intracranial hemorrhage following thrombolytic therapy for acute myocardial infarction: Benefit analysis. *Am J Cardiol* 69:21A, 1991.
 111. DeJaegere PB, Arnold AA, Balk AH, Simoons ML: Intracranial hemorrhage in association with thrombolytic therapy: Incidence and clinical predictive factors. *J Am Coll Cardiol* 19:289, 1992.
 112. Longstreth WT, Litwin PE, Weaver WD, MITI project group: Myocardial infarction, thrombolytic therapy and stroke. A community-based study. *Stroke* 24:587, 1993.

113. Gore JM, Sloan M, Price TR, et al: Intracranial hemorrhage, cerebral infarction, and subdural hematoma after acute myocardial infarction and thrombolytic therapy in thrombolysis in myocardial infarction study. Thrombolysis in Myocardial Infarction. Phase II Pilot and Clinical Trial. *Circulation* 83:448, 1991.
114. Sane DE, Califf RM, Topol EJ, et al: Bleeding during thrombolytic therapy for acute myocardial infarction: Mechanisms and management. *Ann Intern Med* 3:1012, 1989.
115. Patel MR, Meine TJ, Lindblad L, et al: Cardiac tamponade in the fibrinolytic era: analysis of >100 000 patients with ST-segment elevation myocardial infarction. *Am Heart J* 151: 316, 2006.
116. Honan MB, Harrell FE, Reiner KA, et al: Cardiac rupture, mortality and timing of thrombolytic therapy: A meta-analysis. *J Am Coll Cardiol* 16:359, 1990.
117. Becker RC, Charlesworth A, Wilcox RG, et al: Cardiac rupture associated with thrombolytic therapy: Impact of time to treatment in the Late Assessment of Thrombolytic Efficacy (LATE) Study. *J Am Coll Cardiol* 25:1063, 1995.
118. Deviri E, Sareli P, Wisenbaugh T, Cronje SL: Obstruction of mechanical heart valve prostheses: Clinical aspects and surgical management. *J Am Coll Cardiol* 17:646, 1991.
119. Kontos GJ, Schaft HV, Orszulak TA, et al: Thrombolytic obstruction of disc valves: Clinical recognition and surgical management. *Ann Thorac Surg* 48:60, 1989.
120. Roudaut R, Labbe T, Lorient-Roudaut MF, et al: Mechanical cardiac valve thrombosis: Is fibrinolysis justified? *Circulation* 86(Suppl. 2):II-8, 1992.
121. Hurrell DG, Schaft HV, Tajik AJ: Thrombolytic therapy for obstruction of mechanical prosthetic valves. *Mayo Clin Proc* 71:605, 1996.
122. Tong AT, Roudaut R, Ozkan M et al. Transesophageal echocardiography improves the risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international PRO-TEE registry. *Circulation* 43: 77, 2004.
123. Shapiro Y, Herz I, Vaturi M, et al. Thrombolysis is an effective and safe therapy in stuck bi-leaflet mitral valves in the absence of high-risk thrombi. *J Am Coll Cardiol* 35:1874, 2000.
124. Ozkan M, Kaymaz C, Kirma C et al: Intravenous thrombolytic treatment of mechanical prosthetic valve thrombosis: A study using serial transesophageal echocardiography. *J Am Coll Cardiol* 35:1881, 2000.
125. Bonow RO, Carabello BA, Chatterjee K et al. 2008 focused update incorporated into the ACC/AHA guidelines for management of patients with valvular heart disease. *Circulation* 118: e523, 2008.
126. Sasahara AA, Myers TH, Cole CM, et al: The Urokinase Pulmonary Embolism Trial. A national cooperative study. *Circulation* 47:1, 1973.
127. Dalla-Volta S, Palla A, Santolicandro A, et al: PAIMS 2: Alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen Activator Italian Multicenter Study 2. *J Am Coll Cardiol* 20; 520, 1992.
128. Meyer G, Sors H, Charbonnier B, et al: Effects of intravenous urokinase versus alteplase on total pulmonary resistance in acute massive pulmonary embolism: A European multicenter double-blind trial. *J Am Coll Cardiol* 19:239, 1992.
- 128a. Wang C, Zhai Z, Yang Y, et al: Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism. A randomized, multicenter, controlled trial. *Chest* 137: 254, 2010.
129. Goldhaber SZ: Contemporary pulmonary embolism thrombolysis. *Chest* 107:45, 1995.
130. Goldhaber SZ, Kessler CM, Heit JA, et al: A randomized control trial of recombinant tissue plasminogen activator versus urokinase in the treatment of acute pulmonary embolism. *Lancet* 2:193, 1988.
131. Goldhaber SZ, Kessler CM, Heit JA, et al: Recombinant tissue type plasminogen activator versus a novel dosing regimen of urokinase in acute pulmonary embolism: A randomized controller multicenter trial. *J Am Coll Cardiol* 20:20,1992.
132. Goldhaber SZ, Haire WD, Feldstein ML, et al: Alteplase versus heparin in acute pulmonary embolism: Randomized trial assessing right ventricular and pulmonary perfusion. *Lancet* 341:507, 1993.
133. Goldhaber SZ: Thrombolytic therapy for patients with pulmonary embolism who are hemodynamically stable but have right ventricular dysfunction. *Pro. Arch Intern Med* 165: 2197, 2005.
134. Verstraete M, Miller GAH, Bounamcaux H, et al: Intravenous and intra pulmonary recombinant tissue - type plasminogen activator in the treatment of acute massive pulmonary embolism. *Circulation* 77:353, 1988.
135. Kanstantinedes S, Geibel A, Olschewski M, et al: Association between thrombolytic treatment and prognosis of hemodynamically stable patients with major pulmonary embolism. *Circulation* 96:882, 1997.
136. Thabut G, Thabut D, Myers RP et al. Thrombolytic therapy of pulmonary embolism. A meta-analysis. *J Am Coll Cardiol* 40:1660, 2002.
137. Wan S, Quinlan DJ, Agnelli G et al. Thrombolysis

- compared with heparin for the initial treatment of pulmonary embolism. A meta-analysis of the randomized control trials. *Circulation* 110:744,2004.
138. Konstantinides S, Giebel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Eng J Med* 347:1143, 2002.
 139. Goldhaber SZ: Pulmonary embolism thrombolysis. Broadening the paradigm for its administration. *Circulation* 96:716, 1997.
 140. Hommel M, Boissel JP, Connu C, et al: Termination of trial: Streptokinase in severe acute ischemic stroke. *Lancet* 345:57, 1995.
 141. Donnan GA, Hommel M, Davis SM, McNeil JJ: Streptokinase in acute ischemic stroke. *Lancet* 346:56, 1995.
 142. The Multicenter Acute Stroke Trial—Europe Study Group: Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med* 335:145, 1996.
 143. Hacke W, Kaste M, Fieschi C, et al: Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA* 274:1017, 1995.
 144. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 333:1581, 1995.
 145. Wahlgren N, Ahmed N, Davalos A, et al for the SITS-MOST Investigators: Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 369: 275, 2007.
 146. Hacke W, Kaste M, Bluhmki E. et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Eng J Med* 359:1317, 2008.
 147. The ATLANTIS, ECASS and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment; pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 363:768, 2004.
 148. Adams HP, del Zoppo G, Alberts MJ et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/ American Stroke Association Stroke Council, and the Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational learning tool for neurologists. *Stroke* 38:1655, 2007.
 149. Weintraub MI: Thrombolysis (tissue plasminogen activator) in stroke. A medicolegal quagmire. *Stroke* 37: 1917, 2006.
 150. Furlan A, Higashida R, Wechsler L, et al: Intra-arterial pro-urokinase for acute ischemic stroke: The PROACT II Study: A randomized control trial. *JAMA* 282:2003, 1999.
 151. Argaral P, Kumar S, Hariharan S, et al: Hyperdense middle cerebral artery sign: can it be used to select intra-arterial versus intravenous thrombolysis in acute ischemic stroke? *Cerebrovasc Dis* 17:182, 2004.
 152. Francis CW, Marde VJ: Fibrinolytic therapy for venous thrombosis. *Progr Cardiovasc Dis* 34:193, 1991.
 153. Comeroto AJ, et al: Venous thromboembolism. In: Rutherford RB, ed. *Vascular Surgery*, 4th ed. Philadelphia: Saunders, 1995:1800.
 154. Schweizer J, Kirch W, Koch R, et al: Short- and long-term results after thrombolytic treatment of deep venous thrombosis. *J Am Coll Cardiol* 36:1336, 2000.
 155. Kearon C, Kahn SR, Angelli G et al. Anti thrombotic therapy for venous thromboembolic disease. American College of *Chest* Physicians evidence-based clinical practice guidelines (8th edition) *Chest* 2008; 133:454S-554S.
 156. Wagstaff AJ, Gillis JC, Goa KL: Alteplase. A reappraisal of its pharmacology and therapeutic use in vascular disorders other than acute myocardial infarction. *Drugs* 50:289, 1995.
 157. Hess H: Thrombolytic therapy in peripheral vascular disease. *Br J Surg* 77:1083, 1990.
 158. Lonsdale RJ, Berridge DC, Earnshaw JJ: Recombinant tissue-type plasminogen activator is superior to streptokinase for local intra-arterial thrombolysis. *Br J Surg* 79:272, 1992.
 159. The Stile Investigators: Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. *Ann Surg* 220:251, 1994.
 160. Tabriziani H, Schieu A, Frishman WH, Brandt LJ: Drug therapies for mesenteric vascular disease. *Heart Dis* 4:306, 2002.
 161. Trans Atlantic Intersociety Consensus (TASC): Management of peripheral vascular disease. *J Vasc Surg* 31:S151, 2000.
 162. Sobel M, Verhaeghe R. Antithrombotic therapy for peripheral artery occlusive disease. American College of *Chest* Physicians evidence-based clinical practice guidelines (8th edition) *Chest* 133:815S, 2008.
 163. New applications for thrombolytics: Alteplase in the periphery. *Formulary* 36(Suppl 4): 4, 2001.
 164. Clase CM, Crowther MA, Ingram AJ, Cina CS: Thrombolysis for restoration of patency to haemodialysis central venous catheters: A systematic review. *J Thromb Thrombolysis* 11:127, 2001.

References for Chapter 20

Lipid-Lowering Drugs

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1. Stamler J, Wentworth D, Neaton J: Is the relationship between serum cholesterol and risk of death from coronary heart disease continuous and graded? *JAMA* 256:2823, 1986.
2. LaRosa JC, Hunninghake D, Bush D, et al: The cholesterol facts: A summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. A joint statement by the American Heart Association and the National Heart, Lung and Blood Institute. *Circulation* 81:1721, 1990.
3. Verschuren WMM, Jacobs DR, Bloemberg BPM, et al: Serum total cholesterol and s-term coronary heart disease mortality in different cultures. Twenty-five year follow-up of the Seven Countries Study. *JAMA* 274:131, 1995.
4. Chien PC, Frishman WH: Lipid disorders. In: Crawford MH, ed. *Current Diagnosis and Treatment in Cardiology*, 2nd ed. New York: McGraw Hill, 2002:17.
5. Aronow WS, Ahn C. Risk factors for new coronary events in a large cohort of very elderly patients with and without coronary artery disease. *Am J Cardiol* 77:864, 1996.
6. Aronow WS, Ahn C. Correlation of serum lipids with the presence or absence of coronary artery disease in 1,793 men and women aged 62 years. *Am J Cardiol* 73:702, 1994.
7. Lipid Research Clinics Program: The Lipid Research Clinics Coronary Primary Prevention Trial Results: I. Reduction in the incidence of coronary heart disease. *JAMA* 251:351, 1986.
8. Canner PL, Berge KG, Wenger NK, et al: Fifteen year mortality in Coronary Drug Project patients: Long-term benefit with niacin. *J Am Coll Cardiol* 8:1245, 1986.
9. Frick MH, Elo MO, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 317:1237, 1987.
10. Blankenhorn DH, Nessim SA, Johnson RL, et al: Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 257:3233, 1987.
11. The Post Coronary Artery Bypass Graft Investigators. The effect of aggressive and moderate lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary artery bypass grafts. *N Engl J Med* 336:153, 1997.
12. Alaupovic P, Fesmire JD, Hunninghake D, et al: The effect of aggressive and moderate lowering of LDL-cholesterol and low dose anticoagulation on plasma lipids, apolipoproteins and lipoprotein families in post coronary artery bypass graft trial. *Atherosclerosis* 146:369, 1999.
13. Frick MH, Syv anne M, Nieminen MS et al: Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. *Circulation* 96:2137, 1997.
14. Ornish D, Brown SE, Scherwitz LW, et al: Can lifestyle reverse coronary heart disease? *Lancet* 336:129, 1990.
15. Kane JP, Malloy MJ, Ports TA, et al: Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. *JAMA* 264:3007, 1990.
16. Brown G, Albers JJ, Fisher LD, et al: Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 323:1289, 1990.
17. Buchwald H, Varco RL, Matts JP, et al: Effect of par-

- tial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. *N Engl J Med* 323:946, 1990.
18. Holme I: Cholesterol reduction and its impact on coronary artery disease and total mortality. *Am J Cardiol* 76:10C, 1995.
 19. Haskell WI, Alderman EL, Fair JM, et al: The effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease: The Stanford Coronary Risk Intervention Project (SCRIP). *Circulation* 89:975, 1994.
 20. Gould AL, Rossouw JE, Santanello NC, et al: Cholesterol reduction yields clinical benefit. A new look at old data. *Circulation* 91:2274, 1995.
 21. Grundy SM, Friedman D: Rationale for cholesterol-lowering strategies. *Curr Probl Cardiol* 20:281, 1995.
 22. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 344:1383, 1994.
 23. Miettinen TA, Pyorala K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris. Findings from the Scandinavian Simvastatin Survival Study (4S). *Circulation* 96:4211, 1997.
 24. Pedersen TR, Kjekshus J, Pyorala K, et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol* 81:333, 1998.
 25. Pedersen TR, Wilhelmsen L, Faergeman O, et al. Follow-up study of patients randomized in the Scandinavian Simvastatin Survival Study (4S) of cholesterol lowering. *Am J Cardiol* 86: 257, 2000.
 26. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 335:1001, 1996.
 27. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 339:1349, 1998.
 28. The LIPID Study Group: Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. *Lancet* 359:1379, 2002.
 29. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 360:7, 2002.
 30. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 360:1623, 2002.
 31. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL study: a randomized controlled trial. *JAMA* 285:1711, 2001.
 32. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 361:1149, 2003.
 33. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes mellitus in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. *Lancet* 364: 685, 2004.
 34. Hitman GA, Colhoun H, Newman C, et al on behalf of the CARDS investigators: Stroke prediction and stroke prevention with atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS). *Diabet Med* 24: 1313, 2007.
 35. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. A randomized controlled trial. *JAMA* 291:1071, 2004.
 36. Cannon CP, Braunwald E, McCabe CH, et al. Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 350:1495, 2004.
 37. Murphy SA, Cannon CP, Wiviott SD, et al. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials). *Am J Cardiol* 100: 1047, 2007.
 - 37a. Murphy SA, Cannon CP, Wiviott SD, et al: Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes. From the PROVE-IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial. *J Am Coll Cardiol* 54: 2358, 2009.
 38. LaRosa JC, Grundy SM, Waters DD, et al. Intensive

- lipid lowering with atorvastatin in patients with stable coronary disease. *N Eng J Med* 352: 1425, 2005.
39. Waters DD, LaRosa JC, Barter P, et al: Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (Treating to New Targets) study. *J Am Coll Cardiol* 48: 1793, 2006.
 40. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 366:1267, 2005.
 41. Deedwania P, Stone PH, Merz CNB, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease. Results of the Study Assessing Goals in the Elderly (SAGE). *Circulation* 115: 700,2007.
 42. Ridker PM, Danielson E, Francisco MIA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 359: 2195, 2008.
 43. Aronow WS, Ahn C. Incidence of new coronary events in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol ≥ 125 mg/dL treated with statins versus no lipid-lowering drug. *Am J Cardiol* 89:67, 2002.
 44. Aronow WS, Ahn C. Reduction of coronary events with aspirin in older patients with prior myocardial infarction treated with and without statins. *Heart Disease* 4:159, 2002.
 45. Aronow WS, Ahn C, Gutstein H. Reduction of new coronary events and of new atherothrombotic brain infarction in older persons with diabetes mellitus, prior myocardial infarction, and serum low-density lipoprotein cholesterol ≥ 125 mg/dL treated with statins. *J Gerontol: Med Sci* 57A:M747, 2002.
 46. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction. The IDEAL study: a randomized controlled trial. *JAMA* 294: 2437, 2005.
 47. Aronow WS, Ahn C. Frequency of new coronary events in older persons with peripheral arterial disease and serum low-density lipoprotein cholesterol ≥ 125 mg/dl treated with statins versus no lipid-lowering drug. *Am J Cardiol* 90:789, 2002.
 48. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486, 2001.
 49. Kannel WB, Castelli WP, Gordon T: Cholesterol in the prediction of atherosclerotic disease: New perspectives in the Framingham Study. *Ann Intern Med* 90:85, 1979.
 50. Stampfer MJ, Sacks FN, Salvini S, et al: A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med* 325:373, 1991.
 51. Gordon DJ, Probstfeld JL, Garrison RJ, et al: High-density lipoprotein cholesterol and cardiovascular disease: Four prospective American series. *Circulation* 79:8, 1989.
 52. Rubins HB, Robins SJ, Collins D et al: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 341:410, 1999.
 53. Hodis HN, Mack WJ: Triglyceride-rich lipoproteins and the progression of coronary artery disease. *Curr Opin Lipidol* 6:209, 1995.
 54. Pasternak RC, Grundy SM, Levy D, Thompson PD: Task Force 3: spectrum of risk factors for coronary heart disease. *J Am Coll Cardiol* 27:978, 1996.
 55. Kannel WB, Neaton JD, Wentworth D, et al: Overall and CHD mortality rates in relation to major risk factors in 325,348 men screened for the MRFIT. *Am Heart J* 112:825, 1986.
 56. Gould AL, Roussouw JE, Santanello NC, et al: Cholesterol reduction yields clinical benefit. Impact of statin trials. *Circulation* 97:946-952, 1998.
 57. Steinberg D, Gotto AM Jr: Preventing coronary artery disease by lowering cholesterol levels. Fifty years from bench to bedside. *JAMA* 282:2043, 1999.
 58. Faergeman O: Hypertriglyceridemia and the fibrates trials. *Curr Opin Lipidol* 11:609, 2000.
 - 58a. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration: Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 375: 1634, 2010.
 - 58b. Jun M, Foote C, Lv J, et al: Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 375: 1875, 2010.
 59. Stampfer MJ, Krauss RM, Ma J, et al: A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA* 276:882, 1996.
 60. Lemieux I, Pascot A, Couillard C, et al: Hypertriglyceridemic waist. A marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapoprotein B; small, dense LDL) in men? *Circulation* 102:179, 2000.
 61. Myers LH, Phillips NR, Havel RJ: Mathematical evaluation of methods for estimation of the concentration of the major lipid components of human serum lipoproteins. *J Lab Clin Med* 88:491, 1976.

62. Crouse JR III, Byington RP, Furberg CD: HMG-CoA reductase inhibitor therapy and stroke risk reduction: An analysis of clinical trials data. *Atherosclerosis* 138:11, 1998.
63. Warshafsky S, Packard D, Marks SJ, et al: Efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for prevention of stroke. *J Gen Intern Med* 14:763, 1999.
64. Tsimikas S, Brilakis ES, Miller ER, et al: Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med* 353: 46, 2005.
65. Sharrett AR, Ballantyne CM, Coady SA, et al: Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 104:1108, 2001.
66. Johnson CL, Rifkind BM, Sempos CT, et al: Declining serum total cholesterol levels among US adults. The National Health and Nutrition Examination Surveys. *JAMA* 269:3002, 1993.
67. Ridker PM, Stampfer MJ, Rifai N: Novel risk factors for systemic atherosclerosis. A comparison of C-reactive protein, fibrinogen, lipoprotein (a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 285:2481, 2001.
68. American College of Physicians: Guidelines for using serum cholesterol, high-density lipoprotein cholesterol, and triglyceride levels as screening tests for preventing coronary heart disease in adults. *Ann Intern Med* 124:515, 1996.
69. Task Force on Risk Reduction, American Heart Association: Cholesterol screening in asymptomatic adults. No cause to change. *Circulation* 93:1067, 1996.
70. Lauer RM, Clarke WR: Use of cholesterol measurements in childhood for the prediction of adult hypercholesterolemia. The Muscatine Study. *JAMA* 264:3034, 1990.
71. Newman TB, Browner WS, Hulley SB: The case against childhood cholesterol screening. *JAMA* 264:3039, 1990.
72. Grundy SM, Cleeman JJ, Merz CNB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110: 227-239.
73. Sarwar N, Sattar N: Triglycerides and coronary heart disease: have recent insights yielded conclusive answers? *Curr Opin Lipidol* 20: 275, 2009.
74. Sarwar N, Danesh J, Eiriksdottir G, et al: Triglycerides and the risk of coronary heart disease. 10,158 incident cases among 262,525 participants in 29 western prospective studies. *Circulation* 115: 450, 2007.
75. Brunzell JD: Hypertriglyceridemia. *N Engl J Med* 357: 1009, 2007.
76. Ford ES, Li C, Zhao G, et al: Hypertriglyceridemia and its pharmacologic treatment among US adults. *Arch Intern Med* 169: 572, 2009.
77. Phillips NR, Havel RJ, Kane JP: Levels and interrelationships of serum and lipoprotein cholesterol and triglycerides: association with adiposity and the consumption of ethanol, tobacco, and beverages containing caffeine. *Arteriosclerosis* 1:13, 1981.
78. Ashen MD, Blumenthal RS: Low HDL cholesterol levels. *N Engl J Med* 353: 1252, 2005.
79. Brown BG, Zhao X-Q, Chait A, et al: Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 345:1583, 2001.
80. von Eckardstein A, Assmann G: Prevention of coronary heart disease by raising high-density lipoprotein cholesterol? *Curr Opin Lipidol* 11:627, 2000.
- 80a. Ridker PM, Genest J, Boekholdt M, et al: HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. *Lancet* 376: 333, 2010.
81. Diabetes Atherosclerosis Intervention Study (DAIS) Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes. *Lancet* 357:905, 2001.
82. Betteridge D: Lipid-lowering trials in diabetes. *Curr Opin Lipidol* 12:619, 2001.
83. Haffner SM, Alexander CM, Cook TJ et al: Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels. Subgroup analysis in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 159:2661, 1999.
84. Goldberg R, Mellies MJ, Scaks FM, et al: Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels. Subgroup analysis in the Cholesterol and Recurrent Events (CARE) Trial. *Circulation* 98:2513, 1998.
85. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 339:1349, 1998.
86. Grover SA, Coupal L, Zowall H, Dorais M: Cost-effectiveness of treating hyperlipidemia in the presence of diabetes. Who should be treated? *Circulation* 102:722, 2000.
87. Solano MP, Goldberg RB: Management of dyslipid-

- emia in diabetes. *Cardiol in Rev* 14: 125, 2006.
88. Haffner SM, Lehto S, Ronnema T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229, 1998.
 89. Howard BV, Robbins DC, Sievers ML, et al: LDL-cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL. The Strong Heart Study. *Arterioscler Thromb Vasc Biol* 20:830, 2000.
 90. American Diabetes Association: Management of dyslipidemia in adults with diabetes. *Diabetes Care* 25(Suppl 1):S74, 2002.
 91. Anonymous: Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837, 1998.
 92. Wenger NK: Lipid abnormalities in women. Data for risk, data for management. *Cardiol in Rev* 14: 276, 2006.
 - 92a. Sattar N, Preiss D, Murray HM, et al: Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 375: 735, 2010.
 93. Lerner DJ, Kanner WB: Patterns of coronary heart disease morbidity and mortality in the sexes: a 26 year follow-up of the Framingham population. *Am Heart J* 111:383, 1986.
 94. Cholesterol Treatment Trialists' (CTT) Collaborators: Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 371: 117, 2008.
 95. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 344:1383, 1994.
 96. Downs JR, Clearfield M, Weis S, et al: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 279:1615, 1998.
 97. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen Progestin Interventions (PEPI). *JAMA* 273:199, 1995.
 98. Hulley S, Grady D, Bush T, et al: Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in post-menopausal women. *JAMA* 280:605, 1998.
 99. Wakatsuki A, Ikenoue N, Okatani Y, et al: Estrogen-induced small low density lipoprotein particles may be atherogenic in postmenopausal women. *J Am Coll Cardiol* 37:425, 2001.
 100. Herrington DM, Reboussin DM, Brosnihan KB, et al: Effects of estrogen replacement on the progression of coronary artery atherosclerosis. *N Engl J Med* 343:522, 2000.
 101. Writing Group for the Women's Health Initiative Investigators: Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA* 288:321, 2002.
 102. Report of the National Cholesterol Education Program Expert Panel on Blood Cholesterol Levels in Children and Adults. *Pediatrics* 89(3 Pt 2):525, 1992.
 103. McCrindle BW, Urbina EM, Dennison BA, et al: Drug therapy of high-risk lipid abnormalities in children and adolescents. A scientific statement from the American Heart Association, Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation* 115: 1948, 2007.
 104. Arnold SV, Rich MW: Hyperlipidemia in older adults. *Clin Geriatr* 17: 18, 2009/
 105. Zimetbaum P, Frishman WH, Ooi WL, et al: Plasma lipids and lipoproteins and the incidence of cardiovascular disease in the old: The Bronx Longitudinal Aging Study. *Arteriol Thromb* 12:416, 1992.
 106. Szadkowska I, Stanczyk A, Aronow WS, et al: Statin therapy in the elderly. A review. *Arch Geront Geriatr* 50: 114, 2010.
 107. Alexander KP, Blazing MA, Rosenson RS, et al: Management of hyperlipidemia in older adults. *J Cardiovasc Pharmacol Therap* 14: 49, 2009.
 108. O'Regan C, Wu P, Aror P, et al: Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. *Am J Med* 121: 24, 2008.
 109. Lemaitre RN, Psaty BM, Heckbert SR, et al: Therapy with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) and associated risk of incident cardiovascular events in older adults: Evidence from the Cardiovascular Health Study. *Arch Intern Med* 162:1395, 2002.
 110. Working Group on Management of Patients with Hypertension and High Blood Cholesterol: National Education Programs Working Group Report on the Management of Patients with Hypertension and High Blood Cholesterol. *Ann Intern Med* 114:224, 1991.

111. Bonaa KH, Thelle DS: Association between blood pressure and serum lipids in a population. *Circulation* 83(4):1305, 1991.
112. Frishman WH, Clark A, Johnson B: The effects of cardiovascular drugs on plasma lipids and lipoproteins. In: Frishman WH, Sonnenblick EH (eds). *Cardiovascular Pharmacotherapeutics*. New York: McGraw-Hill, 1997, p 1515.
113. Smith SC Jr, Blair SN, Bonow RO, et al: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. *Circulation* 104:1577, 2001.
114. Ahnve S, Angelin B, Edhag O, et al: Early determination of serum lipids and apolipoproteins in acute myocardial infarction: Possibility for immediate intervention. *J Intern Med* 226:297, 1989.
115. Aronow HD, Topol EJ, Roe MT, et al: Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: An observational study. *Lancet* 357:1063, 2001.
116. Rossouw JE: Lipid-lowering interventions in angiographic trials. *Am J Cardiol* 76:86C, 1995.
117. Falk E: Why do plaques rupture? *Circulation* 86(Suppl III):III30, 1992.
118. Fuster V, Badimon L, Badimon JJ, Chesebro JH: The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 326:310, 1992.
119. Richardson PD, Davies MJ, Born GV: Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. *Lancet* 2:941, 1989.
120. OKeefe JH Jr., Conn RD, Lavie CJ Jr., Bateman TM: The new paradigm for coronary artery disease: altering risk factors, atherosclerotic plaques, and clinical prognosis. *Mayo Clin Proc* 71:957, 1996.
121. Farmer JA, Gotto AM Jr: Dyslipidemia and the vulnerable plaque. *Prog Cardiovasc Dis* 44:415, 2002.
122. Fayad ZA, Fuster V: Clinical imaging of the high-risk or vulnerable atherosclerotic plaque. *Circ Res* 89:305, 2001.
123. Schini VB, Vanhoutte P: Endothelium-derived vasoactive factors. In: Loscalzo J, Schaefer AI (eds). *Thrombosis and Hemorrhage*. Boston: Blackwell Science, 1994, p 349.
124. Egashira K, Hirooka Y, Kai H, et al: Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. *Circulation* 89:2519, 1994.
125. Shiode N, Nakayama K, Morishima N, et al: Nitric oxide production by coronary conductance and resistance vessels in hypercholesterolemia patients. *Am Heart J* 131:1051, 1996.
126. Campeau L, Enjalbert M, Lesperance J, et al: The relation of risk factors to the development of atherosclerosis in saphenous vein bypass grafts and the progression of disease in the native *Circulation: A study 10 years after aortocoronary bypass surgery*. *N Engl J Med* 311:1329, 1984.
127. Popma JJ, Sawyer M, Selwyn AP, Kinlay S: Lipid-lowering therapy after coronary revascularization. *Am J Cardiol* 86(Suppl H):18H, 2000.
128. Shah SJ, Waters DD, Barter P, et al: Intensive lipid-lowering with atorvastatin for secondary prevention in patients after coronary artery bypass surgery. *J Am Coll Cardiol* 51: 1938, 2008.
129. Knatterud GL, Rosenberg Y, Campeau L, et al: Long-term effects on clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass graft trial. *Circulation* 102:157, 2000.
130. Leimgruber PP, Roubin GS, Hollman J, et al: Restenosis after successful coronary angioplasty in patients with single vessel disease. *Circulation* 73:710, 1986.
131. Virmani R, Farb A: Pathology of in-stent restenosis. *Curr Opin Lipidol* 10:49, 1999.
132. Austin GE, Ratliff NB, Hollman J, et al: Intimal proliferation of smooth muscle cells as an explanation for recurrent coronary artery stenosis after percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 6:369, 1985.
133. Ross R, Bowen-Pope D, Raines EW: Platelets, macrophages, endothelium and growth factors: Their effects upon cells and their possible roles in atherogenesis. *Ann NY Acad Sci* 454:254, 1985.
134. Serruys PWJC, de Feyter P, Macaya C, et al for the Lescol Intervention Prevention Study (LIPS) Investigators: Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: A randomized controlled trial. *JAMA* 287:3215, 2002.
135. Meng CQ: Restenosis drug discovery—a formidable task. *Curr Opin Invest Drugs* 2:1237, 2001.
136. de Feyter PJ, Vos J, Rensing BJ: Anti-restenosis trials. *Curr Intervent Cardiol Rep* 2:326, 2000.
137. Chan AW, Moliterno DJ: In-stent restenosis: Update on intracoronary radiotherapy. *Cleve Clin J Med* 68:796, 2001.
138. Butman S: Hyperlipidemia after cardiac transplantation: Be aware and possibly wary of drug therapy for lowering of serum lipids. *Am Heart J* 121:1585, 1991.
139. Ballantyne CM, Podet EJ, Patsch WP, et al: Effects of cyclosporine therapy on plasma lipoprotein levels. *JAMA* 262:53, 1989.

140. Olivari MT, Homans DC, Wilson RF, et al: Coronary artery disease in cardiac transplant patients receiving triple-drug immunosuppressive therapy. *Circulation* 80(Suppl III):III-111, 1989.
141. Johnson DE, Gao SZ, Schroeder JS, et al: The spectrum of coronary artery pathological findings in human cardiac allografts. *J Heart Transplant* 8:349, 1989.
142. Kobashigawa JA, Katznelson S, Laks H, et al: Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med* 333:621, 1995.
143. Wenke K, Meiser B, Thiery J, et al: Simvastatin reduces graft vessel disease and mortality after heart transplantation: A four-year randomized trial. *Circulation* 96:1398, 1997.
144. Kobashigawa J: What is the optimal prophylaxis for treatment of cardiac allograft vasculopathy? *Curr Control Trials Cardiovasc Med* 1:166, 2000.
145. Crouse JR: Effects of statins on carotid disease and stroke. *Curr Opin Lipidol* 10:535, 1999.
146. Aronow WS, Ahn C, Gutstein H. Incidence of new atherothrombotic brain infarction in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol ≥ 125 mg/dL treated with statins versus no lipid-lowering drug. *J Gerontol: Med Sci* 57A: M333, 2002.
147. Ravipati G, Aronow WS, Ahn C, et al. Incidence of new stroke or new myocardial infarction or death in patients with severe carotid arterial disease treated with and without statins. *Am J Cardiol* 98: 1170, 2006.
148. Amarenco P, Bogousslavsky J, Callahan A, 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 355: 549, 2006.
- 148a. Zambon D, Quintana M, Mata P, et al: Higher incidence of mild cognitive impairment in familial hypercholesterolemia. *Am J Med* 123: 267, 2010.
149. Jick H, Zomberg GL, Jick SS, et al. Statins and the risk of dementia. *Lancet* 356: 1627, 2000.
150. Rockwood K, Kirkland S, Hogan DB, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Arch Neurol* 59: 223, 2002.
151. Attman P-O, Samuelsson O: Dyslipidemia of kidney disease. *Curr Opin Lipid* 20: 293, 2009.
152. Joven J, Villabona C, Vilella E, et al: Abnormalities of lipoprotein metabolism in patients with nephrotic syndrome. *N Engl J Med* 323:579, 1990.
153. Keane WF, Kasiske BL: Hyperlipidemia in nephrotic syndrome. *N Engl J Med* 323:603, 1990.
154. Vega GL, Grundy SM: Lovastatin therapy in nephrotic hyperlipidemia. Effects on lipoprotein metabolism. *Kidney Int* 33:1160, 1988.
155. Chui MCK, Newby DE, Panarelli M, et al: Association between calcific aortic stenosis and hypercholesterolemia: Is there a need for a randomized controlled trial of cholesterol-lowering therapy? *Clin Cardiol* 24:52, 2001.
156. Rajamannan NM, Subramaniam M, Springett M, et al: Atorvastatin inhibits hypercholesterolemia-induced cellular proliferation and bone matrix production in the rabbit aortic valve. *Circulation* 105:2660, 2002.
157. Aronow WS, Ahn C, Kronzon I, Goldman ME. Association of coronary risk factors and use of statins with progression of mild valvular aortic stenosis in older persons. *Am J Cardiol* 88:693, 2001.
158. Antonini-Canterin F, Leiballi E, Enache R, et al: Hydroxymethylglutaryl coenzyme-A reductase inhibitors delay the progression of rheumatic aortic valve stenosis. A long-term echocardiographic study. *J Am Coll Cardiol* 53: 1874, 2009.
159. Novaro GM, Tiong IY, Pearce GL, et al. Effect of hydroxymethylglutaryl coenzyme A reductase inhibitors on the progression of calcific aortic stenosis. *Circulation* 104: 2205, 2001.
160. Bellamy MF, Pellikka PA, Klarich KW, et al. Association of cholesterol levels, hydroxymethylglutaryl coenzyme-A reductase inhibitor treatment, and progression of aortic stenosis in the community. *J Am Coll Cardiol* 40:1723, 2002.
161. Moura LM, Ramos SF, Zamorano JL, et al. Rosuvastatin affecting aortic valve endothelium to slow the progression of aortic stenosis. *J Am Coll Cardiol* 49: 554, 2007.
162. Cowell SJ, Newby DE, Preston RJ, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 352: 2389, 2005.
163. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 359: 1343, 2008.
- 163a. Hermans H, Herijgers P, Holvoet P, et al: Statins for calcific aortic valve stenosis: into oblivion after SALTIRE and SEAS? An extensive review from bench to bedside. *Curr Probl Cardiol* 35: 277, 2010.
164. Rosenhek R: Statins for aortic stenosis. *N Engl J Med* 352: 2441, 2005.
165. Davidson MH, Dillon MA, Gordon B, et al: Colesevelam hydrochloride (Cholestagel). A new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med* 159:1893, 1999.
166. Frishman WH, Ast M: Bile acid sequestrants. In: Frishman WH (ed). *Medical Management of Lipid Disorder. Focus on Prevention of Coronary Artery Disease*. Mt. Kisco: Futura Publ. Co. Inc., 1992:103-123.
167. Lipid Research Clinics Program: The Lipid Re-

- search Clinics Coronary Primary Prevention Trial Results: II. The relationship in reduction of incidence of coronary heart disease to cholesterol lowering. *JAMA* 251:365, 1984.
168. Glueck CJ: Pediatric primary prevention of atherosclerosis. *N Engl J Med* 314:175, 1986.
 169. Witzum J: Drugs used in the treatment of hyperlipoproteinemias. In: Hardman JG, Limbird LE (eds). In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th ed, New York: McGraw Hill, 1996, pp 875-897.
 170. Grundy SM, Ahrens EH, Salen S: Interruption of the enterohepatic *Circulation* of bile acids in man: Comparative effects of cholestyramine and ileal exclusion on cholesterol metabolism. *J Lab Clin Med* 78:94, 1971.
 171. Packard CJ, Shepherd J: The hepatobiliary axis and lipoprotein metabolism: Effects of bile acid sequestrants and ileal bypass surgery. *J Lipid Res* 23:1081, 1982.
 172. Shepherd J: Mechanism of action of bile acid sequestrants and other lipid lowering drugs. *Cardiology* 76(Suppl 1):65, 1982.
 173. Innis SM: The activity of HMG-CoA reductase and acyl-CoA cholesterol acyltransferase in hepatic microsomes in male, female and pregnant rats. The effect of cholestyramine treatment and the relationship of enzyme activity to microsomal lipid composition. *Biochim Biophys Acta* 875:355, 1986.
 174. Shepherd J, Packard CJ, Bicker S, et al: Cholestyramine promotes receptor-mediated low-density lipoprotein catabolism. *N Engl J Med* 302:1219, 1980.
 175. Donovan JM, Stypinski D, Stiles MR, et al: Drug interactions with colesevelam hydrochloride, a novel, potent lipid-lowering agent. *Cardiovasc Drugs Ther* 14:681, 2000.
 176. Illingworth RD: Lipid lowering drugs: An overview of indications and optimum therapeutic use. *Drugs* 33:259, 1987.
 177. Davidson MH, Dillon MA, Gordon B, et al: Colesevelam hydrochloride (cholestagel): A new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med* 159:1893, 1999.
 178. Runeberg L, Miettinen TA, Nikkils EA: Effect of cholestyramine on mineral excretion in man. *Acta Med Scand* 192:71, 1972.
 179. Brensike JF, Levy RI, Kelsey SF, et al: Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: Results of the NHLBI type II coronary intervention study. *Circulation* 69:313, 1984.
 180. Levy RI, Brensike JF, Epstein SE, et al: The influence of changes in lipid values induced by cholestyramine and diet on progression of coronary artery disease: Results of the NHLBI type II coronary prevention study. *Circulation* 69:325, 1984.
 181. Krauss RM, Williams PT, Brensike J, et al: Intermediate-density lipoproteins and progression of coronary artery disease in hypercholesterolemic men. *Lancet* 2:62, 1987.
 182. Blankenhorn DH, Nessim SA, Johnson RL, et al: Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 257:3233, 1987.
 183. Cashin-Hemphill L, Mack WJ, Pogoda JM, et al: Beneficial effects of colestipol-niacin on coronary atherosclerosis. *JAMA* 264:3013, 1990.
 184. Brown G, Albers JJ, Fisher LD, et al: Regression of coronary artery disease as a result of intensive lipid lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 323:1289, 1990.
 185. Kane JP, Malloy MJ, Ports TA, et al: Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. *JAMA* 264:3007, 1990.
 186. Watts GF, Lewis B, Brunt JNH, et al: Effects of coronary artery disease on lipid-lowering diet or diet plus cholestyramine, in the St. Thomas Atherosclerosis Regression Study (STARS). *Lancet* 339:563, 1992.
 187. Duffield RGT, Lewis B, Miller NE, et al: Treatment of hyperlipidaemia retards progression of symptomatic femoral atherosclerosis: A randomized controlled trial. *Lancet* 2:639, 1983.
 188. Blankenhorn DH, Azen SP, Crawford DW, et al: Effects of colestipol-niacin therapy on human femoral atherosclerosis. *Circulation* 83:438, 1991.
 189. Marais AD: Therapeutic modulation of low-density lipoprotein size. *Curr Opin Lipidol* 11:597, 2000.
 190. Witzum JL, Schonfeld G, Weidman JW, et al: Bile sequestrant therapy alters the composition of low-density and high-density lipoprotein. *Metabolism* 28:221, 1979.
 191. Goldberg RB, Fonseca VA, Truitt KE, Jones MR: Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. *Arch Intern Med* 168: 1531, 2008.
 192. Beil U, Crouse JR, Einarsson K, Grundy SM: Effect of interruption of the enterohepatic *Circulation* of bile acids on the transport of very low density lipoprotein triglycerides. *Metabolism* 31:438, 1982.
 193. Crouse JR: Hypertriglyceridemia: A contraindication for use of bile acid binding resins. *Am J Med* 83:243, 1987.
 194. Gordon DJ, Knoke J, Probstfield JL, et al, for the Lipid Research Clinics Program: High-density li-

- poprotein cholesterol and coronary heart disease in hypercholesterolemic men: The Lipid Research Clinics Coronary Primary Prevention Trial. *Circulation* 74:1217, 1986.
195. Lyons D, Webster J, Fowler G, et al: Colestipol at various dosage intervals in the treatment of moderate hypercholesterolemia. *Br J Clin Pharmacol* 37:59, 1994.
 196. Tonstad S, Bing RF, Frohlich J, et al: Effectiveness of colestipol tablets vs granules in patients with moderate to severe hypercholesterolaemia. *Clin Drug Invest* 10:257, 1995.
 197. Insull W, Marquis NR, Tsianco MC: Comparison of the efficacy of Questran Light, a new formulation of cholestyramine powder, to regular Questran in maintaining lowered plasma cholesterol levels. *Am J Cardiol* 67:501, 1991.
 198. Kane JP, Malloy MJ, Tun P, et al: Normalization of low-density lipoprotein levels in heterozygous familial hypercholesterolemia with a combined drug regimen. *N Engl J Med* 304:251, 1981.
 199. Hoogerbrugge N, Mol M, VanDormaal JJ, et al: Efficacy and safety of pravastatin, compared to and in combination with bile acid binding resins in familial hypercholesterolemia. *J Intern Med* 228:261, 1990.
 200. Schrott HG, Stein EA, Dujoune CA, et al: Enhanced low-density lipoprotein cholesterol reduction and cost-effectiveness by low dose colestipol plus lovastatin combination therapy. *Am J Cardiol* 75:34, 1995.
 - 200a. Goldberg RB, Fonseca VA, Truitt KE, Jones MR: Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. *Arch Intern Med* 168: 1531, 2008.
 - 200b. Fonseca VA, Rosenstock J, Wang AC, et al: Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care* 31: 1479, 2008.
 - 200c. Bays HE, Goldberg RB, Truitt KE, Jones MR: Colesevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: glucose and lipid effects. *Arch Intern Med* 168: 1975, 2008.
 201. Masclee AAM, Jansen JBMJ, Rovati LC, et al: Effect of cholestyramine and cholecystokinin receptor antagonist CR1505 (loxiglumide) on lower esophageal sphincter pressure in man. *Dig Dis Sci* 38:1889, 1993.
 202. Pattison M, Lee SM: Life-threatening metabolic acidosis from cholestyramine in an infant with renal insufficiency (letter). *Am J Dis Child* 141:479, 1987.
 203. Kleinman PA: Cholestyramine and metabolic acidosis (letter). *N Engl J Med* 290:861, 1974.
 204. Hartline JV: Hyperchloremia, metabolic acidosis, and cholestyramine. *J Pediatr* 89:155, 1976.
 205. Scheel PJ, Whelton A, Rossiter K, Watson A: Cholestyramine induced hyperchloremic metabolic acidosis. *J Clin Pharmacol* 32:536, 1992.
 206. Melkem MF, Galoriet HF, Eskander ED, Rao KN: Cholestyramine promotes 7,12 dimethylbenzanthracene induced mammary cancer in Wistar rats. *J Cancer* 56:45, 1987.
 207. Shosania AM, Grewar D: Hypoprothrombinemic hemorrhage due to cholestyramine therapy. *Can Med Assn J* 134:609, 1986.
 208. Witztum JL, Jacobs LS, Schonfeld G: Thyroid hormone and thyrotropin levels in patients placed on colestipol hydrochloride. *J Clin Endocrinol Metab* 46:838, 1978.
 209. Hertz R, Bishara-Shieban J, Bar-Tana J: Mode of action of peroxisome proliferators as hypolipidemic drugs suppression of apolipoprotein C-III. *J Biol Chem* 270:13470, 1995.
 210. Gervois P, Torra IP, Fruchart JC, et al: Regulation of lipid and lipoprotein metabolism by PPAR activators. *Clin Chem Lab Med* 38:3, 2000.
 211. Staels B, Dallongeville J, Auwerx J, et al: Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation* 98:2088, 1998.
 212. Thorp JM: Modification of metabolism and distribution of lipids by chlorphenoxyisobutyrate. *Nature* 194:948, 1962.
 213. Report from the Committee of Principal Investigators: A cooperative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br Heart J* 40:1069, 1978.
 214. Coronary Drug Project Research Group: Clofibrate and niacin in coronary artery disease. *JAMA* 231:360, 1975.
 215. Zimetbaum P, Frishman WH, Kahn S: Effects of gemfibrozil and other fibric acid derivatives on blood lipids and lipoproteins. In: Frishman WH (ed). *Medical Management of Lipid Disorders: Focus on Prevention of Coronary Artery Disease*. Mt. Kisco: Futura Publishing Co Inc. 1992:125-151.
 216. Manninen V, Elo O, Frick H, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 260:41, 1988.
 217. Spencer CM, Barradell LB: Gemfibrozil. *Drugs* 51:982, 1996.
 218. Brown WV: Potential use of fenofibrate and other fibric acid derivatives in the clinic. *Am J Med* 83(5B):85, 1987.
 219. Balfour JA, Heel RC: Fenofibrate: A review of its

- pharmacodynamic and pharmacokinetic properties and therapeutic use in dyslipidaemia. *Drugs* 40:260, 1990.
220. Grutzmacher P, Scheuermann EH, Siede W, et al: Lipid lowering treatment with bezafibrate in patients on chronic haemodialysis: Pharmacokinetics and effects. *Klin Wochenschr* 64(19):910, 1986.
221. Betteridge DJ: Ciprofibrate—a profile. *Postgrad Med J* 69(Suppl 1):S42, 1993.
222. Monk JP, Todd PA: Bezafibrate: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hyperlipidaemia. *Drugs* 33:539, 1987.
223. Auboeuf D, Rieusset J, Fajas L, et al: Tissue distribution and quantification of the expression of the peroxisome proliferator activated receptors and of LXR alpha mRNAs in human: Effect of obesity and NIDDM in adipose tissue. *Diabetes* 46:1319, 1997.
224. Shepherd J: Mechanism of action of fibrates. *Postgrad Med J* 69(Suppl 1):S34, 1993.
225. Grundy SM, Vega GL: Fibrates: Effects on lipids and lipoprotein metabolism. *Am J Med* 83(5B):9, 1987.
226. Eckel RH: Lipoprotein lipase: A multifunctional enzyme relevant to common metabolic disease. *N Engl J Med* 320:1060, 1989.
227. Heller F, Harvengt C: Effect of clofibrate, bezafibrate, fenofibrate and probucol on plasma lipolytic enzymes in normolipidemic subjects. *Eur J Clin Pharmacol* 25:57, 1983.
228. Gavish D, Oschry Y, Fainaru M, Eisenberg S: Changes in very low, low, and high density lipoproteins during lipid lowering (bezafibrate) therapy: Studies in type IIA and IIB hyperlipoproteinemia. *Eur J Clin Invest* 16(1):61, 1986.
229. Gervaise, N, Garrigue MA, Lasfargues G, et al: Triglycerides, apo C3 and Lp B:C3 and cardiovascular risk in type II diabetes. *Diabetologia* 43:703, 2000.
230. Luc G, Fievet C, Arveiler D, et al: Apolipoproteins C3 and E in apoB- and non apo B-containing lipoproteins in two populations at contrasting risk for myocardial infarction: the ECTIM study. *J Lipid Res* 37:508, 1996.
231. Sacks FM, Alaupovic P, Moye LA, et al: VLDL, apolipoproteins B, CIII, and E, and risk of recurrent coronary events in the Cholesterol and Recurrent Events (CARE) trial. *Circulation* 102:1886–1892, 2000.
232. Hunninghake DB, Peters JR: Effects of fibric acid derivatives on blood lipid and lipoprotein levels. *Am J Med* 83(5B):44, 1987.
233. Eisenberg S, Gavish D, Oschry Y, et al: Abnormalities in very low, low and high density lipoproteins in hypertriglyceridemia. *J Clin Invest* 74:470, 1984.
234. Vega GL, Grundy SM: Kinetic heterogeneity of low density lipoproteins in primary hypertriglyceridemia. *Arteriosclerosis* 6:395, 1986.
235. Ginsberg HN: Changes in lipoprotein kinetics during therapy with fenofibrate and other fibric acid derivatives. *Am J Med* 83(5B):66, 1987.
236. Kasaniemi YA, Grundy SM: Influence of gemfibrozil and clofibrate on metabolism of cholesterol and plasma triglycerides in man. *JAMA* 251(17):2241, 1984.
237. Shepard J, Caslake MJ, Lorimer AR, et al: Fenofibrate reduces low density catabolism in hypertriglyceridemic subjects. *Arteriosclerosis* 5:162, 1985.
238. Packard CJ, Clegg RJ, Dominiczak MH, et al: Effect of bezafibrate on apolipoprotein B metabolism in type III hyperlipidemic subjects. *J Lipid Res* 27(9):930, 1986.
239. Eisenberg S: High density lipoprotein metabolism. *J Lipid Res* 25:1012, 1984.
240. Schwandt P, Weisweiler P: Effect of bezafibrate on the high density lipoprotein subfractions HDL2 and HDL3 in primary hyperlipoproteinemia type IV. *Artery* 7(6):464, 1980.
241. Kleinman Y, Eisenberg S, Oschry Y, et al: Defective metabolism of hypertriglyceridemic lipoprotein in cultured human skin fibroblasts. Normalization with bezafibrate. *J Clin Invest* 75:1796, 1985.
242. Grundy SM, Ahrens EGJ, Salen G, et al: Mechanism of action of clofibrate on cholesterol metabolism in patients with hyperlipidemia. *J Lipid Res* 13:531, 1972.
243. Hudson K, Mojumder S, Day AJ: The effect of bezafibrate and clofibrate on cholesterol ester metabolism in rabbit peritoneal macrophages stimulated with acetylated low density lipoproteins. *Exp Mol Pathol* 38(1):77, 1983.
244. Schneider A, Stange EF, Ditschuneit HH, Ditschuneit H: Fenofibrate treatment inhibits HMG-CoA reductase activity in mononuclear cells from hyperlipoproteinemic patients. *Atherosclerosis* 56(3):257, 1985.
245. Blasi F, Sommariva D, Cosentini R, et al: Bezafibrate inhibits HMG-CoA reductase activity in incubated blood mononuclear cells from normal subjects and patients with heterozygous familial hypercholesterolemia. *Pharmacol Res* 21(3):247, 1989.
246. Palmer RH: Effects of fibric acid derivatives on biliary lipid composition. *Am J Med* 83(5B):37, 1987.
247. Kasaniemi YA, Grundy SM: Clofibrate, caloric restriction, supersaturation of bile, and cholesterol crystals. *Scand J Gastroenterol* 18:897, 1983.
248. Blane GF: Review of European clinical experience with fenofibrate. *Cardiology* 76(Suppl 1):1, 1989.
249. Leiss O, Meyer-Krahmer K, Von Bergmann K: Bili-

- ary lipid secretion in patients with heterozygous familial hypercholesterolemia and combined hyperlipidemia. Influence of bezafibrate and fenofibrate. *J Lipid Res* 27(7):213, 1986.
250. Carvalho ACA, Colman RW, Lees RS: Platelet function in hyperlipoproteinemia. *N Engl J Med* 290:434, 1974.
 251. Hamsten A, Wiman B, DeFaire U, Blomback M: Increased plasma levels of a rapid inhibitor of tissue plasminogen activator in young survivors of myocardial infarction. *N Engl J Med* 313:1557, 1985.
 252. Torstila I, Kaukola S, Malkonen M, et al: Effect of gemfibrozil on plasma lipoproteins, apolipoproteins and the kallikrein-kinin system *Proceedings of an International Symposium: 8th Asian Pacific Congress of Cardiology*. 1984, pp 36–42.
 253. Laustiola K, Lassila R, Koskinen P, et al: Gemfibrozil decreases platelet reactivity in patients with hypercholesterolemia during physical stress. *Clin Pharm Ther* 43:302, 1988.
 254. Sirtori CR, Franceschini G, Gianfranceschi G, et al: Effects of gemfibrozil on plasma lipoprotein-apolipoprotein distribution and platelet reactivity in patients with hypertriglyceridemia. *J Lab Clin Med* 110:279, 1987.
 255. Kloer HU: Structure and biochemical effects of fenofibrate. *Am J Med* 83(5B):3, 1987.
 256. Niort G, Bulgarelli A, Cassader M, Pagano G: Effect of short term treatment with bezafibrate on plasma fibrinogen, fibrinopeptide A, platelet activation, and blood filterability in atherosclerotic hyperfibrinogenemic patients. *Arteriosclerosis* 71(2–3):113, 1988.
 257. Ericsson C-G, Hamsten A, Nilsson J, et al: Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet* 347:849, 1996.
 258. Lesch M, Hoffken H, Schmidtsdorff A, et al: Effect of fenofibrate on fibrinogen concentration and blood viscosity. Consequences for myocardial microcirculation in coronary heart disease? *Dtsch Med Wochenschr* 114(24):939, 1989.
 259. Gotto AM: The Helsinki Heart Study Trial. *Cardiol Bd Rev* 6(3 Suppl):47, 1989.
 260. Faergeman O: Hypertriglyceridemia and the fibrate trials. *Curr Opin Lipidol* 11:609, 2000.
 261. Tenkanen L, Manttari M, Kovanen PT, et al: Gemfibrozil in the treatment of dyslipidemia. An 18-year mortality follow up of the Helsinki Heart Study. *Arch Intern Med* 166: 743, 2006.
 262. Ruotolo G, Ericsson CG, Tettamanti C, et al: Treatment effects on serum lipoprotein lipids, apolipoproteins and low density lipoprotein particle size and relationships of lipoprotein variables to progression of coronary artery disease in the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT). *J Am Coll Cardiol* 32:1648, 1998.
 263. Goldenberg I, Benderly M, Goldbourt U for the BIP Study Group: Secondary prevention with bezafibrate therapy for the treatment of dyslipidemia. An extended follow up of the BIP trial. *J Am Coll Cardiol* 51: 459, 2008.
 264. Mooney A: Treating patients with hypertriglyceridemia saves lives: Triglyceride revisited. *Curr Med Res Opin* 15:65, 1999.
 265. Rubins HB, Davenport J, Babikian V, et al for the VA-HIT Study Group: Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol. The Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation* 103:2828, 2001.
 266. The FIELD Study Investigators: Effects of long-term fenofibrate therapy on cardio-vascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 366: 1849, 2005.
 267. Keech AC, Mitchell P, Summanen PA, et al: for the FIELD study investigators: Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 370: 1687, 2007.
 - 267a. The ACCORD Study Group: Effects of combination lipid therapy on type 2 diabetes mellitus. *N Engl J Med* 362: 1563, 2010.
 - 267b. Tonkin AM, Chen L: Effects of combination lipid therapy in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Circulation* 122: 850, 2010.
 268. Gordon DJ, Rifkind BM: High density lipoprotein—the clinical implications of recent studies. *N Engl J Med* 321:1311, 1989.
 269. Virtamo J, Manninen V, Malkonen M: A placebo controlled rising dose, double-blind trial with gemfibrozil in dieting patients with primary hyperlipoproteinemia. *Vasc Med* 2:22, 1984.
 270. Goldberg AC, Bays HE, Ballantyne CM, et al: Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. *Am J Cardiol* 103: 515, 2009.
 271. Fenofibric acid (Trilipix). *The Medical Letter* 51: 33, 2009.
 272. Knopp R: Review of the effects of fenofibrate on lipoproteins, apoproteins, and bile saturability. U.S. Studies. *Cardiology* 76(Suppl 1):14, 1989.
 273. Pierce LR, Gysowski DK, Gross TP: Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *JAMA* 264:71, 1990.

274. Manninen V, Tenkanen L, Koskinen P, et al: Joint effects of serum triglycerides and LDL-cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: Implications for treatment. *Circulation* 85:37, 1992.
275. Remick J, Weintraub H, Setton R, et al: Fibrate therapy, an update. *Cardiol in Rev* 16: 129, 2008.
276. Keating GM, Croom KF: Fenofibrate. A review of its use in primary dyslipidaemia, the metabolic syndrome and type 2 diabetes mellits. *Drugs* 67: 121, 2007.
277. Alberts AW, Chen J, Kuron G, et al: Mevinolin: A highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. *Proc Natl Acad Sci U S A* 77:3957, 1980.
278. Endo A, Kuroda M, Tsujita Y: ML-236B and ML-236C, new inhibitors of cholesterol synthesis produced by *Penicillium citrium*. *J Antibiot* 29:1346, 1976.
279. Brown MS, Goldstein JL: Multivalent feedback regulation of HMG-CoA reductase, a control mechanism coordinating isoprenoid synthesis and cell growth. *J Lipid Res* 21:505, 1980.
280. Alberts AW: Discovery, biochemistry and biology of lovastatin. *Am J Cardiol* 62(15):10J, 1988.
281. Tobert JA: New developments in lipid-lowering therapy. The role of inhibitors of hydroxymethylglutaryl coenzyme A reductase. *Circulation* 76:534, 1987.
282. Krukemyer JJ, Talbert RL: Lovastatin: A new cholesterol-lowering agent. *Pharmacotherapy* 7:198, 1987.
283. Parker TS, McNamara DJ, Brown C: Mevalonic acid in human plasma: relationship of concentration and circadian rhythm to cholesterol synthesis rates in man. *Proc Natl Acad Sci U S A* 79:3037, 1982.
284. Cromwell WC, Ziajka PE: Development of tachyphylaxis among patients taking HMG CoA reductase inhibitors. *Am J Cardiol* 86:1123, 2000.
285. Grundy SM: HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. *N Engl J Med* 319:24, 1988.
286. Henwood JM, Heel AC: Lovastatin. *Drugs* 36:429, 1988.
287. Vega GL, Grundy SM: Treatment of primary moderate hypercholesterolemia with lovastatin (Mevinolin) and colestipol. *JAMA* 257:33, 1987.
288. Bradford RH, Shear CL, Chremos AN, et al: Expanded Clinical Evaluation of Lovastatin (EXCEL) study. Results: I. Efficacy in modifying plasma lipoproteins and adverse effect profile in 8245 patients with moderate hypercholesterolemia. *Arch Intern Med* 151:43, 1991.
289. Brown G, Albers JJ, Fisher LD, et al: Regression of coronary artery disease as a result of intensive lipid lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 323:1289, 1990.
290. Blankenhorn DH, Azen SP, Krams DM, et al: Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med* 119:969, 1993.
291. Hodis HN, Mack WJ, LaBree L, et al: Reduction in carotid arterial wall thickness using lovastatin and dietary therapy. A randomized, controlled clinical trial. *Ann Intern Med* 124:548, 1996.
292. Waters D, Higginson L, Gladstone P, et al: Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. *Circulation* 89:959, 1994.
293. Waters D, Higginson L, Gladstone P, et al: Effects of cholesterol lowering on the progression of coronary atherosclerosis in women. A Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) substudy. *Circulation* 92:2404, 1995.
294. Furberg CD, Adams HP, Applegate WB, et al: Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation* 90:1679, 1994.
295. Probstfield JL, Margitic SE, Byington RP, et al: Results of the primary outcome measure and clinical events from the Asymptomatic Carotid Artery Progression Study. *Am J Cardiol* 76:47C, 1995.
296. Downs JR, Clearfield M, Weis S, et al: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA* 279:1615, 1998.
297. Cobb MM, Teitelbaum HS, Breslow JL: Lovastatin efficacy in reducing low-density lipoprotein cholesterol levels on high vs low fat diets. *JAMA* 265:997, 1991.
298. Gupta EK, Ito MK: Lovastatin and extended-release niacin combination product. The first drug combination for the treatment of hyperlipidemia. *Heart Dis* 4:124, 2002.
299. Kashyap ML, McGovern ME, Berra K, et al: Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. *Am J Cardiol* 89:672, 2002.
300. Knodel LC, Talbert RL: Adverse effects of hypolipidaemic drugs. *Med Toxicol* 2:10, 1987.
301. Davidson MH: Safety profile for the HMG-CoA reductase inhibitors. Treatment and trust. *Drugs* 61:197, 2001.
302. Blais L, Desgagne A, LeLorier J: 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors

- and the risk of cancer. *Arch Intern Med* 160:2363, 2000.
303. Norman DJ, Illingworth DR, Munson J, Hosenspud J: Myolysis and acute renal failure in a heart transplant recipient receiving lovastatin (letter). *N Engl J Med* 318:46, 1988.
 304. Harper CR, Jacobson TA: The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. *Curr Opin Lipidol* 18: 401, 2007.
 305. Nawarskas JJ: HMG-CoA reductase inhibitors and coenzyme Q10. *Cardiol in Rev* 13: 76, 2005.
 306. Joy TR, Hegele RA: Narrative review: statin-related myopathy. *Ann Intern Med* 150: 858, 2009.
 307. Evans M, Rees A: The myotoxicity of statins. *Curr Opin Lipidol* 13:415, 2002.
 308. Pasternak RC, Smith SC Jr., Bairey-Merz CN, et al: ACC/AHA/NHLBT Clinical Advisory on the Use and Safety of Statins. *J Am Coll Cardiol* 40:567, 2002.
 309. Frishman WH, Zimetbaum P, Nadelmann J: Lovastatin and other HMG CoA reductase inhibitors. *J Clin Pharmacol* 29:975, 1989.
 310. Neuvonen PJ, Jalava K-M: Intraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 60:54, 1996.
 311. Kuo PC, Kirshenbaum JM, Gordon J, et al: Lovastatin therapy for hypercholesterolemia in cardiac transplant recipients. *Am J Cardiol* 64:631, 1989.
 312. Pierce LR, Wysowski DK, Gross T: Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *JAMA* 264:71, 1990.
 313. Goldman JA, Fishman AB, Lee JE, Johnson RJ: The role of cholesterol-lowering agents in drug-induced rhabdomyolysis and polymyositis. *Arthritis Rheum* 32:358, 1989.
 314. Tobert JA: Efficacy and long-term adverse effect pattern of lovastatin. *Am J Cardiol* 62:28J, 1988.
 315. Tobert JA, Shear CL, Cremos AN, Mantell GE: Clinical experience with lovastatin. *Am J Cardiol* 65:23F, 1990.
 316. Weir MR, Berger ML, Weeks ML, et al: Comparison of the effects on quality of life and the efficacy and tolerability of lovastatin versus pravastatin. *Am J Cardiol* 77:475, 1996.
 317. Plosker GL, McTavish D: Simvastatin: A reappraisal of its pharmacology and therapeutic efficacy in hypercholesterolemia. *Drugs* 50:334, 1995.
 318. Stalenhoef AFH, Mol MJTM, Stuyt PMJ: Efficacy and tolerability of simvastatin (MK 733). *Am J Med* 87(4A):39S, 1989.
 319. Quercia RA: Focus on simvastatin: a potent HMG CoA reductase inhibitor for the treatment of hypercholesterolemia. *Hosp Form* 24:559, 1989.
 320. Pietro DA, Sidney A, Mantell G, et al: Effects of simvastatin and probucol in hypercholesterolemia (Simvastatin Multicenter Study Group II). *Am J Cardiol* 63:682, 1989.
 321. Stein E, Kreisberg R, Miller V, et al: Multicenter group I: Effects of simvastatin and cholestyramine in familial and nonfamilial hypercholesterolemia. *Arch Intern Med* 150:341, 1990.
 322. Tikkanan XJ, Bocanegra TS, Walker JF, Cook T, the Simvastatin Study Group: Comparison of low-dose simvastatin and gemfibrozil in the treatment of elevated plasma cholesterol. *Am J Med* 87(4A):47S, 1989.
 323. Erkelens DW, Baggen MGA, Van Doormaal JJ, et al: Clinical experience with simvastatin compared with cholestyramine. *Drugs* 36(Suppl 3):87, 1988.
 324. Dacol PG, Cattin L, Valenti M, et al: Efficacy of simvastatin plus cholestyramine in the two-year treatment of heterozygous hypercholesterolemia. *Curr Ther Res Clin Exp* 48:798, 1990.
 325. Havel RJ: Simvastatin: A once a day treatment of hypercholesterolemia: Introduction to a symposium. *Am J Med* 87(4A):2S, 1989.
 326. Mol MJT, Stalenhoef AFH: Adrenocortical function in patients with simvastatin. *Lancet* 335:412, 1990.
 327. Stein E: Management of hypercholesterolemia: Guide to diet and drug therapy. *Am J Med* 87(4A):24S, 1989.
 328. Illingworth DR, Stein EA, Knopp RH, et al: A randomized multicenter trial comparing the efficacy of simvastatin and fluvastatin. *Cardiovasc Pharmacol Ther* 1:23, 1996.
 - 328a. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group: Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet* 376: 1658, 2010.
 329. Rabelink AJ, Henle RJ, Erkelens DW, et al: Effects of simvastatin and cholestyramine on lipoprotein profile in hyperlipidaemia of nephrotic syndrome. *Lancet* 10:1335, 1988.
 330. Duane WC, Hunninghake DB, Freeman ML, et al: Simvastatin, a competitive inhibitor of HMG-CoA reductase, lowers cholesterol saturation index of gallbladder bile. *Hepatology* 8(5):1147, 1988.
 331. MAAS Investigators: Effect of simvastatin on coronary atheroma: The Multicentre Anti-Atheroma Study (MAAS). *Lancet* 344:633, 1994.
 332. Corti R, Fayad ZA, Fuster V, et al: Effects of lipid-lowering by simvastatin on human atherosclerotic lesions. A longitudinal study by high-resolution, noninvasive magnetic resonance imaging. *Circula-*

- tion 104:249, 2001.
333. Kjekshus J, Pedersen TR for the Scandinavian Simvastatin Survival Study Group (4S): Reducing the risk of coronary events: Evidence from the Scandinavian Simvastatin Survival Study. *Am J Cardiol* 76:64C, 1995.
 334. Pedersen TR, Kjekshus J, Berg K, et al: Cholesterol lowering and the use of healthcare resources. Results of the Scandinavian Simvastatin Survival Study. *Circulation* 93:1796, 1996.
 335. Alessandri C, Basili S, Maurelli M, et al: Effect of hydroxy methylglutaryl-coenzyme A reductase inhibitors on some blood coagulation parameters. *Curr Ther Res* 53:188, 1993.
 336. Giroux LM, Davignon J, Naruszewicz M: Simvastatin inhibits the oxidation of low-density lipoproteins by activated human monocyte derived macrophages. *Biochim Biophys Acta* 1165:335, 1993.
 337. Szczeklik A, Musial J, Undas A, et al: Inhibition of thrombin generation by simvastatin and lack of additive effects of aspirin in patients with marked hypercholesterolemia. *J Am Coll Cardiol* 33:1286, 1999.
 338. Undas A, Brummel KE, Musial J, et al: Simvastatin depresses blood clotting by inhibiting activation of prothrombin, factor V and factor XIII and by enhancing factor Va inactivation. *Circulation* 103:2248, 2001.
 339. Ray JG, Mamdani M, Tsuyuki RT, et al: Use of statins and the subsequent development of deep vein thrombosis. *Arch Intern Med* 161:1405, 2001.
 340. Patel R, Nagueh SF, Tsybouleva N, et al: Simvastatin induces regression of cardiac hypertrophy and fibrosis and improves cardiac function in a transgenic rabbit model of human hypertrophic cardiomyopathy. *Circulation* 104:317, 2001.
 341. Knapp HH, Schrott H, Ma P, et al: Efficacy and safety of combination simvastatin and colesvelam in patients with primary hypercholesterolemia. *Am J Med* 110:352, 2001.
 342. Bays H, Weiss S, Gagne C, et al: Ezetimibe added to ongoing statin therapy for treatment of primary hypercholesterolemia (abst.). *J Am Coll Cardiol* 39 (Suppl A): 245A, 2002.
 343. Davidson M, McGarry T, Bettis R, et al: Ezetimibe co-administered with simvastatin in 668 patients with primary hypercholesterolemia (abst.). *J Am Coll Cardiol* 39(Suppl A):226A, 2002.
 344. Sanford M, Curran MP: Niacin extended-release/simvastatin. *Drugs* 68: 2373, 2008.
 345. McTavish D, Sorkin EM: Pravastatin. A review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. *Drugs* 42:65, 1991.
 346. Tsujita Y, Kuroda M, Simada Y, et al: CS 514, a competitive inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A reductase: Tissue selective inhibitor of steroid synthesis and hypolipidemic effects on various animal species. *Biochem Biophys Acta* 877:50, 1986.
 347. Germershausen JI, Hunt VM, Bostedor RG, et al: Tissue selectivity of the cholesterol-lowering agents lovastatin, simvastatin and pravastatin in rats in vivo. *Biochem Biophys Res Commun* 158(3):667, 1989.
 348. Reihner E, Rudling M, Stahlberg D, et al: Influence of pravastatin, a specific inhibitor of HMG CoA reductase, on hepatic metabolism of cholesterol. *N Engl J Med* 323:224, 1990.
 349. Hunninghake DB, Knopp RH, Schonfeld G, et al: Efficacy and safety of pravastatin in patients with primary hypercholesterolemia. 1. A dose-response study. *Atherosclerosis* 85:81, 1990.
 350. Mabuchi A, Kamon N, Fujita H, et al: The effects of CS 514 on serum lipoprotein, lipid and apolipoprotein levels in patients with familial hypercholesterolemia. *Metabolism* 36:475, 1987.
 351. Nakaya N, Yasuhiko H, Hiromitsu T, et al: The effect of CS 514 on serum lipids and apolipoproteins in hypercholesterolemic subjects. *JAMA* 257(22):3088, 1987.
 352. Chan P, Lee C-B, Lin T-S, et al: The effectiveness and safety of low dose pravastatin in elderly hypertensive hypercholesterolemic subjects on antihypertensive therapy. *Am J Hypertens* 8:1099, 1995.
 353. LaRosa JC, Applegate W, Crouse JR, et al: Cholesterol lowering in the elderly. *Arch Intern Med* 154:529, 1994.
 354. ALLHAT Collaborative Research Group: Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 288: 2998, 2002.
 355. Raskin P, Ganda OP, Schwartz S, et al: Efficacy and safety of pravastatin in the treatment of patients with type I or type II diabetes mellitus and hypercholesterolemia. *Am J Med* 99:362, 1995.
 356. Prisant LM, Downton M, Watkins LO: Efficacy and tolerability of lovastatin in 459 African-Americans with hypercholesterolemia. *Am J Card* 78:420, 1996.
 357. The Simvastatin Pravastatin Study Group: Comparison of the efficacy, safety and tolerability of simvastatin and pravastatin for hypercholesterolemia. *Am J Cardiol* 71:1408, 1993.
 358. The Lovastatin Pravastatin Study Group: A multi-

- center comparative trial of lovastatin and pravastatin in the treatment of hypercholesterolemia. *Am J Cardiol* 71:810, 1993.
359. Bekhoonek BD, McGovern ME, Markowitz JS, et al: Effects of pravastatin in patients with total serum cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dL) plus two additional atherosclerotic risk factors. *Am J Cardiol* 72:1031, 1993.
 360. Pitt B, Mancini J, Ellis SG, et al: Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): Reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol* 26:1133, 1995.
 361. Crouse JR III, Byington RP, Bond MG, et al: Pravastatin, lipids and atherosclerosis in the coronary arteries (PLAC II). *Am J Cardiol* 75:455, 1995.
 362. Salonen R, Nyyssonen K, Porkkala E, et al: Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation* 92:1758, 1995.
 363. Jukema JW, Bruschke AVG, van Boven AJ, et al: Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 91:2528, 1995.
 364. Byington RP, Jukema JW, Salonen JT, et al: Reduction in cardiovascular events during pravastatin therapy. Pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. *Circulation* 92:2419, 1995.
 365. Albert MA, Danielson E, Rifai N, et al: Effect of statin therapy on C-reactive protein levels. The Pravastatin Inflammation/CRP Evaluation (PRINCE): A randomized trial and cohort study. *JAMA* 286:64, 2001.
 366. Azar RR, Waters DD: PRINCE's prospects: Statins, inflammation, and coronary risk. *Am Heart J* 141:881, 2001.
 367. Ridker PM, Rifai N, Pfeffer MA, et al: Long-term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation* 100:230, 1999.
 368. Horne BD, Muhlestein JB, Carlquist JF, et al: Statin therapy, lipid levels, C-reactive protein and the survival of patients with angiographically severe coronary artery disease. *J Am Coll Cardiol* 36:1774, 2000.
 369. Glorioso N, Troffa C, Filigheddu F, et al: Effect of the HMG-CoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolemia. *Hypertension* 34:1281, 1999.
 370. Dupuis J, Tardif JC, Cernacek P, Theroux P: Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RE-CIFE (Reduction of Cholesterol in Ischemia and Function of the Endothelium) trial. *Circulation* 99:3227, 1999.
 371. Kaesemeyer WH, Caldwell RB, Huang J, Caldwell RW: Pravastatin sodium activates endothelial nitric oxide synthase independent of its cholesterol-lowering actions. *J Am Coll Cardiol* 33:234, 1999.
 372. Dangas G, Badimon JJ, Smith DA, et al: Pravastatin therapy in hyperlipidemia: effects on thrombus formation and the systemic hemostatic profile. *J Am Coll Cardiol* 33:1294, 1999.
 373. Shepherd J, Cobbe SM, Ford I, et al: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 333:1301, 1995.
 374. Ford I, Murray H, Packard CJ, et al for the West of Scotland Coronary Prevention Study Group: Long-term follow up of the West of Scotland Coronary Prevention Study. *N Engl J Med* 357: 1477, 2007.
 375. Pfeffer MA, Sacks F, Moye LA, et al: Cholesterol and Recurrent Events: A secondary prevention trial for normolipidemic patients. *Am J Cardiol* 76:98C, 1995.
 376. Plehn JF, Davis BR, Sacks FM, et al: Reduction of stroke incidence after myocardial infarction with pravastatin. The Cholesterol and Recurrent Events (CARE) study. *Circulation* 99:216, 1999.
 377. Tonkin AM, Colquhoun D, Emberson J, et al: Effects of pravastatin in 3260 patients with unstable angina: results from the LIPID study. *Lancet* 355:1871, 2000.
 378. Hunt D, Young P, Simes J, et al: Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: Results from the LIPID trial. *Ann Intern Med* 134:931, 2001.
 379. Simes RJ, Marschner IC, Hunt D, et al: Relationship between lipid levels and clinical outcomes in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial. To what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? *Circulation* 105:1162, 2002.
 380. White HD, Simes J, Anderson NE, et al: Pravastatin therapy and the risk of stroke. *N Engl J Med* 343:317, 2000.
 381. Vgontzas AN, Kales A, Bixler EO, et al: Effects of lovastatin and pravastatin on sleep efficiency and sleep stages. *Clin Pharmacol Ther* 50:730, 1991.

382. Langtry HD, Markham A: Fluvastatin: A review of its use in lipid disorders. *Drugs* 57:583, 1999.
383. Davidson MH, FLUENT investigation group: Fluvastatin Long-Term Extension Trial (FLUENT): Summary of efficacy and safety. *Am J Med* 96:4S, 1994.
384. Jacotot B, Banga JD, Waite R, et al: Long-term efficacy with fluvastatin as monotherapy, and combined with cholestyramine (a 156 week multicenter study). *Am J Cardiol* 76(Suppl): 41A, 1995.
385. Leitersdorf E, Muratti EN, Eliav O, et al: Efficacy and safety of a combination fluvastatin-bezafibrate treatment for familial hypercholesterolemia: Comparative analysis with a fluvastatin-cholestyramine combination. *Am J Med* 96:401, 1994.
386. Foley DP, Bonnier H, Jackson G, et al: Prevention of restenosis after coronary balloon angioplasty: Rationale and design of the Fluvastatin Angioplasty Restenosis (FLARE) trial. *Am J Cardiol* 73:5D, 1994.
387. Herd JA, Ballantyne C, Farmer JA, et al: Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations [Lipoprotein and Coronary Atherosclerosis Study (LCAS)]. *Am J Cardiol* 80:278, 1997.
388. Liem A, van Boven AJ: Effects of fluvastatin administered immediately after an acute MI on myocardial ischemia. Presented at the American Heart Association Scientific Sessions 2000, New Orleans, La. Nov 12-15, 2000.
389. Marz W, Scharnagl H, Abletshauer C, et al: Fluvastatin lowers atherogenic dense low-density lipoproteins in postmenopausal women with the atherogenic lipoprotein phenotype. *Circulation* 103:1942, 2001.
390. Sabia H, Prasad P, Smith HT, et al: Safety, tolerability, and pharmacokinetics of an extended-release formulation of fluvastatin administered once daily to patients with primary hypercholesterolemia. *J Cardiovasc Pharmacol* 37:502, 2001.
391. Nawrocki JW, Weiss SR, Davidson MH, et al: Reduction of LDL-cholesterol by 25% to 69% in patients with primary hypercholesterolemia by atorvastatin: A new HMG-CoA reductase inhibitor. *Arterioscler Thromb Vasc Biol* 15:678, 1995.
392. Bakker-Arkema RG, Davidson MH, Hgoldstein RJ, et al: Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA* 275:128, 1996.
393. Cilla DD Jr, Gibson DM, Whitfield LR, Sedman AJ: Pharmacodynamic effects and pharmacokinetics of atorvastatin after administration in normocholesterolemic subjects in the morning and evening. *J Clin Pharmacol* 36:604, 1996.
- 393a. Athyros VG, Tziomalos K, Gossios TD, et al: Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study: a post-hoc analysis. *Lancet* 376: 1916, 2010.
394. Smilde TJ, van Wissen S, Wollersheim H, et al: Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): A prospective, randomised, double-blind trial. *Lancet* 357:577, 2001.
395. Illingworth DR, Crouse JR 3rd, Hunninghake DB, et al: A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. *Curr Med Res Opin* 17:43, 2001.
396. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment investigators. *N Engl J Med* 341: 70, 1999.
397. Statins for high-risk patients without heart disease or high cholesterol. *The Medical Letter* 48: 1, 2006.
398. Davidson MH: Rosuvastatin: A highly efficacious statin for the treatment of dyslipidaemia. *Expert Opin Investig Drugs* 11:125, 2002.
399. McTaggart F, Buckett L, Davidson R, et al: Pre-clinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Am J Cardiol* 87(Suppl):28B, 2001.
400. Olsson AG: Statin therapy and reductions in low-density lipoprotein cholesterol: Initial clinical data on the potent new statin rosuvastatin. *Am J Cardiol* 87(Suppl):33B, 2001.
401. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol* 2003; 92: 152-160.
402. Alsheikh-Ali AA, Ambrose MS, Kuvin JT, Karas RH: The safety of rosuvastatin as used in common clinical practice. A postmarketing analysis. *Circulation* 111: 3051, 2005.
403. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis. The ASTEROID trial. *JAMA* 2006; 295: 156-1565.
404. Nicholls SJ, Tuzcu EM, Sipahi I, et al: Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 297: 499, 2007.
405. Ballantyne CM, Raichlen JS, Nicholls SJ, et al. Effect

- of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography: a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. *Circulation* 2008; 117: 2458-2466.
406. Crouse JR III, Raichlen JS, Riley WA, et al for the METEOR Study Group: Effect of rosuvastatin on progression of carotid intima-media thickness in low risk individuals with subclinical atherosclerosis. The METEOR trial. *JAMA* 297: 1344, 2007.
- 406a. Ridker PM, MacFadyen J, Cressman M, Glynn RJ: Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitive C-reactive protein. A secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. *J Am Coll Cardiol* 55: 1266, 2010.
- 406b. Mora S, Glynn RJ, Hsia J, et al: Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia. Results from the Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation* 121: 1069, 2010.
407. Kjekshus J, Apetrei E, Barrios V, et al for the CORONA Group: Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 357: 2248, 2007.
408. Fellstrom BC, Jardine AG, Schmieder RE, et al for the AURORA Study Group: Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 360: 1395, 2009.
409. Glynn RJ, Danielson E, Fonseca FAH, et al: A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med* 360: 1851, 2009.
410. Hiro T, Kimura T, Morimoto T, et al. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan Assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). *J Am Coll Cardiol* 54: 293, 2009.
411. Kawashiri M-a, Nohara A, Tada H, et al: Comparison of effects of pitavastatin and atorvastatin on plasma coenzyme Q10 in heterozygous familial hypercholesterolemia: results from a crossover study. *Clin Pharmacol Therap* 83: 731, 2008.
412. Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. *Am J Cardiol* 92: 711, 2003.
413. Mohler ER III, Hiatt WR, Creager MA, for the Study Investigators. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 108:1481, 2003.
414. Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med* 114: 359, 2003.
415. De Sutter J, Tavernier R, De Buyzere M, et al. Lipid lowering drugs and recurrences of life-threatening ventricular arrhythmias in high-risk patients. *J Am Coll Cardiol* 36:766, 2000.
416. Mitchell LB, Powell JL, Gillis AM, et al. Are lipid-lowering drugs also antiarrhythmic drugs? An analysis of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. *J Am Coll Cardiol* 42: 81, 2003.
417. Chiu JH, Abdelhadi RH, Chung MK, et al. Effect of statin therapy on risk of ventricular arrhythmia among patients with coronary artery disease and an implantable cardioverter-defibrillator. *Am J Cardiol* 95: 490, 2005.
418. Vyas AK, Guo H, Moss AJ, et al. Reduction in ventricular tachyarrhythmias with statins in the Multicenter automatic Defibrillator Implantation trial (MADIT)-II. *J Am Coll Cardiol* 47: 769, 2006.
419. Lai HM, Aronow WS, Kruger A, et al. Effect of beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins on mortality in patients with implantable cardioverter-defibrillators. *Am J Cardiol* 102: 77, 2008.
420. Desai H, Aronow WS, Tsai FS, et al. Statins reduce appropriate cardioverter-defibrillator shocks and mortality in patients with heart failure and combined cardiac resynchronization and implantable cardioverter-defibrillator therapy. *J Cardiovasc Pharmacol Therap* 14: 176, 2009.
421. Durazzo AES, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg* 39: 967, 2004.
422. Kertai MD, Boersma E, Westerhout CM, et al. Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. *Am J Med* 116: 96, 2004.
423. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major non-cardiac vascular surgery. *Circulation* 107: 1848,

- 2003.
424. O'Neil-Callahan K, Katsimaglia MR, Ryan J, et al. Statins decrease perioperative cardiac complications in patients undergoing noncardiac vascular surgery. The Statins for Risk Reduction in Surgery (StaRRS) Study. *J Am Coll Cardiol* 45: 336, 2005.
 425. Desai H, Aronow WS, Ahn C, et al. Incidence of perioperative myocardial infarction and of 2-year mortality in 577 elderly patients undergoing noncardiac vascular surgery treated with and without statins. *Arch Gerontol Geriatr* 51: 149, 2010.
 426. Abuissa H, O'Keefe JH, Bybee KA: Statins as antiarrhythmics: a systematic review. Part 1: effects on risk of atrial fibrillation. *Clin Cardiol* 32: 544, 2009.
 427. Abuissa H, O'Keefe JH, Bybee KA: Statins as antiarrhythmics: a systematic review. Part II: effects on risk of ventricular arrhythmias. *Clin Cardiol* 32: 549, 2009.
 428. Patti G, Chello M, Candura D, et al: Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery. Results of the ARMYDA-3 Study. *Circulation* 114: 1455, 2006.
 429. Majmudar MD, Tompkins C, Bachmann JM, et al: Effects of lipid-altering therapies on ventricular arrhythmias and sudden cardiac death. *Cardiol in Rev* 17: 60, 2009.
 430. Greenwood J, Steinman L, Zamvil SS: Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nature Rev Immunol* 6: 358, 2006.
 431. Donnino MW, Cocchi MN, Howell M, et al: Statin therapy is associated with decreased mortality in patients with infection. *Acad Emerg Med* 16: 230, 2009.
 432. Tleyjeh IM, Kashour T, Hakim FA, et al: Statins for the prevention and treatment of infections. A systematic review and meta-analysis. *Arch Intern Med* 169: 1658, 2009.
 - 432a. Khemasuwan D, DiVietro ML, Tangdhanakanond K, et al: Statins decrease the occurrence of venous thromboembolism in patients with cancer. *Am J Med* 123: 60, 2010.
 433. Davignon J, Laaksonen R: Low-density lipoprotein-independent effects of statins. *Curr Opin Lipidol* 10:543, 1999.
 - 433a. Hayward RA, Krumholz HM, Zulman DM, et al: Optimizing statin treatment for primary prevention of coronary artery disease. *Ann Intern Med* 152: 69, 2010.
 - 433b. Cholesterol Treatment Trialists (CTT) Collaboration: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376: 1670, 2010.
 - 433c. Cheung BMY, Lam KS: Is intensive LDL-cholesterol lowering beneficial and safe? *Lancet* 376: 1622, 2010.
 434. Gotto AM Jr., Farmer JA: Pleiotropic effects of statins: Do they matter? *Curr Opin Lipidol* 12:391, 2001.
 435. Alber HF, Dulak J, Frick M, et al: Atorvastatin decreases vascular endothelial growth factor in patients with coronary artery disease. *J Am Coll Cardiol* 39:1951, 2002.
 436. Yeung AC, Tsao P: Statin therapy. Beyond cholesterol lowering and anti-inflammatory effects. *Circulation* 105:2937, 2002.
 437. Wang PS, Solomon DH, Mogun H, Avorn J: HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA* 283:3211, 2000.
 438. Chan KA, Andrade SE, Boles M, et al: Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. *Lancet* 355:2185, 2000.
 439. Jick H, Zornberg GL, Jick SS, et al: Statins and the risk of dementia. *Lancet* 356:1627, 2000.
 440. Herrington DM, Vittinghoff E, Lin F, et al: Statin therapy, cardiovascular events, and total mortality in the Heart and Estrogen/Progestin Replacement Study (HERS). *Circulation* 105:2962, 2002.
 441. Marcelino JJ, Feingold KR: Inadequate treatment with HMG-CoA reductase inhibitors by health care providers. *Am J Med* 100:605, 1996.
 442. Teo KK, Burton JR: Who should receive HMG CoA reductase inhibitors? *Drugs* 62:1707, 2002.
 443. Brown WV: Safety of statins. *Curr Opin Lipidol* 19: 558, 2008.
 444. Kashani A, Phillips CO, Foody JM, et al: Risks associated with statin therapy. A systematic overview of randomized clinical trials. *Circulation* 114: 2788, 2006.
 445. Aronow HD, Topol EJ, Roe MT, et al: Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: An observational study. *Lancet* 357:1063, 2001.
 446. Stenestrand U, Wallentin L, for the Swedish Register of Cardiac Intensive Care (RIKS-HIA): Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA* 285:430, 2001.
 447. Newby LK, Kristinsson A, Bhapkar MV, et al: Early statin initiation and outcomes in patients with acute coronary syndromes. *JAMA* 287:3087, 2002.
 448. Heeschen C, Hamm CW, Laufs U, et al: Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation* 105:1446, 2002.
 449. Altschul R, Hoffer A, Stephen JD: Influence of

- nicotinic acid on serum cholesterol in man. *Arch Biochem* 54:558, 1955.
450. Guyton JR: Niacin in cardiovascular prevention: mechanisms, efficacy, and safety. *Curr Opin Lipidol* 18: 415, 2007.
 451. Fumagalli R: Pharmacokinetics of nicotinic acid and some of its derivatives. In: Gey KF, Carlson LA (eds): *Metabolic Effects of Nicotinic Acid and Its Derivatives*. Bern: Hans Huber, 1971, pp 33–49.
 452. Petrack B, Greengard P, Kalinsky H: On the relative efficacy of nicotinamide and nicotinic acid as precursors of nicotinamide adenine dinucleotide. *J Biol Chem* 241(10):2367, 1966.
 453. See M, Hoppichler F, Reavely D, et al: Relation of serum lipoprotein(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. *N Engl J Med* 322:1494, 1990.
 454. Mahley RW, Bersot TP: Drug therapy for hypercholesterolemia and dyslipidemia. In: Hardman JG, Limbird LE (eds): *Goodman and Gilman's. The Pharmacological Basis of Therapeutics*, 10th ed. New York: McGraw Hill 2001:971–1002.
 455. Alderman JD, Pasternak RC, Sacks FM, et al: Effect of a modified, well-tolerated niacin regimen on serum total cholesterol, high density lipoprotein cholesterol and the cholesterol to high density lipoprotein ratio. *Am J Cardiol* 64:725, 1989.
 456. Arner P, Ostman J: Effect of nicotinic acid on acylglycerol metabolism in human adipose tissue. *Clin Sci* 64:235, 1983.
 457. Canner PL, Berge KG, Wenger NK, et al: Fifteen year mortality in Coronary Drug Project patients: Long term benefit with niacin. *J Am Coll Cardiol* 8(6):1245, 1986.
 458. Carlson LA, Danielson M, Ekberg I, et al: Reduction of myocardial reinfarction by the combined treatment with clofibrate and nicotinic acid. *Atherosclerosis* 28:81, 1977.
 459. Azen SP, Mack WJ, Cashin-Hemphill L, et al: Progression of coronary artery disease predicts clinical coronary events. Long-term follow-up from the Cholesterol Lowering Atherosclerosis Study. *Circulation* 93:34, 1996.
 460. Brown G, Albers JJ, Fisher LD, et al: Regression of coronary artery disease as a result of intensive lipid lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 323:1289, 1990.
 461. Blumenthal RS, Michos ED: The HALTS trial—halting atherosclerosis or halted too early? *N Engl J Med* 361: 2178, 2009.
 462. Witztum JL: Current approaches to drug therapy for the hypercholesterolemic patient. *Circulation* 80(5):1101, 1989.
 463. McCormack PL, Keating GM: Prolonged-release nicotinic acid. A review of its use in the treatment of dyslipidaemia. *Drugs* 65: 2719, 2005.
 464. Knopp RH, Ginsberg J, Albers JJ, et al: Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: Clues to mechanism of action of niacin. *Metabolism* 34(7):642, 1985.
 465. Goldberg A, Alagona P Jr., Capuzzi DM, et al: Multiple dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. *Am J Cardiol* 85:1100, 2000.
 466. Etchason JA, Miller TD, Squires RW, et al: Niacin-induced hepatitis: A potential side effect with low-dose time-release niacin. *Mayo Clin Proc* 66:23, 1991.
 467. Dalton TA, Berry RS: Hepatotoxicity associated with sustained-release niacin. *Am J Med* 93:102, 1992.
 468. Grundy SM, Vega GL, McGovern ME, et al: Efficacy, safety and tolerability of once-daily niacin for the treatment of dyslipidemia associated with Type 2 diabetes: Results of the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial. *Arch Intern Med* 162:1568, 2002.
 469. Morgan JM, Capuzzi DM, Guyton JR, et al: Treatment effect of Niaspan, a controlled-release niacin in patients with hypercholesterolemia: A placebo-controlled trial. *J Cardiovasc Pharmacol Ther* 1:195, 1996.
 470. Keenan JM, Fontaine PL, Wenz JB, et al: Niacin revisited. *Arch Intern Med* 151:1424, 1991.
 471. Laurant B, Dishy V, Luo W-L, et al: Laropiprant in combination with extended-release niacin does not alter urine 11-dehydrothromboxane B2, a marker of in vivo platelet function, in healthy, hypercholesterolemia and diabetic subjects. *J Clin Pharmacol* 49: 1426, 2009.
 472. Gibbons LW, Gonzalez V, Gordon N, Grundy S: The prevalence of side effects with regular and sustained-release nicotinic acid. *Am J Med* 99:378, 1995.
 - 472a. Jacobson TA: A “hot” topic in dyslipidemia management – “how to beat a flush”: optimizing niacin tolerability to promote long-term treatment adherence and coronary disease prevention. *Mayo Clin Proc* 85: 365, 2010.
 473. Patterson DJ, Dew EW, Gyorkey F, Graham DY: Niacin hepatitis. *South Med J* 76(2):239, 1983.
 474. Clementz GL, Holmes AW: Nicotinic-acid-induced fulminant hepatic failure. *J Clin Gastroenterol* 9(5):582, 1987.
 475. Elam MB, Hunninghake DB, Davis KB, et al: Effect of niacin on lipid and lipoprotein levels and

- glycemic control in patients with diabetes and peripheral arterial disease. The ADMIT Study: A randomized trial. *JAMA* 284:1263, 2000.
476. Litin SC, Anderson CF: Nicotinic-acid associated myopathy: A report of three cases. *Am J Med* 86:481, 1989.
 477. Reaven P, Witztum JL: Lovastatin, nicotinic acid, and rhabdomyolysis (letter). *Ann Intern Med* 109:597, 1988.
 478. Rader JI, Calvert RJ, Hathcock JN: Hepatic toxicity of unmodified and time-release preparations of niacin. *Am J Med* 92:77, 1992.
 - 478a. Udiawar MV, Rees A: Therapy and clinical trials: nicotinic acid in the management of atherosclerotic disease. *Curr Opin Lipidol* 21: 286, 2010.
 479. Ashikaga H, Blumenthal RS, Jones SR: Utility of ezetimibe. *Am J Cardiol* 103: 1321, 2009.
 480. Garcia-Calvo M, Lisnock J, Bull HG, et al: The target of ezetimibe is Niemann-Pick C1-like 1 (NPC1L1). *Proc Natl Acad Sci USA* 102: 8132, 2005.
 481. Yatskar L, Fisher EA, Schwartzbard A: Ezetimibe: rationale and role in the management of hypercholesterolemia. *Clin Cardiol* 29: 52, 2006.
 482. Dujoyve CA, Ettinger MP, McNeer F, et al for the Ezetimibe Study Group: Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol* 90: 1092, 2002.
 483. Gagne C, Bays HE, Weiss SR, et al for the Ezetimibe Study Group: Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 90: 1084, 2002.
 484. Davidson MH, McGarry T, Bettis R, et al: Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 40: 2135, 2002.
 485. Kastelein JJP, Akdim F, Stroes ESG, et al for the ENHANCE Investigators: Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 358: 1431, 2008.
 486. Greenland P, Lloyd-Jones D: Critical lessons from the ENHANCE trial (commentary). *JAMA* 299: 953, 2008.
 487. Fleg JL, Mete M, Howard BV, et al: Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes. The SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. *J Am Coll Cardiol* 52: 2198, 2008.
 488. Taylor AJ, Villines TC, Stanek EJ, et al: Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 361: 2113, 2009.
 - 488a. Villines TC, Stanek EJ, Devine PJ, et al: The ARBITER 6-HALTS trial (arterial biology for the investigation of the treatment effects of reducing cholesterol 6-HDL and LDL treatment strategies in atherosclerosis). *J Am Coll Cardiol* 55: 2721, 2010.
 489. Kastelein JJP, Bots ML: Statin therapy with ezetimibe or niacin in high-risk patients. *N Engl J Med* 361: 2180, 2009.
 490. Shachter NS, Frishman WH: Lipid-lowering drugs. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics Manual 2nd ed.* New York: McGraw Hill 2004: 328.
 491. Gagne C, Gaudet D, Bruckert E, for the Ezetimibe Study Group. Efficacy and safety of ezetimibe co-administered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 105: 2469, 2002.
 492. Prueksaritanont T, Tang C, Qiu Y, et al. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos* 30:1280, 2002.
 493. Fish oil supplements. *The Medical Letter* 48: 59, 2006.
 494. Burr ML, Fehily AM, Filbert JF, et al: Effects of changes in fat, fish and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 2: 757, 1989.
 495. Marchioli R, Barzi F, Bomba E, et al: Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) Prevenzione. *Circulation* 105: 1897, 2002.
 - 495a. Kromhout D, Giltay EJ, Geleijnse JM for the Alpha Omega Trial Group: n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med* 363: 2015, 2010.
 496. Burr ML, Ashfield-Watt PA, Dunstan FD, et al: Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* 57: 193, 2003.
 497. Raitt MH, Connor WE, Morris C, et al: Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *JAMA* 293: 2884, 2005.
 498. Leaf A: Omega-3 fatty acids and prevention of arrhythmias. *Curr Opin Lipidol* 18: 31, 2007.
 499. Hartweg J, Farmer AJ, Holman RR, Neil A: Potential impact of omega-3 treatment on cardiovascular disease in type 2 diabetes. *Curr Opin Lipidol* 20: 30, 2009.
 500. Harris WS, Miller M, Tighe AP, et al: Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. *Atherosclerosis* 197: 12, 2008.
 - 500a. Saravanan P, Davidson NC, Schmidt EB, Calder

- PC: Cardiovascular effects of marine omega-3 fatty acids. *Lancet* 375: 540, 2010.
501. Kakar P, Watson T, Lip GYH: New approaches to therapy with omega-3 fatty acids. *Curr Athero Rep* 10: 79, 2008.
 502. Leaf A: The role of omega-3 fatty acids in heart disease prevention. *JCOM* 16: 323, 2009.
 503. Frishman WH, Gomberg-Maitland M, Freeman R, et al: Hormones as cardiovascular drugs: estrogens, progestins, thyroxine, growth hormone, corticosteroids and testosterone. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed.* 2003: 617.
 504. Schwartz J, Freeman R, Frishman W: Clinical pharmacology of estrogens: focus on their cardiovascular actions and cardioprotective benefits of replacement therapy in postmenopausal women. *J Clin Pharm* 35:314, 1995.
 505. Grodstein F, Stampfer MJ, Manson JE, et al: Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 335:453, 1996.
 506. Hulley S, Grady D, Bush T, et al: Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 280:7, 1998.
 507. Walsh BW, Schiff I, Rosner B, et al: Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med* 325:1196, 1991.
 508. The Writing Group for the PEPI Trial: Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The postmenopausal estrogen/progestin interventions (PEPI) trial. *JAMA* 273:199, 1995.
 509. Wakatsuki A, Ikenoue N, Sagara Y: Effect of estrogen on the size of low-density lipoprotein particles in postmenopausal women. *Obstet Gynecol* 90:22, 1997.
 510. Wakatsuki A, Ikenoue N, Okatani Y, Fukaya T: Estrogen-induced small low density lipoprotein particles may be atherogenic in postmenopausal women. *J Am Coll Cardiol* 37: 425, 2001.
 511. Herrington DM, Howard TD, Hawkins GA, et al: Estrogen-receptor polymorphisms and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. *N Engl J Med* 346:967, 2002.
 512. Hodis HN, St John JA, Xiang M, et al: Inflammatory markers and progression of subclinical atherosclerosis in healthy postmenopausal women (from the Estrogen in the Prevention of Atherosclerosis Trial). *Am J Cardiol* 101: 1131, 2008.
 513. Kuller LH for the Womens Health Initiative: Hormone replacement therapy and risk of cardiovascular disease: implications of the results of the Womens Health Initiative. *Arterioscler Thromb Vasc Biol* 23: 11, 2003.
 514. Steele RE, Wasvary JM, Dardik BN, et al: CGS 26214, the thyroxine connection revised. In: Woodford FP, Davignon J, Sniderman A, eds. *Atherosclerosis X.* Amsterdam: Elsevier, 1995:321–324.
 - 514a. Angelin B, Rudling M: Lipid lowering with thyroid hormone and thyromimetics. *Curr Opin Lipidol* 21: 499, 2010.
 515. Chong PH, Bachenheimer BS: Current, new and future treatments in dyslipidaemia and atherosclerosis. *Drugs* 60: 55, 2000.
 516. Taylor AH, Stephan ZF, Steele RE, Wong NCW: Beneficial effects of a novel thyromimetic on lipoprotein metabolism. *Mol Pharmacol* 52: 542, 1997.
 517. Knopp RH, Superko HR, Davidson M, et al: Long-term blood cholesterol-lowering effects of a dietary fiber supplement. *Am J Prev Med* 17:18, 1999.
 518. Maki KC, Davidson MH, Malik KC, et al: Cholesterol lowering with high-viscosity hydroxypropylmethylcellulose. *Am J Cardiol* 84:1198, 1999.
 519. Wolk A, Manson JE, Stampfer MJ, et al: Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *JAMA* 281:1998, 1999.
 520. Petchetti L, Frishman WH, Petrillo R, Raju K: Nutriceuticals in cardiovascular disease. *Psyllium. Cardiol in Rev* 15: 116, 2007.
 521. Stamler J: Coronary heart disease: Doing the right things. *N Engl J Med* 312:1053, 1985.
 522. Wright A, Burstyn PG, Gibney MJ: Dietary fiber and blood pressure. *Br Med J* 2:1541, 1979.
 523. Anderson JW, Ward K: High-carbohydrate, high-fiber diets for insulin-treated men with diabetes mellitus. *Am J Clin Nutr* 32:2312, 1979.
 524. Anderson JW: Dietary fiber and diabetes, in Vahouny GV, Kritchevsky D (eds): *Dietary Fiber in Health and Disease.* New York: Plenum Press, 1982, pp 151–165.
 525. Miettinen TA: Dietary fiber and lipids. *Am J Clin Nutr* 45(Suppl): 1237, 1987.
 526. Eastwood MA, Passmore R: Dietary fibre. *Lancet* 2:202, 1983.
 527. Chan JKC, Wypyszyk V: A forgotten natural dietary fiber: Psyllium mucilloid. *Cereal Foods World* 33:919, 1988.
 528. Jenkins DJA, Kendall CWC, Axelsen M, et al: Viscous and nonviscous fibres, nonabsorbable and low glycaemic index carbohydrates, blood lipids and coronary heart disease. *Curr Opin Lipidol* 11:49, 2000.
 529. Jenkins DJ, Axelsen M, Kendall CW, et al: Dietary

- fibre, lente carbohydrates and the insulin-resistant diseases. *Br J Nutr* 83:S157, 2000.
530. Kennedy JF, Sandhu JS, Southgate DAT: Structural data for the carbohydrate of ispaghula husk (ex *Plantago ovata* Forsk). *Carbohydr Res* 75:269, 1979.
 531. Levin EG, Miller VT, Muesing RA, et al: Comparison of psyllium hydrophilic mucilloid and cellulose as adjuncts to a prudent diet in the treatment of mild to moderate hypercholesterolemia. *Arch Intern Med* 150:1822, 1990.
 532. Pietinen P, Rimm EB, Korhonen P, et al: Intake of dietary fiber and risk of coronary artery disease in a cohort of Finnish men: The Alpha Tocopherol, Beta-Carotene Cancer Prevention Study. *Circulation* 94:2320, 1996.
 533. Chen WL, Anderson JW, Jennings D: Propionate may mediate the hypocholesterolemic effects of certain soluble plant fiber in cholesterol fed rats. *Proc Soc Exp Biol Med* 175:215, 1984.
 534. Lantner RR, Espiritu BR, Zumerchik P, Tobin MC: Anaphylaxis following ingestion of a psyllium-containing cereal. *JAMA* 264:2534, 1990.
 535. Behall KM, Scholfield DJ, Lee K, et al: Mineral balance in adult men: Effect of 4 refined fibers. *Am J Clin Nutr* 46:307, 1987.
 536. Kwiterovich PO Jr: The role of fiber in the treatment of hypercholesterolemia in children and adolescents. *Pediatrics* 96(5, Pt 2 of 2):1005, 1995.
 537. Rimm EB, Ascherio A, Giovannucci E, et al: Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA* 275:447, 1996.
 538. Davidson MH, Dugan LD, Burns JH, et al: The hypocholesterolemic effects of b-glucan in oatmeal and oat bran. A dose-controlled study. *JAMA* 265:1833, 1991.
 539. Lipsky H, Gloger M, Frishman WH: Dietary fiber for reducing blood cholesterol. *J Clin Pharmacol* 30:699, 1990.
 540. Spence JD, Huff MW, Heidenheim P, et al: Combination therapy with colestipol and psyllium mucilloid in patients with hyperlipidemia. *Ann Intern Med* 123:493, 1995.
 541. Ikeda I, Tanaka K, Sugano M, et al: Inhibition of cholesterol absorption in rats by plant sterols. *J Lipid Res* 29:1573, 1988.
 542. Ikeda I, Tanaka K, Sugano M, et al: Discrimination between cholesterol and sitosterol for absorption in rats. *J Lipid Res* 29:1583, 1988.
 543. Gylling H, Radhakrishnan R, Miettinen TA: Reduction of serum cholesterol in post-menopausal women with previous myocardial infarction and cholesterol malabsorption induced by dietary sitostanol ester margarine. *Circulation* 16:4226, 1997.
 544. Hallikainen MA, Uusitupa MIJ: Effects of 2 low-fat stanol ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolemic. *Am J Clin Nutr* 69:403, 1999.
 545. Miettinen TA, Puska P, Gylling H, et al: Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med* 333:1308, 1995.
 546. Kesaniemi YA, Miettinen TA: Cholesterol absorption efficiency regulates plasma cholesterol level in the Finnish population. *Eur J Clin Invest* 17:391, 1987.
 547. Miettinen TA, Kesaniemi YA: Cholesterol absorption: Regulation of cholesterol synthesis and elimination and within-population variations of serum cholesterol levels. *Am J Clin Nutr* 49:629, 1989.
 548. von Bergmann K: Lipid-lowering drugs working in the intestine. *Curr Opin Lipid* 1:48, 1990.
 549. Boberg KM, Akerlund J-E, Bjorkhem I: Effects of sitosterol on the rate-limiting enzymes in cholesterol synthesis and degradation. *Lipids* 24:9, 1989.
 550. Shefer S, Salen G, Nguyen L, et al: Competitive inhibition of bile acid synthesis by endogenous cholestanol and sitosterol in sitosterolemia with xanthomatosis. Effect of cholesterol 7-alpha hydroxylase. *J Clin Invest* 82:1833, 1988.
 551. Heinemann T, Pietruck B, Kullak-Ublick G, von Bergmann K: Comparison of sitosterol and sitostanol on inhibition of intestinal cholesterol absorption. *Agents Actions* 26(Suppl):117, 1988.
 552. Hallikainen MA, Sarkkinen ES, Uusitupa MIJ: Plant stanol esters affect serum cholesterol concentrations of hypercholesterolemic men and women in a dose-dependent manner. *J Nutr* 130:767, 2000.
 553. Nguyen TT, Dale LC, von Bergmann K, Croghar IT: Cholesterol-lowering effect of stanol ester in a U.S. population of mildly hypercholesterolemic men and women: Randomized, controlled trial. *Mayo Clin Proc* 74:1198, 1999.
 554. Gylling H, Miettinen TA: Effects of inhibiting cholesterol absorption and synthesis on cholesterol and lipoprotein metabolism in hypercholesterolemic non-insulin-dependent diabetic men. *J Lipid Res* 37:1776, 1996.
 555. Blair SN, Capuzzi DM, Gottlieb SO, et al: Incremental reduction of serum total cholesterol and low-density lipoprotein cholesterol with the addition of plant stanol ester-containing spread to statin therapy. *Am J Cardiol* 86:46, 2000.
 556. Stone NJ: Drugs for elevated LDL-cholesterol. In Antman EM (ed): *Cardiovascular Therapeutics 3rd ed* Saunders: Philadelphia, 2007: 528.
 557. Goldberg AC, Ostlund RE, Bateman JH, et al: Effect of plant stanol tablets on low-density lipo-

- protein cholesterol lowering in patients on statin drugs. *Am J Cardiol* 97: 376, 2006.
558. Gylling H, Siimes MA, Miettinen TA: Sitostanol ester margarine in dietary treatment of children with familial hypercholesterolemia. *J Lipid Res* 36:1807, 1995.
 559. Davignon J: Prospects for drug therapy for hyperlipoproteinemia. *Diabetes Metab* 21:139, 1995.
 560. Batista JF, Stusser RJ, Padron R, et al: Functional improvement in coronary artery disease after 20 months of lipid-lowering therapy with policosanol. *Adv Ther* 13:137, 1996.
 561. Gouni-Berthold I, Berthold HK: Policosanol: Clinical pharmacology and therapeutic significance of a new lipid-lowering agent. *Am Heart J* 143:356, 2002.
 562. Batista J, Stusser R, Penichet M, Uguet E: Doppler-ultrasound pilot study of the effects of long-term policosanol therapy on carotid-vertebral atherosclerosis. *Curr Ther Res* 56:906, 1995.
 563. Batista J, Stusser R, Saez F, Perez B: Effect of policosanol on hyperlipidemia and coronary heart disease in middle-aged patients. A 14-month pilot study. *Int J Pharmacol Ther* 34:134, 1996.
 564. Noa M, Mas R, Mesa R: A comparative study of policosanol vs lovastatin on intimal thickening in rabbit cuffed carotid artery. *Pharm Res* 43:31, 2001.
 565. Berthold HK, Unverdorben S, Degenhardt R, et al: Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia. A randomized controlled trial. *JAMA* 295: 2262, 2006.
 566. Vega G, Von Bergmann K, Grundy S, et al: Effect of lifibrol on the metabolism of low-density lipoproteins and cholesterol. *J Intern Med* 246:1, 1999.
 567. Schwandt P, Elsasser, Schmidt C, Gertz B, et al: Safety and efficacy of lifibrol upon four-week administration to patients with primary hypercholesterolaemia. *Eur J Clin Pharmacol* 47:133, 1994.
 568. Locker P, Jungbluth G, Francom S, Hughs G Jr, for the Lifibrol Study Group. Lifibrol: A novel lipid-lowering drug for the therapy of hypercholesterolemia. *Clin Pharmacol Ther* 57:73, 1995.
 569. Grundy S: HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. *N Engl J Med* 319:24, 1988.
 570. Todd P, Goa K: Simvastatin: A review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. *Drugs* 40:583, 1990.
 571. McTavish D, Sorkin E: Pravastatin: A review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. *Drugs* 42:65, 1990.
 572. Winkler K, Schaefer J, Klima B, et al: HDL steady state levels are not affected, but HDL apo A-I turnover is enhanced by lifibrol in patients with hypercholesterolemia and mixed hyperlipidemia. *Atherosclerosis* 150:113, 2000.
 573. Scharnagl H, Marz W, Wieland H: Lifibrol: First member of a new class of lipid-lowering drugs? *Expert Opin Investig Drugs* 6:583, 1997.
 574. Scharnagl H, Schliack M, Loser R, et al: The effects of lifibrol (K12.148) on the cholesterol metabolism of cultured cells: Evidence for sterol independent stimulation of the LDL pathway. *Atherosclerosis* 153:69, 2000.
 575. Seiki S, Frishman WH: Pharmacologic inhibition of squalene synthase and other downstream enzymes of the cholesterol synthesis pathway. A new therapeutic approach to treatment of hypercholesterolemia. *Cardiol in Rev* 17: 70, 2009.
 576. Nishimoto T, Amano Y, Tozawa R, et al. Lipid-lowering properties of TAK-475, a squalene synthase inhibitor, in vivo and in vitro. *Br J Pharmacol* 139:911, 2003.
 577. Piper E, Price G, Chen Y: TAK-475, a squalene synthase inhibitor provides lipid profile in hyperlipidemic subjects (abst). *Circulation* 114 (18 Suppl): II-288. 2006.
 578. Perez A, Kupfer S, Chen Y: Addition of TAK-475 to atorvastatin provides incremental lipid benefits (abstr). *Circulation* 114 (18 Suppl): II-113, 2006.
 579. Goldstein J, Brown M. Regulation of the mevalonate pathway. *Nature* 343: 425. 1990.
 580. Ross R: The pathogenesis of atherosclerosis: A perspective for the 1990s. *Nature* 362: 801, 1993.
 581. Sliskovic D, White A: Therapeutic potential of ACAT inhibitors as lipid lowering and anti-atherosclerotic agents. *Trends Pharmacol Sci* 12:194, 1991.
 582. Rival Y, Junquéro D, Bruniguel F, et al: Anti-atherosclerotic properties of the acyl-coenzyme A: cholesterol acyltransferase inhibitor F 12511 in casein-fed New Zealand rabbits. *J Cardiovasc Pharmacol* 39:181, 2002.
 583. Libby P, Geng YJ, Aikawa M, et al: Macrophages and atherosclerotic plaque stability. *Curr Opin Lipidol* 7:330, 1996.
 584. Delsing D, Offerman E, van Duyvenvoorde W, et al: Acyl-CoA: cholesterol acyltransferase inhibitor avasimibe reduces atherosclerosis in addition to its cholesterol-lowering effect in ApoE3-Leiden mice. *Circulation* 103:1778, 2001.
 585. Schaefer EJ, Asztalos BF: Cholesteryl ester transfer protein inhibition, high-density lipoprotein metabolism and heart disease risk reduction. *Curr Opin Lipidol* 17: 394, 2006.
 586. Nissen SE, Tuzcu EM, Brewer HB, et al for the ACAT Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) Investigators: Effect of ACAT inhibi-

- tion on the progression of coronary atherosclerosis. *N Engl J Med* 354: 1253, 2006.
587. Meuwese MC, Franssen R, Stroes ESG, Kastelein JJP: And then there were acyl coenzyme A: cholesterol acyl transferase inhibitors. *Curr Opin Lipidol* 17: 426, 2006.
 588. Fazio S, Linton M: Failure of ACAT inhibition to retard atherosclerosis. *N Engl J Med* 354: 1307, 2006.
 589. Singh IM, Shishehbor MH, Ansell BJ: High-density lipoprotein as a therapeutic target. A systematic review. *JAMA* 298: 786, 2007.
 590. Barkowski RS, Frishman WH: HDL metabolism and CETP inhibition. *Cardiol in Rev* 16: 154, 2008.
 591. Inazu A, Brown M, Hesler C, et al. Increased high-density lipoprotein levels caused by a common cholesteryl-ester transfer protein gene mutation. *N Engl J Med* 323:1234, 1990.
 592. Tall A. Plasma cholesteryl ester transfer protein. *J Lipid Res* 34:1255, 1993.
 - 592a. Sofat R, Hingorani AD, Smeeth L, et al: Separating the mechanism-based and off-target actions of cholesteryl ester transfer protein inhibitors with CETP gene polymorphisms. *Circulation* 121: 52, 2010.
 593. Clark R, Ruggeri R, Cunningham D, Bamberger M. Description of the torcetrapib series of cholesteryl ester transfer protein inhibitors, including mechanism of action. *J Lipid Res* 47: 537, 2006.
 594. Plump A, Massuci-Magoulas L, Bruce C, et al. Increased atherosclerosis in apoE and LDL receptor knock-out mice as a result of human cholesteryl ester transfer protein transgene expression. *Arterioscler Thromb Vasc Biol* 19:1105, 1999.
 595. Okamoto H, Yonemori F, Wakitani K, et al. A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits. *Nature* 406: 203, 2000.
 596. Boekholdt S, Kuivenhoven J, Wareham N, et al. Plasma levels of cholesteryl ester transfer protein and the risk of future coronary artery disease in apparently healthy men and women: the prospective EPIC (European Prospective Investigation into Cancer and nutrition)-Norfolk population study. *Circulation*. 110: 1338, 2004.
 597. Klerkx A, de Grooth G, Zwinderman A, et al Cholesteryl ester transfer protein concentration is associated with progression of atherosclerosis and response to pravastatin in men with coronary artery disease (REGRESS). *Eur J Clin Invest* 34: 21, 2004.
 598. Clark R, Sutfin T, Ruggeri R, et al Raising high density lipoprotein in humans through inhibition of cholesteryl ester transfer protein: an initial multi-dose study of torcetrapib. *Arterioscler Thromb Vasc Biol* 24: 490, 2004.
 599. McKenney JM, Davidson MH, Shear CL, Revkin JH, Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below average high-density lipoprotein cholesterol levels on a background of atorvastatin. *J Am Coll Cardiol* 48: 1782, 2006.
 600. Barter PJ, Caulfield M, Eriksson M, et al for the ILLUMINATE Investigators: Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 357: 2109, 2007.
 601. Nissen S, Tardiff JC, Nicholis S, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. *New Engl J Med* 356:1304, 2007.
 602. Kastelein JJ, van Leuven SI, Burgess L, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *New Engl J Med* 356:1620, 2007.
 603. Bots ML, Visseren FL, Evans GW, et al for the RADIANCE 2 Investigators: Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomized, double-blind trial. *Lancet* 370-153, 2007.
 604. Tall AR: CETP inhibitors to increase HDL cholesterol levels. *N Engl J Med* 356: 1364, 2007.
 605. Sviridov D, Nestel PJ: Genetic factors affecting HDL levels, structure, metabolism and function. *Curr Opin Lipid* 18: 157, 2007.
 606. Ansell BJ, Fonarow GC, Fogelman AM: The paradox of dysfunctional high-density lipoprotein. *Curr Opin Lipidol* 18: 427, 2007.
 607. Krishna R, Anderson MS, Bergman AJ, et al: Effect of the cholesteryl ester transfer protein inhibitor, anacetrapib, on lipoproteins in patients with dyslipidaemia and on 24-h ambulatory blood pressure in health individuals: two double-blind, randomized placebo-controlled phase 1 studies. *Lancet* 370: 1907, 2007.
 - 607a. Cannon CP, Shah S, Dansky HM, et al: Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* November 27, 2010 (epub).
 608. Frishman WH, Barkowski RS: Cholesteryl ester transfer protein inhibition for coronary heart disease prevention: real hope or despair? *Am J Med* 121: 644, 2008.
 609. Vergeer M, Stroes ESG: The pharmacology and off-target effects of some cholesterol ester transfer protein inhibitors. *Am J Cardiol* 104(10A): 32E, 2009.
 610. Khakpour H, Frishman WH: Lipoprotein-associated phospholipase A2, an independent predictor of cardiovascular risk and a novel target for immunomodulation therapy. *Cardiol in Rev* 17: 222, 2009.
 611. Manolio T. Novel risk markers and clinical prac-

- tice. *N Engl J Med* 349:1587, 2003.
612. Khuseyinova N, Greven S, Ruckerl R, et al. Variability of serial lipoprotein-associated phospholipase A2 measurements in post myocardial infarction patients: Results from the AIRGENE study center Augsburg. *Clin Chem*. 54:124, 2008.
 613. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 348:383, 2003.
 614. Koenig W. Treating residual cardiovascular risk: Will lipoprotein-associated phospholipase A2 inhibition live up to its promise? *J Am Coll Cardiol*. 51:1642, 2008.
 - 614a. Rosenson RS: Phospholipase A2 inhibition and atherosclerotic vascular disease: prospects for targeting secretory and lipoprotein-associated phospholipase A2 enzymes. *Curr Opin Lipidol* 21: 473, 2010.
 615. GlaxoSmithKline Website. Available at: http://www.gsk.com/investors/product_pipeline/pp.htm. Accessed May 3, 2008.
 616. Blackie JA, Bloomer JC, Brown MJ, et al. The identification of clinical candidate SB-480848: A potent inhibitor of lipoprotein-associated phospholipase A2. *Bioorg Med Chem Lett*. 13:1067, 2003.
 617. Zalewski A, Macphee C, Nelson JJ. Lipoprotein-associated phospholipase A2: A potential therapeutic target for atherosclerosis. *Curr Drug Targets Cardiovasc Haematol Disord*. 5:527, 2005.
 618. Mohler ER, 3rd, Ballantyne CM, Davidson MH, et al. The effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: The results of a multicenter, randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol*. 51:1632, 2008.
 619. Serruys PW, Garcia-Garcia HM, Buszman P, et al: Effects of the direct lipoprotein-associated phospholipase A2 inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 118: 1172, 2008.
 620. The stabilization of atherosclerotic plaque by initiation of darapladib therapy trial (STABILITY). <http://clinicaltrials.gov/ct2/show/NCT00799903>. Accessed 12/15/08.
 621. Wilensky RL, Macphee CH: Lipoprotein-associated phospholipase A2 and atherosclerosis. *Curr Opin Lipidol* 20: 415, 2009.
 622. Kermani T, Frishman WH: Nonpharmacologic approaches for the treatment of hyperlipidemia. *Cardiol in Rev* 13: 247, 2005.
 - 622a. Waksman R, Torguson R, Kent KM, et al: A first-in-man, randomized, placebo-controlled study to evaluate the safety and feasibility of autologous delipidated high-density lipoprotein plasma infusions in patients with acute coronary syndrome. *J Am Coll Cardiol* 55: 2727, 2010.
 623. Kannel WB, Neaton JD, Wentworth D, et al. Overall and coronary heart disease mortality rates in relation to major risk factors in 325,348 men screened for the MRFIT (Multiple Risk Factor Intervention Trial). *Am Heart J* 112:825, 1986.
 624. Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. *JAMA*. 256:2835, 1986.
 625. Gordon DJ, Rifkind BM. High density lipoprotein: the clinical implications of recent studies. *N Eng J Med*. 321:1311, 1989.
 626. Stein O, Stein Y. Atheroprotective mechanisms of HDL. *Atherosclerosis*. 144:285, 1999.
 627. Spady DK. Reverse cholesterol transport and atherosclerosis regression. *Circulation*. 100:576, 1999.
 628. Franceschini G, Maderna P, Sirtori CR. Reverse cholesterol transport: physiology and pharmacology. *Atherosclerosis*. 88:99, 1991.
 629. Rothblat GH, de la Llera-Moya M, Atger V, et al. Cell cholesterol efflux: integration of old and new observations provides new insight. *J Lipid Res*. 40:781, 1999.
 630. Navab M, Berliner JA, Watson AD, et al. The yin and yang of oxidation in the development of the fatty streak: a review based on the 1994 George Lyman Duff Memorial Lecture. *Arterioscler Thromb Vasc Biol*. 16:831, 1996.
 631. Bonnefont-Rousselot D, Therond P, Beaudoux JL, et al. High density lipoproteins (HDL) and the oxidative hypothesis of atherosclerosis. *Clin Chem Lab Med*. 37:939, 1999.
 632. Naqvi TZ, Shah PK, Ivey PA, et al. Evidence that high-density lipoprotein cholesterol is an independent predictor of acute platelet-dependent thrombus formation. *Am J Cardiol*. 84:1011, 1999.
 633. Saku K, Ahmad M, Glas-Greenwalt P, et al. Activation of fibrinolysis by apolipoproteins of high-density lipoproteins in man. *Thromb Res*. 39:1, 1985.
 634. Cockerill GW, Rye KA, Gamble JR, et al. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. *Arterioscler Thromb Vasc Biol*. 15: 1987, 1995.
 635. Barter PJ. Inhibition of endothelial cell adhesion molecule expression by high-density lipoproteins. *Clin Exp Pharmacol Physiol*. 24:286, 1997.
 636. Calabresi L, Franceschini G, Sirtori CR, et al. Inhibition of VCAM-1 expression in endothelial cells reconstituted high density lipoproteins. *Biochem Biophys Res Commun*. 238:61, 1997.

637. Franceschini G, Sirtori CR, Capurso A, et al. A-I Milano apoprotein: decreased high density lipoprotein cholesterol levels with significant lipoprotein modifications and without clinical atherosclerosis in an Italian family. *J Clin Invest.* 66:892,1980.
638. Roma P, Gregg RE, Meng MS, et al. In vivo metabolism of a mutant form of apolipoprotein A-I, apo A-I milano, associated with familial hypo-alpha-lipoproteinemia. *J Clin Invest.* 38: 16307, 1993.
639. Badimon JJ, Badimon L, Galvez A, et al. High density lipoprotein plasma fractions inhibit aortic fatty streaks in cholesterol-fed rabbits. *Lab Invest.* 60:455, 1989.
640. Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. *J Clin Invest.* 85:1234, 1990.
641. Miyazaki A, Sakuma S, Morikawa W, et al. Intravenous injection of rabbit apolipoprotein A-I inhibits the progression of atherosclerosis in cholesterol-fed rabbits. *Arterioscler Thromb Vasc Biol.* 15:1882, 1995.
642. Shah PK, Nilsson J, Kaul S, et al. Effects of recombinant apolipoprotein A-I (Milano) on aortic atherosclerosis in apolipoprotein E-deficient mice. *Circulation.* 97:780, 1989.
643. Nissen Se, Tsunoda T, Tuzcu EM, et al. Effect of recombinant apoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes. *JAMA.* 290:2292, 2003.
644. Tardif J-C, Gregoire J, L'Allier PL, et al: Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis. A randomized controlled trial. *JAMA* 297: 1675, 2007.
645. Rader DJ. High-density lipoproteins as an emerging therapeutic target for atherosclerosis (editorial). *JAMA.* 290:2322, 2003.
646. Erickson B, Sperber K, Frishman WH: Toll-like receptors. New therapeutic targets for the treatment of atherosclerosis, acute coronary syndromes and myocardial failure. *Cardiol in Rev* 16: 273, 2008.
647. Sherman CB, Peterson SJ, Frishman WH: Apolipoprotein A-I mimetic peptides. A potential new therapy for the prevention of atherosclerosis. *Cardiol in Rev* 18: 141, 2010.
648. Gordon T, Castelli WP, Hjortland MC, et al: High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med* 62:707, 1977.
649. Shah PK: High-density lipoprotein mimetics: focus on synthetic high-density lipoprotein. *Am J Cardiol* 100[suppl]:62N, 2007.
650. Navab M, Anantharamaiah GM, Reddy ST, et al: Potential clinical utility of high-density lipoprotein-mimetic peptides. *Curr Opin Lipidol* 17: 440, 2006.
651. Getz GS, Wool GD, Reardon CA: Apoprotein A-I mimetic peptides and their potential anti-atherogenic mechanisms of action. *Curr Opin Lipidol* 20: 171, 2009.
- 651a. Hovingh GK, Bochem AE, Kastelein JJP: Apolipoprotein A-1 mimetic peptides. *Curr Opin Lipidol* 21: 481, 2010.
652. Hara S, Higaki J, Higashino K, et al: S-8921, an ileal Na⁺/bile acid cotransporter inhibitor decreases serum cholesterol in hamsters. *Life Sci* 60:365, 1997.
653. Ichihashi T, Izawa M, Miyata K, et al: Mechanism of hypocholesterolemic action of S-8921 in rats: S-8921 inhibits ileal bile acid absorption. *J Pharmacol Exp Ther* 284:43, 1998.
654. Higaki J, Hara S, Takasu N, et al: Inhibition of ileal Na⁺/bile acid cotransporter by S-8921 reduces serum cholesterol and prevents atherosclerosis in rabbits. *Arterioscler Thromb Vasc Biol* 18:1304, 1998.
655. Benson M, Alston DR, Hickey DMB, et al: SK&F 97426-A: A novel bile acid sequestrant with higher affinities and slower dissociation rates for bile acids in vitro than cholestyramine. *J Pharm Sci* 86(1):76, 1997.
656. Benson GM, Alston DR, Bond BC, et al: SKYF 97426, a more potent bile acid sequestrant and hypercholesterolemic agent than cholestyramine in the hamster. *Atherosclerosis* 101:51, 1993.
657. Wilson TA, Nicolosi RJ, Rogers EJ, et al: Studies of cholesterol and bile acid metabolism, and early atherogenesis in hamsters fed GT16-239, a novel bile acid sequestrant (BAS). *Atherosclerosis* 140:315, 1998.
658. Eisenberg S: High-density lipoprotein metabolism. *J Lipid Res* 25:1017, 1984.
659. Patsch J, Gotto A Jr, Olivecrona T, Eisenberg S: Formation of high density lipoprotein-like particles lipolysis of very low density lipoproteins in vitro. *Proc Natl Acad Sci U S A* 75:4519, 1978.
660. Lewis B: Relation of high-density lipoproteins to coronary artery disease. *Am J Cardiol* 52:5B, 1983.
661. Eckel R: Lipoprotein lipase: A multifunctional enzyme relevant to common metabolic diseases. *N Engl J Med* 320:1060, 1989.
662. Tsutsumi K, Inoue Y, Shima A, et al: The novel compound NO-1886 increases lipoprotein lipase activity with resulting elevation of high density lipoprotein cholesterol, and long-term administration inhibits atherogenesis in the coronary arteries of rats with experimental atherosclerosis. *J Clin Invest* 92:411, 1993.
663. Tsutsumi K, Inoue Y, Hagi A, Murase T: The novel

- compound NO-1886 elevates plasma high-density lipoprotein cholesterol levels in hamsters and rabbits by increasing lipoprotein lipase without any effect on cholesteryl ester transfer protein activity. *Metabolism* 46:257, 1997.
664. Chiba T, Miura S, Sawamura F, et al: Antiatherogenic effects of a novel lipoprotein lipase-enhancing agent in cholesterol-fed New Zealand white rabbits. *Arterioscler Thromb Vasc Biol* 17:2601, 1997.
665. Tsutsumi K, Inoue Y, Shima A, Murase T: Correction of hypertriglyceridemia with low high-density lipoprotein cholesterol by the novel compound NO-1886, a lipoprotein lipase-promoting agent, in STZ-induced diabetic rats. *Diabetes* 44:414, 1995.
666. Hara T, Cameron-Smith D, Cooney GJ, et al: The actions of a novel lipoprotein lipase activator, NO-1886, in hypertriglyceridemic fructose-fed rats. *Metabolism* 47:149, 1998.
667. Kusunoki M, Hara T, Tsutsumi K, et al: The lipoprotein lipase activator, NO-1886, suppresses fat accumulation and insulin resistance in rats fed a high-fat diet. *Diabetologia* 43:875, 2000.
668. Noshiro N, Nishimoto M, Morohashi K, Okuda K: Molecular cloning of cDNA for cholesterol 7 α -hydroxylase from rat liver microsomes. Nucleotide sequence and expression. *FEBS Lett* 257:97, 1989.
669. Chiang JYL, Kimmel R, Weinberger C, Stroup D: Farnesoid X receptor responds to bile acids and represses cholesterol 7 α -hydroxylase gene (CYP7A1) transcription. *J Biol Chem* 275:10918, 2000.
670. Gupta S, Stravitz RT, Ent P, Hylemon PB: Down-regulation of cholesterol 7 α -hydroxylase (CYP7A1) gene expression by bile acids in primary rat hepatocytes is mediated by the c-Jun N-terminal kinase pathway. *J Biol Chem* 276:15816, 2001.
671. De Fabiani E, Mitro N, Anzulovich AC, et al: The negative effects of bile acids and tumor necrosis factor- α on the transcription of cholesterol 7 α -hydroxylase gene (CYP7A1) converge to hepatic nuclear factor-4. A novel mechanism of feedback regulation of bile acid synthesis mediated by nuclear receptors. *J Biol Chem* 276:30708, 2001.
672. Kuroki S, Naito T, Chijiwa K, Tanaka M: Effects of cholestyramine on hepatic cholesterol 7 α -hydroxylase and serum 7 α -hydroxycholesterol in the hamster. *Lipids* 34:817, 1999.
673. Spady DK, Cuthbert JA, Willard MN, Meidell RS: Overexpression of cholesterol 7 α -hydroxylase (CYP7A) in mice lacking the low-density lipoprotein (LDL) receptor gene. LDL transport and plasma LDL concentrations are reduced. *J Biol Chem* 273:126, 1998.
674. Wang J, Freeman DJ, Grundy SM, et al: Linkage between cholesterol 7 α -hydroxylase and high-plasma low-density lipoprotein cholesterol concentrations. *J Clin Invest* 101:1283, 1998.
675. Mangelsdorf D, Evans R: The RXR heterodimers and orphan receptors. *Cell* 83:841, 1995.
676. Xu E, Lambert M, Montana V, et al: Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Mol Cell* 3:397, 1999.
677. Schoonjans K, Staels B, Auwerx J: Role of the peroxisome proliferator-activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression. *J Lipid Res* 37:907, 1996.
678. Willson T, Wahli W: Peroxisome proliferator-activated receptor agonists. *Curr Opin Chem Biol* 1:235, 1997.
679. Schoonjans K, Peinado-Onsurbe J, Lefebvre A, et al: PPAR α and PPAR γ activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *EMBO J* 15:5336, 1996.
680. Willson T, Brown P, Sternbach D, Henke B: The PPARs: From orphan receptors to drug discovery. *J Med Chem* 43:527, 2000.
681. Israelian-Konarakis Z, Reaven PD: Peroxisome proliferator-activated receptor- α and atherosclerosis. From basic mechanisms to clinical implications. *Cardiol in Rev* 13: 240, 2005.
682. Staels B, Dallongeville J, Auwerx J, et al: Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation* 98:2088, 1998.
683. Kockx M, Gervois P, Poulain P, et al: Fibrates suppress fibrinogen gene expression in rodents via activation of the peroxisome proliferator-activated receptor- α . *Blood* 93:2991, 1999.
684. Bisgaier C, Essenburg A, Barnett B, et al: A novel compound that elevates high-density lipoprotein and activates the peroxisome proliferator-activated receptor. *J Lipid Res* 39:17, 1998.
685. Windler E, Chao Y, Havel R: Regulation of the hepatic uptake of triglyceride-rich lipoproteins in the rat. *J Biol Chem* 255:8303, 1980.
686. Willson T, Lambert M, Kliewer S: Peroxisome proliferator-activated receptor γ and metabolic disease. *Annu Rev Biochem* 70:341, 2001.
687. Tontonoz P, Nagy L, Alvarez J, et al: PPAR γ promotes monocyte/macrophage differentiation and uptake of oxidized LDL. *Cell* 93:241, 1998.
688. Ricote M, Huang J, Fajas L, et al: Expression of the peroxisome proliferator-activated receptor gamma (PPAR γ) in human atherosclerosis and regulation in macrophages by colony stimulating factors and oxidized low density lipoprotein. *Proc Natl Acad Sci U S A* 95:7614, 1998.

689. Oliver W Jr, Shenk J, Snaith M, et al: A selective peroxisome proliferator-activated receptor δ agonist promotes reverse cholesterol transport. *Proc Natl Acad Sci U S A* 98:5306, 2001.
690. Brooks D, Etgen G, Rito C, et al: Design and synthesis of 2-methyl-{4-[2-(5-methyl-2-aryloxazol-4-yl)ethoxy]phenoxy}propionic acids: A new class of dual PPAR α/γ agonists. *J Med Chem* 44:2061, 2001.
691. Riley E, Dasari V, Frishman WH, Sperber K: Vaccines in development to prevent and treat atherosclerotic disease. *Cardiol in Rev* 16: 288, 2008.
692. Travis J: Army targets a potential vaccine against cholesterol. *Science* 262:1974, 1975.
693. Bailey JM, Right R, Tomar R, Butler J: Antiatherogenic effects of cholesterol vaccination. *Biochem Soc Trans* 22:433S, 1994.
694. Nilsson A, Calara F, Regnstrom J, et al: Immunization with homologous oxidized low-density lipoprotein reduces neointimal formation after balloon injury in hypercholesterolemia rabbits. *J Am Coll Cardiol* 30:1886, 1997.
695. Parikh N, Frishman WH: The Liver X receptors. *Cardiol in Rev* 18: ____: 2010 in press.
696. Torocsik D, Szanto A, Nagy L: Oxysterol signaling links cholesterol metabolism and inflammation via the liver X receptor in macrophages. *Molec Aspects Med* 30: 134, 2009.
697. Kazuhiro O, Davis A, Chan L: Recent advances in liver-directed gene therapy: implications for the treatment of dyslipidemia. *Curr Opin Lipidol* 11:176, 2000.
698. Lehrman S: Virus treatment questioned after gene therapy death. *Nature* 401:517, 1999.
699. Kockanek S: High-capacity adenoviral vectors for gene transfer and somatic gene therapy. *Hum Gene Ther* 10:2451, 1999.
700. Herz J, Gerard R: Adenovirus-mediated transfer of low density lipoprotein receptor gene acutely accelerates cholesterol clearance in normal mice. *Proc Natl Acad Sci U S A* 90:2812, 1993.
701. Kass-Eisler A, Falck-Pedersen E, Elfenbein D, et al: The impact of developmental stage, route of administration and the immune system on adenovirus-mediated gene transfer. *Gene Ther* 1:395, 1994.
702. Yang Y, Nunes F, Berencsi K, et al: Cellular immunity to viral antigens limits E1-deleted adenoviruses for gene therapy. *Proc Natl Acad Sci U S A* 91:4407, 1994.
703. Stein C, Martins I, Davidson B: Long-term reversal of hypercholesterolemia in low density lipoprotein receptor (LDLR)-deficient mice by adenovirus-mediated LDLR gene transfer combined with CD154 blockade. *J Gene Med* 2:41, 2000.
704. Desurmont C, Caillaud J-M, Emmanuel F, et al: Complete atherosclerosis regression after human apoE gene transfer in apoE-deficient/nude mice. *Arterioscler Thromb Vasc Biol* 20:435, 2000.
705. Plump A, Smith J, Hayek T, et al: Severe hypercholesterolemia and atherosclerosis in apolipoprotein-e-deficient mice created by homologous recombination in ES cells. *Cell* 71:343, 1992.
706. Chong P, Bachenheimer B: Current, new and future treatments in dyslipidaemia and atherosclerosis. *Drugs* 60:55, 2000.
707. Akdim F, Stroes ESG, Kastelein JJP: Antisense apolipoprotein B therapy: where do we stand? *Curr Opin Lipidol* 18: 397, 2007.
- 707a. Akdim F, Stroes ESG, Sijbrands EJG, et al: Efficacy and safety of mipomersen, an antisense inhibitor of apolipoprotein B, in hypercholesterolemic subjects receiving stable statin therapy. *J Am Coll Cardiol* 55: 1611, 2010.
- 707b. Akdim F, Visser ME, Tribble DL, et al: Effect of mipomersen, an apolipoprotein B synthesis inhibitor, on low-density lipoprotein cholesterol in patients with familial hypercholesterolemia. *Am J Cardiol* 105: 1413, 2010.
- 707c. Santos RFJ, Blom DJ, Marais AD, et al: Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolemia: a randomised, double-blind, placebo-controlled trial. *Lancet* 375: 998, 2010.
708. Stephenson J: New method to repair faulty genes stirs interest in chimeraplasty technique. *JAMA* 281:119, 1999.
709. Mahley R, Huang Y, Rall S: Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia). Questions, quandaries, and paradoxes. *J Lipid Res* 40:1933, 1999.
710. Alexeev V, Yoon K: Stable and inheritable changes in genotype and phenotype of albino melanocytes induced by an RNA-DNA oligonucleotide. *Nat Biotechnol* 16:1343, 1998.
711. Kren B, Parashar B, Bandyopadhyay P, et al: Correction of the UDP-glucuronosyltransferase gene defect in the Gunn rat model of Crigler-Najjar syndrome type I with a chimeric oligonucleotide. *Proc Natl Acad Sci U S A* 96:10349, 1999.
712. Tagalakis A, Graham I, Riddell D, et al: Gene correction of the apolipoprotein (apo) E2 phenotype to wild-type apoE3 by in situ chimeraplasty. *J Biol Chem* 276:13226, 2001.
713. Rondinone CM: RNA interference to target lipid disorders. *Curr Opin Lipidol* 19:285, 2008.
714. Peterson SJ, Frishman WH: Targeting heme oxygenase: therapeutic implications for diseases of the

- cardiovascular system. *Cardiol in Rev* 17: 99, 2009.
715. Dulak J, Loboda A, Jozkowicz A: Effect of heme oxygenase-1 on vascular function and disease. *Curr Opin Lipidol* 19: 505, 2008.
716. Cuchel M, Bloedon LT, Szapary PO, et al: Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N Engl J Med* 356: 148, 2007.
717. Lilly SM, Rader DJ: New targets and emerging therapies for reducing LDL cholesterol. *Curr Opin Lipidol* 18: 650, 2007.

References for Chapter 21

New Aspects of Combination Therapy

Focus on Hypertension

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1. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 27:2121, 2009.
2. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). *J Hypertens* 25:1105, 2007.
3. Chobanian AV, Bakris GL, Black HR, et al and the National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. The JNC7 Report. *JAMA* 289:2560, 2003.
- 3a. Gradman AH, Basile JN, Carter BL, Bakris GL: Combination therapy in hypertension. *J Am Soc Hypertens* 4: 42, 2010.
4. Weber MA, Julius S, Kjeldsen SE, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. *Lancet* 19:2049, 2004.
5. Black HR: Triple fixed-dose combination therapy. Back to the past. *Hypertension* 54: 19, 2009.
- 5a. ACCORD Study Group: Effects of intensive blood pressure control in type 2 diabetes mellitus. *N Engl J Med* 362: 1575, 2010.
6. Izzo J, Neutel J, Dubiel R, Walker F. Efficacy of olmesartan medoxomil (O) and O/hydrochlorothiazide (H) in achieving blood pressure (BP) control and normalization in stage 2 systolic hypertension (HTN). *Am J Hypertens* 18:64A, 2005.
7. Bakris GL, Smith DH, Giles TD, et al. Comparative antihypertensive efficacy of angiotensin receptor blocker-based treatment in African-American and white patients. *J Clin Hypertens* 10:587, 2005.
8. Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther* 30:587, 2008.
9. Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther* 29:563, 2007.
10. Neutel JM, Smith DHG, Weber MA. A comparison of the effects of amlodipine 5 mg/benazepril 20 mg combination therapy to component monotherapy on arterial distensibility and left ventricular hypertrophy in patients with mild to moderate hypertension. *Am J Hypertens* 15: 166A, 2002.
11. Dahlöf B, Sever PS, Poulter NR, et al for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. *Lancet* 366:895, 2005.
12. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 113:1213, 2006.
13. Jamerson K, Weber MA, Bakris GL, et al for the ACCOMPLISH investigators. Benazepril plus am-

- lodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 359:2417, 2008.
- 13a. Bakris GL, Sarafidis PA, Weir MR, et al for the ACCOMPLISH Trial Investigators: Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet* 375: 1173, 2010.
 14. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 358:1547, 2008.
 15. Oparil S, Yarows SA, Patel S, et al. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 370:221, 2007.
 16. Calhoun DA, Lacourcière Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension* 54:32, 2009.

References for Chapter 22

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1. US Department of Health and Human Services: *The Health Benefits of Smoking Cessation: A Report of the Surgeon General*. Publication CDC 90-8416. Washington DC: DHHS, 1990.
2. US Department of Health and Human Services: *The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General's Office on Smoking and Health*. DHHS (PHS) 84-50204. Rockville, MD: DHHS, 1983.
3. Hammond EC, Horn D: Smoking and death rates. Report on forty-four months of follow up of 187,783 men: I. Total mortality. *JAMA* 166:1159,1958.
4. US Public Health Service: *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service Center for Disease Control*. PHS No. 1103. Washington, DC: DHHS, 1964.
5. US Department of Health, Education and Welfare: *Smoking and Health: A Report of the Surgeon General's Office on Smoking and Health*. DHEW PHS 79-50066. Washington, DC: DHHS, 1979.
6. Matetzky S, Tani S, Kangavari S, et al: Smoking increases tissue factor expression in atherosclerotic plaques. Implications for plaque thrombogenicity. *Circulation* 2000; 102:602, 2000.
7. Jee SH, Suh I, Kim IS, Appel LJ: Smoking and atherosclerotic cardiovascular disease in men with low levels of serum cholesterol. The Korea Medical Insurance Corporation Study. *JAMA* 282:2149,1999.
- 7a. Rusanen M, Kivipelto M, Quesenberry CP Jr., et al: Heavy smoking in midline and long-term risk of Alzheimer disease and vascular dementia. *Arch Intern Med* October 25, 2010 (epub).
8. Teo KK, Ounpuu S, Hawken S: Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case control study. *Lancet* 368: 647, 2006.
9. Al-Delaimy WK, Manson JE, Solomon CG, et al: Smoking and risk of coronary heart disease among women with type 2 diabetes mellitus. *Arch Intern Med* 162:273, 2002.
10. Jacobs EJ, Thun MJ, Apicella LF: Cigar smoking and death from coronary heart disease in a prospective study of US men. *Arch Intern Med* 159:2413,1999.
11. Escobedo LG, Caspersen CJ: Risk factors for sudden coronary death in the United States. *Epidemiology* 8:175,1997.
12. Escobedo LG, Zack MM: Comparison of sudden and nonsudden coronary deaths in the United States. *Circulation* 93:2033,1996.
13. Suskin N, Sheth T, Negassa A, Yusuf S: Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. *J Am Coll Cardiol* 37:1677, 2001.
14. Heeringa J, Kors JA, Hofman A, et al: Cigarette smoking and risk of atrial fibrillation: the Rotterdam Study. *Am Heart J* 156: 1163, 2008.
15. Critchley JA, Capewell S: Mortality risk reduction associated with smoking cessation in patients with coronary heart disease. *JAMA* 290:86, 2003.
16. Goldenberg I, Jonas M, Tenenbaum A, et al: Current smoking, smoking cessation, and the risk of sudden cardiac death in patients with coronary artery disease. *Arch Intern Med* 163:2301, 2003.
17. Taylor DH Jr, Hasselblad V, Henley SJ, et al: Benefits of smoking cessation for longevity. *Am J Public Health* 92:990, 2002.
18. Anthonisen NR, Skeans MA, Wise RA, et al: The effects of a smoking cessation intervention on 14.5-year mortality. A randomized clinical trial. *Ann Intern Med* 142:233, 2005.
19. Fichtenberg CM, Glantz SA: Association of the

- California tobacco control program with declines in cigarette consumption and mortality from heart disease. *N Engl J Med* 343:1772, 2000.
20. Jacobs DR Jr, Adachi H, Mulder I, et al: Cigarette smoking and mortality risk. Twenty-five-year follow-up of the Seven Countries Study. *Arch Intern Med* 159:733,1999.
 21. Ludvig J, Miner B, Eisenberg MJ: Smoking cessation in patients with coronary artery disease. *Am Heart J* 149: 565, 2005.
 22. Hilleman DE, Mohiuddin SM, Packard KA: Comparison of conservative and aggressive smoking cessation treatment strategies following coronary artery bypass graft surgery. *Chest* 125:435, 2004.
 23. Narkiewicz K, van de Borne PJH, Hausberg M, et al: Cigarette smoking increases sympathetic outflow in humans. *Circulation* 98:528, 1998.
 24. Fisher SD, Zareba W, Moss AJ, et al: Effect of smoking on lipid and thrombogenic factors two months after acute myocardial infarction. *Am J Cardiol* 86:813, 2000.
 25. Hioki Y, Aoki N, Kawano K, et al: Acute effects of cigarette smoking on platelet-dependent thrombin generation. *Eur Heart J* 22:56, 2001.
 26. Newby DE, Wright RA, Labinjoh C, et al: Endothelial dysfunction, impaired endogenous fibrinolysis, and cigarette smoking. A mechanism for arterial thrombosis and myocardial infarction. *Circulation* 99:1411,1999.
 27. Zedler BK, Kinser R, Oey J, et al: Biomarkers of exposure and potential harm in adult smokers of 3-7 mg tar yield (Federal Trade Commission) cigarettes and in adult non-smokers. *Biomarkers* 11:201, 2006.
 28. Sobczak A, Wardas W, Zielinska-Danch W, Pawlicki K: The influence of smoking on plasma homocysteine and cysteine levels in passive and active smokers. *Clin Chem Lab Med* 42:408, 2004.
 29. Bazzano LA, He J, Muntner P, et al: Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med* 138:891, 2003.
 30. Lu JT, Creager MA: The relationship of cigarette smoking to peripheral arterial disease. *Rev Cardiovasc Med* 5:189, 2004.
 31. Stenvinkel P: Interactions between inflammation, oxidative stress, and endothelial dysfunction in end-stage renal disease. *J Ren Nutr* 13:144, 2003.
 32. Rodriguez JJ, Al Dashti R, Schwarz ER: Linking erectile dysfunction and coronary artery disease. *Int J Impot Res* 17(Suppl 1):S12, 2005.
 33. Panagiotakos D, Pitsavos C, Chrysoshoou C, et al: Effect of secondhand smoke on markers of inflammation: the ATTICA Study. *Am J Med* 116:145, 2004.
 34. Sellers EM: Pharmacogenetics and ethnorracial differences in smoking. *JAMA* 280:179, 1998.
 35. Stapleton J: Cigarette smoking prevalence, cessation and relapse. *Stat Methods Med Res* 7:187, 1998.
 36. Pomerleau OF: Nicotine and the central nervous system: biobehavioral effects of cigarette smoking. *Am J Med* 93(1A):2S, 1992.
 37. Pomerleau OF, Pomerleau CS: Neuroregulators and the reinforcement of smoking: Towards a biobehavioral explanation. *Neurosci Biobehav Rev* 8:503, 1984.
 38. Russell MAH, Peto J, Patel UA: The classification of smoking by factorial structure of motives. *J R Statist Soc* 137:313, 1974.
 39. Tate JC: Pharmacological and nonpharmacological smoking motives: A replication and extension. *Addiction* 89:321, 1994.
 40. Lanca AJ, Adamson KL, Coen KM, et al: The pedunculo-pontine tegmental nucleus and the role of cholinergic neurons in nicotine self-administration in the rat: a correlative neuroanatomical and behavioral study. *Neuroscience* 96:735, 2000.
 41. Corrigan WA, Coen KM, Zhang J, Adamson L: Pharmacological manipulations of the pedunculo-pontine tegmental nucleus in the rat reduce self-administration of both nicotine and cocaine. *Psychopharmacology (Berl)* 160:198, 2002.
 42. Corringer PJ, Sallette J, Changeux JP: Nicotine enhances intracellular nicotinic receptor maturation: a novel mechanism of neural plasticity? *J Physiol Paris* 99:162, 2006.
 43. Gonzalez S, Cascio MG, Fernandez-Ruiz J, et al. Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine. *Brain Res* 954:73, 2002.
 44. Zhu PJ, Chiappinelli VA: Nicotinic receptors mediate increased GABA release in brain through a tetrodotoxin-insensitive mechanism during prolonged exposure to nicotine. *Neuroscience* 115:137, 2002.
 45. Mathieu-Kia AM, Kellogg SH, Butelman ER, Kreek MJ: Nicotine addiction: insights from recent animal studies. *Psychopharmacology (Berl)* 162:102, 2002.
 46. Li MD: The genetics of nicotine dependence. *Curr Psychiatry Rep* 8:158, 2006.
 47. Picciotto MR, Corrigan WA: Neuronal systems underlying behaviors related to nicotine addiction: neural circuits and molecular genetics. *J Neurosci* 22:3338, 2002.
 48. Otsuka R, Watanabe H, Hirata K, et al: Acute effects of passive smoking on the coronary *Circulation* in healthy young adults. *JAMA* 286:436, 2001.

49. He J, Vupputuri S, Allen K, et al: Passive smoking and the risk of coronary heart disease – a meta-analysis of epidemiologic studies. *N Engl J Med* 340:920, 1999.
50. Kato M, Roberts-Thomson P, Phillips BG, et al: The effects of short-term passive smoke exposure on endothelium-dependent and independent vasodilation. *J Hypertens* 17:1395, 1999.
51. Tonkin AM, Beauchamp A, Stevenson C: The importance of extinguishing secondhand smoke (editorial). *Circulation* 120: 1339, 2009.
52. Lightwood JM, Glantz SA: Declines in acute myocardial infarction after smoke-free laws and individual risk attributable to secondhand smoke. *Circulation* 120: 1373, 2009.
53. Benowitz N: Clinical pharmacology of inhaled drugs of abuse: Implications in understanding nicotine dependence. *Natl Inst Drug Abuse Res Monogr* 99:12, 1990.
54. Patterson F, Benowitz N, Shields P, et al: Individual differences in nicotine intake per cigarette. *Cancer Epidemiol Biomarkers Prev* 12:468, 2003.
55. Henningfield JE: Higher levels of nicotine in arterial than venous blood after cigarette smoking. *Drug Alcohol Depend* 33:23, 1993.
56. Benowitz NL, Zevin S, Jacob P III: Sources of variability in nicotine and cotinine levels with use of nicotine nasal spray, transdermal nicotine, and cigarette smoking. *Br J Clin Pharmacol* 43:259, 1997.
57. Benowitz NL: Establishing nicotine threshold for addiction: The implications for tobacco regulation. *N Engl J Med* 331:123, 1994.
58. Jarvis MJ. ABC of smoking cessation. Why people smoke. *BMJ* 328: 277, 2004.
59. Bliden KP, DiChiara J, Lawal L, et al: The association of cigarette smoking with enhanced platelet inhibition by clopidogrel. *J Am Coll Cardiol* 52: 531, 2008.
60. Ford CL, Zlabek JA: Nicotine replacement therapy and cardiovascular disease. *Mayo Clin Proc* 80:652, 2005.
61. Silagy C, Lancaster T, Stead L, et al: Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2004; No.3:CD000146.
62. Benowitz NL: Nicotine and coronary heart disease. *Trends Cardiovasc Med* 1:315, 1991.
63. Benowitz NL: Nicotine patches. *BMJ* 310:1409, 1995.
64. Benowitz NL: Nicotine replacement therapy during pregnancy. *JAMA* 266:3174, 1991.
65. Coleman T, Britton J, Thornton J: Nicotine replacement therapy in pregnancy. *BMJ* 328: 965, 2004.
66. US Preventive Services Task force. Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: U.S. Preventive Services Task Force Reaffirmation Recommendation Statement. *Ann Intern Med* 150: 551, 2009.
67. US Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General.* Publication CDC 88-8406. Washington, DC: DHHS, 1988.
68. Connolly GN, Winn DM, Hecht SS, et al. The re-emergence of smokeless tobacco. *N Engl J Med* 314:1020, 1986.
69. Critchley JA, Unal B: Is smokeless tobacco a risk factor for coronary heart disease? A systematic review of epidemiological studies. *Eur J Cardiovasc Prev Rehabil* 11:101, 2004.
70. Gupta R, Gurm H, Bartholomew JR: Smokeless tobacco and cardiovascular risk. *Arch Intern Med* 164:1845, 2004.
- 70a. Piano MR, Benowitz NL, FitzGerald GA, et al: Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention, and treatment. A policy statement from the American Heart Association. *Circulation* 122: 1520, 2010.
71. US Department of Health and Human Services: *The Health Consequences of Using Smokeless Tobacco: A Report of the Advisory Committee to the Surgeon General.* publication (NIH) 86-2874. Washington, DC: DHHS, 1986.
72. Frishman WH, Ky T, Ismail A. Tobacco smoking, nicotine and nicotine and non-nicotine smoking cessation therapies. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics*, 2nd ed. New York: McGraw Hill, 2003; pp. 369-80.
73. Gorsline J, Benowitz NL, Rolf, CN, et al: Comparison of plasma nicotine concentrations for nicotine transdermal system (NTS), cigarette smoking and nicotine polacrilex (nicotine gum) [abstract]. *Clin Pharmacol Ther* 51:129, 1992.
74. Fiore MC, Jorenby DE, Baker TB, Kenford SL: Tobacco dependence and the nicotine patch. Clinical guidelines for effective use. *JAMA* 268:2687, 1992.
75. Hughes JR, Goldstein MG, Hurt RD, Shiffman S: Recent advances in the pharmacotherapy of smoking. *JAMA* 281: 72, 1999.
76. Dale LC, Hurt RD, Offord KP, et al: High-dose nicotine patch therapy. Percentage of replacement and smoking cessation. *JAMA* 274:1353, 1995.
77. Jorenby DE, Smith SS, Fiore MC, et al: Varying nicotine patch dose and type of smoking cessation counseling. *JAMA* 274:1347, 1995.
78. Tonnesen P, Paoletti P, Gustavsson G, et al: Higher dosage nicotine patches increase one-year smoking cessation rates: Results from the European CEASE

- trial. *Eur Respir J* 13:238, 1999.
79. Daughton DM, Heatley SA, Prendergast JJ, et al: Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. A randomized, placebo-controlled, double-blind study. *Arch Intern Med* 151:749, 1991.
 - 79a. Lerman C, Jepsen C, Wileyto EP, et al: Genetic variation in nicotine metabolism predicts the efficacy of extended-duration transdermal nicotine therapy. *Clin Pharmacol Therap* 87: 553, 2010.
 80. Page F, Coleman G, Conduit R: The effect of transdermal nicotine patches on sleep and dreams. *Physiol Behav* 88:425, 2006.
 81. Benowitz NL: Nicotine effects on eicosanoid formation and hemostatic function: Comparison of transdermal nicotine and cigarette smoking. *J Am Coll Cardiol* 22:159, 1993.
 82. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease: Nicotine replacement therapy for patients with coronary artery disease. *Arch Intern Med* 154:989, 1994.
 83. Kimmel SE, Berlin JA, Miles C, et al: Risk of acute myocardial infarction and use of nicotine patches in a general population. *J Am Coll Cardiol* 37:1297, 2001.
 84. Meine TJ, Patel MR, Washam JB, et al: Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. *Am J Cardiol* 95:976, 2005.
 85. Sachs DP. Effectiveness of the 4 mg dose of nicotine polacrilex for the initial treatment of high-dependent smokers. *Arch Intern Med* 155: 1973, 1995.
 86. Etter J-F, Huguelet P, Perneger TV, Cornuz J: Nicotine gum treatment before smoking cessation. A randomized trial. *Arch Intern Med* 169: 1028, 2009.
 87. Henningfield JE, Radzius A, Cooper TM, Clayton RR: Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. *JAMA* 264: 1560, 1990.
 88. Murray RP, Bailey WC, Daniels K, et al: Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. *Chest* 109: 438, 1996.
 89. Shiffman S, Dresler CM, Hajek P, et al: Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med* 162: 1267, 2002.
 90. West R. Glucose for smoking cessation: does it have a role?. *CNS Drugs*. 15: 261, 2001.
 91. Schneider NG, Lunell E, Olmstead RE, Fagerstrom KO: Clinical pharmacokinetics of nasal nicotine delivery: a review and comparison to other nicotine systems. *Clin Pharmacokin* 31: 65, 1996.
 92. Bohadana A, Nilsson F, Rasmussen T, Martinet Y: Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation. A randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 160: 3128, 2000.
 93. Hughes JR: Dependence on and abuse of nicotine replacement: an update. In Benowitz NL (ed): *Nicotine Safety and Toxicity*. New York: Oxford University Press 1998: 147-60.
 94. Schuh KJ, Schuh LM, Henningfield JE, Stitzer ML: Nicotine nasal spray and vapor inhaler: abuse liability assessment. *Psychopharmacol* 130: 352, 1997.
 95. Sutherland G: Current approaches to the management of smoking cessation. *Drugs* 62 (Suppl 2):53, 2002.
 96. Bolliger C, Zellweger JP, Danielsson MA, et al: Smoking reduction with oral nicotine inhalers: double-blind, randomized, clinical trial of efficacy and safety. *Br Med J* 321:329, 2000.
 97. Schneider NG, Olmstead RE, Franzon MA, Lunell E: The nicotine inhaler. Clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokin* 40:66, 2001.
 98. Lunell E, Molander L, Andersson SR: Temporary dependency of the release and bioavailability of nicotine from nicotine vapour inhaler: *in vitro/in vivo* correlation. *Eur J Clin Pharmacol* 52: 495, 1997.
 99. Blondal T, Gudmundsson LJ, Tomasson K, et al. The effects of fluoxetine combined with nicotine inhalers in smoking cessation—a randomized trial. *Addiction*. 94:1007,1999.
 - 99a. Yamin CK, Bitton A, Bates DW: E-cigarettes: a rapidly growing internet phenomenon. *Ann Intern Med* 153: 607, 2010.
 100. Etter JF: Cytisine for smoking cessation: a literature review and a meta-analysis. *Arch Intern Med* 166: 1553, 2006.
 101. Slater Y, Houlihan L, Maskell P, et al: Halogenated cytosine derivatives as agonists at human neuronal nicotinic acetylcholine receptor subtypes. *Neuropharmacol* 44:503, 2003.
 102. Gonzales D, Rennard SI, Nides M, et al: Varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist vs sustained-release bupropion and placebo for smoking cessation. A randomized controlled trial. *JAMA* 296:47, 2006.
 103. Jorenby DE, Hays JT, Rigotti NA, et al: Efficacy of varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation. A randomized controlled trial. *JAMA* 296:56, 2006.
 104. Jimenez-Ruiz C, Berlin I, Hering T: Varenicline. A novel pharmacotherapy for smoking cessation. *Drugs* 69: 1319, 2009.
 105. Nides M, Oncken C, Gonzales D, et al: Smoking

- cessation with varenicline, a selective $\alpha 4\beta 2$ nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow up. *Arch Intern Med* 166: 1561, 2006.
106. Oncken C, Gonzales D, Nides M, et al: Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med* 166: 1571, 2006.
 107. Tonstad S, Tonnesen P, Hajek P, et al: Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 296:64, 2006.
 - 107a. Rigotti NA, Pipe AL, Benowitz NL, et al: Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease. A randomized trial. *Circulation* 121: 221, 2010.
 108. Kuehn BM: Studies linking smoking-cessation drug with suicide risk spark concerns. *JAMA* 301: 1007, 2009.
 109. Safety of smoking cessation drugs. *The Medical Letter* 51(Issue 1319); 65, 2009.
 110. Dierker L, Donny E: The role of psychiatric disorders in the relationship between cigarette smoking and DSM-IV nicotine dependence among young adults. *Nicotine Tob Res* 10:439, 2008.
 111. Breslau N, Schulz LR, Johnson EO, et al: Smoking and the risk of suicidal behavior: a prospective study of a community sample. *Arch Gen Psychiatry* 62: 328, 2005.
 112. Goodwin RD, Zvolensky MJ, Keyes KM: Nicotine dependence and mental disorders among adults in the USA: evaluating the role of the mode of administration. *Psychol Med* 38: 1277, 2008.
 113. Miller M, Hemenway D, Rimm E: Cigarettes and suicide: a prospective study of 50,000 men. *Am J Public Health* 90: 768, 2000.
 114. Anonymous: Varenicline (Chantix) warnings: risk versus benefit. *The Medical Letter* 50 (Issue 1290) July 14: 53.
 115. Hays TJ, Ebbert JO. Bupropion sustained release for treatment of tobacco dependence. *Mayo Clinic Proceed.* 78:1020, 2003.
 116. Patterson F, Schnoll RA, Wileyto EP, et al: Toward personalized therapy for smoking cessation: a randomized placebo-controlled trial of bupropion. *Nature* 447: 320, 2008.
 117. Colby SM, Gwaltney CJ: Pharmacotherapy of adolescent smoking cessation (commentary). *JAMA* 298: 2182, 2007.
 118. Fossati R, Apolone G, Negri E, et al: A double-blind, placebo-controlled, randomized trial of bupropion for smoking cessation in primary care. *Arch Intern Med* 167: 1791, 2007.
 119. Ahluwalia JS, Harris KJ, Catley D, et al: Sustained-release bupropion for smoking cessation in African Americans: A randomized controlled trial. *JAMA* 288:468, 2002.
 120. Jorenby D: Clinical efficacy of bupropion in the management of smoking cessation. *Drugs* 62(Suppl 2):25, 2002.
 121. Hatsukami DK, Rennard S, Patel MK, et al. Effects of sustained-release bupropion among persons interested in reducing but not quitting smoking. *Am J Med* 116:151, 2004.
 122. Jorenby DE, Leischow SJ, Nides MA, et al: A controlled trial of sustained release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 340: 685, 1999.
 123. Hurt RD, Sachs DPL, Glover ED, et al: A comparison of sustained release bupropion and placebo for smoking cessation. *N Engl J Med* 337:1195, 1997.
 124. Hayford KE, Patten CA, Rummans TA, et al: Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. *Br J Psychiatry* 174:173, 1999.
 125. Swan GE, McAfee T, Curry SJ, et al. Effectiveness of bupropion sustained release for smoking cessation in a health care setting. *Arch Intern Med* 163: 2337, 2003.
 126. Tonstad S, Farsang C, Klaene G, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: A multicenter randomized study. *Eur Heart J.* 24:946, 2003.
 127. Aubin H-J: Tolerability and safety of sustained-release bupropion in the management of smoking cessation. *Drugs* 62(Suppl 2):45, 2002.
 128. Prochazka A: New developments in smoking cessation. *Chest* 117(4 Suppl 1): 169S, 2000.
 129. Steinberg MB, Greenhaus S, Schemlzer AC, et al: Triple-combination pharmacotherapy for medically ill smokers. A randomized trial. *Ann Intern Med* 150: 447, 2009.
 130. Sandyk R, Gillman MA, Iacono RP, Bamford CR: Clonidine in neuropsychiatric disorders: a review. *Intl J Neurosci* 35: 205, 1987.
 131. Covey LS, Glassman AH: A meta-analysis of double-blind placebo controlled trials of clonidine for smoking cessation. *Br J Addict* 86:991, 1991.
 132. Prichard BN: Drug treatment of hypertension. *Drugs* 35 (Suppl 6): 40, 1988.
 133. Hall SM, Reus VI, Munoz RF, et al: Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Arch Gen Psychiatry* 55:683, 1998.
 134. da Costa CL, Younes RN, Lourenco MT. Stopping smoking: a prospective, randomized, double-blind study comparing nortriptyline to placebo. *Chest.*

- 122:403, 2002.
135. Kahan M: Treatment: nortriptyline was associated with an increased rate of 6 month smoking cessation. *Evid Based Cardiovasc Med* 3: 15, 1999.
 136. Prochazka AV, Kick S, Steinbrunn C, et al: A randomized trial of nortriptyline combined with transdermal nicotine for smoking cessation. *Arch Intern Med* 164: 2229, 2004.
 137. Cook JW, Spring B, McChargue DE, et al. Influence of fluoxetine on positive and negative affect in a clinic-based smoking cessation trial. *Psychopharmacol (Berl)*. 173(1-2):153, 2004.
 138. Murphy JK, Edwards NB, Downs AD, et al. Effects of doxepin on withdrawal symptoms in smoking cessation. *Am J Psychiatry* 147:1353, 1990.
 139. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews*. 2004, Issue 2, CD 000031, pub 2.
 140. Fowler JS, Logan J, Wang GJ, Volkow ND: Monoamine oxidase and cigarette smoking. *Neurotoxicol* 24: 75, 2003.
 141. George TP, Vessicchio J, Termine A, et al: A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. *Biol Psychiatry* 53: 136, 2003.
 142. Zickler P. Manipulating dopamine levels changes smoking behavior. *Natl Institute on Drug Abuse Notes, Research Findings*, June 2003; 18(1). Accessed 10/27/04.
 143. Foulds J, Burke M, Steinberg M, et al. Advances in pharmacotherapy for tobacco dependence. *Expert Opin Emerg Drugs* 2004; 9(1): 39, 2004.
 144. Murphy M, Hey K, Johnstone E, et al. Bromocriptine use is associated with decreased smoking rates. *Addict Biol* 7: 325, 2002.
 145. Zickler P (Staff Writer). Hard-to-treat smokers may benefit from medication that acts on dopamine. *Natl Institute on Drug Abuse Notes, Research Findings*, December 2003; 18(5). Accessed 8/16/06.
 146. Lauro S, Paxeras JA. Update on the treatment of smoking dependence. *Arch Bronconeumol* 40: 123, 2004.
 147. Sellers EM, Ramamoorthy Y, Zeman MV, et al: The effect of methoxsalen on nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNI) metabolism in vivo. *Nicotine Tob Res* 5: 891, 2003.
 148. Riley E, Dasari V, Frishman WH, Sperber K: Vaccines in development to prevent and treat atherosclerotic disease. *Cardiol in Rev* 16: 288, 2008.
 149. Malin DH, Alvarado CL, Woodhouse KS, et al: Passive immunization against nicotine attenuates nicotine discrimination. *Life Sci* 70:2793, 2002.
 150. Pentel P, Malin D. A vaccine for nicotine dependence: targeting the drug rather than the brain. *Respiration* 69:193, 2002.
 151. Hieda Y, Keyler DE, Van DeVoort JT, et al: Immunization of rats reduces nicotine distribution to brain. *Psychopharmacology (Berl)* 143:150, 1999.
 152. Lindblom N, de Villiers SHL, Kalayanov G, et al: Active immunization against nicotine prevents reinstatement of nicotine-seeking behavior in rats. *Respiration* 69:254, 2002.
 153. de Villiers SHL, Lindblom N, Kalayanov G, et al: Active immunization against nicotine suppresses nicotine-induced dopamine release in the rat nucleus accumbens shell. *Respiration* 69:247, 2002.
 154. Xenova Group. Antismoking vaccine TA-NIC preliminary 12 month clinical trial results. Xenova Group: Berkshire, 2005.
 155. Celtic Pharma completes rapid enrollment in phase IIB study for TA-NIC, the nicotine vaccine for smoking cessation. http://www.celticpharma.com/news/pr/release_102907.pdf. Accessed April 22, 2008.
 156. Buchhalter AR, Fant RV, Henningfield JE: Novel pharmacological approaches for treating tobacco dependence and withdrawal: current status. *Drugs* 68: 1067, 2008.
 157. NicVAX (nicotine conjugate vaccine). www.Nabi.com/pipeline/clinicaltrials.php. Accessed March 24, 2008.
 158. Nabi Biopharmaceuticals initiates phase IIB "proof of concept" study for NicVAX (press release). Boca Raton, FL: Nabi Biopharmaceuticals 2006.
 159. Maurer P, Bachmann MF: Vaccination against nicotine: an emerging therapy for tobacco dependence. *Expert Topic Investig Drug* 16: 1775, 2007.
 160. Keyler D, Shoeman D, Lesage M. Maternal vaccination against nicotine reduce nicotine distribution to fetal brain in rats. *JPET* 305: 587, 2003.
 161. Hall W. The prospects for immunotherapy in smoking cessation. *Lancet* 360:1089, 2002.
 162. DiMarzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. *Nat Rev Drug Discov* 3: 771, 2004.
 163. Cohen C, Perrault G, Griebel G, Soubrié P: Nicotine associated cues maintain nicotine-seeking behavior in rats several weeks after nicotine withdrawal: reversal by the cannabinoid (CB1) receptor antagonist, rimonabant (SR141716). *Neuropsychopharmacol* 30: 145, 2005.
 164. Tonstad S: Rimonabant: A cannabinoid receptor blocker for the treatment of metabolic and cardiovascular risk factors. *Nutr Metab Cardiovasc Dis* 16: 156, 2006.
 165. Nissen SE, Nicholls SJ, Wolski K, et al for the

- TRADIVARIUS Investigators: Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease. A STRADIVARIUS randomized controlled trial. *JAMA* 299: 1547, 2008.
166. Rauhut A, Mullins S, Dwoskin L, Bardo M. Reboxetine: Attenuation of intravenous nicotine self-administration in Rats. *J Pharm Exp Ther* 303: 664, 2002.
 167. Epstein A, King A. Naltrexone attenuates acute cigarette smoking behavior. *Pharmacol Biochem Behav* 77:29, 2004.
 168. Krishnan-Sarin S, Meandzija B, O'Malley S. Naltrexone and nicotine patch smoking cessation: a preliminary study. *Nicotine Tob Res* 5(6): 851, 2003.
 169. Botteri E, Iodice S, Bagnardi V, et al. Smoking and colorectal cancer. A meta-analysis. *JAMA* 300: 2765, 2008.
 170. Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA: Smoking and smoking cessation in relation to mortality in women. *JAMA* 299: 2037, 2008.
 171. Strandberg AY, Strandberg TE, Pitkala K, et al: The effect of smoking in midlife on health-related quality of life in old age. *Arch Intern Med* 168: 1968, 2008.
 172. Cesaroni G, Forastiere F, Agabiti N, et al: Effect of the Italian smoking ban on population rates in acute coronary events. *Circulation* 117: 1183, 2008.
 173. Van Domburg RT, Scholte op Reimer W, Hoeks SE, et al: Three life-years gained from smoking cessation after coronary artery bypass surgery: a 30-year follow up study. *Am Heart J* 156: 473, 2008.
 174. Lerman C, Niaura R: Applying genetic approaches to the treatment of nicotine dependence. *Oncogene* 21:7412, 2002.
 175. Keenan PS: Smoking and weight change after new health diagnoses in older adults. *Arch Intern Med* 169: 237, 2009.
 176. Salize HJ, Merkel S, Reinhard I, et al: Cost-effective primary care-based strategies to improve smoking cessation. More value for money. *Arch Intern Med* 169: 230, 2009.
 177. Burke MV, Ebbert JO, Hays JT: Treatment of tobacco dependence. *Mayo Clin Proc* 83: 479, 2004.
 178. Christakis NA, Fowler JH: The collective dynamics of smoking in a large social network. *N Engl J Med* 358: 2249, 2008.
 179. Dawood N, Vaccarino V, Reid KJ, et al for the PREMIER Registry Investigators: Predictors of smoking cessation after a myocardial infarction. The role of institutional smoking cessation programs in improving success. *Arch Intern Med* 168: 1961, 2008.
 180. Fiore MC, Jaén CR: A clinical blueprint to accelerate the elimination of tobacco use (commentary). *JAMA* 299: 2083, 2008.
 181. Rigotti NA, Munafo MR, Stead LF: Smoking cessation interventions for hospitalized smokers. A systematic review. *Arch Intern Med* 168: 1950, 2008.
 182. Sabia S, Marmot M, Dufouil C, Singh-Manoux A: Smoking history and cognitive function in middle age from the Whitehall II study. *Arch Intern Med* 2008; 168: 1165, 2008.
 183. Steinberg MB, Schmelzer AC, Richardson DL, Foulds J: The case for treating tobacco dependence as a chronic disease. *Ann Intern Med* 148: 554, 2008.
 184. Thorndike AN, Regan S, McKool K, et al: Depressive symptoms and smoking cessation after hospitalization for cardiovascular disease. *Arch Intern Med* 168: 186, 2008.
 185. Gostin LO: Global regulatory strategies for tobacco control (commentary). *JAMA* 299: 763, 2008.
 186. Epstein RS: What's needed for personalized therapy in smoking cessation. *Clin Pharm Therap* 84: 309, 2008.
 187. Frishman WH: Smoking cessation pharmacotherapy: nicotine and non-nicotine preparations. *Prevent Cardiol Spring*: 10, 2007.
 188. Frishman WH, Mitta W, Kupersmith A, Ky T: Nicotine and non-nicotine smoking cessation pharmacotherapies. *Cardiol in Rev* 14: 57, 2006.
 189. Kendler KS, Neale MC, Sullivan P, et al: A population-based twin study in women of smoking initiation and nicotine dependence. *Psychol Med* 29: 299, 1999.
 190. Shields AE, Blumenthal D, Weiss KB, et al C: Barriers to translating emerging genetic research on smoking into clinical practice. Perspectives of primary care physicians. *J Gen Intern Med* 20:131, 2005.
 191. Glantz LH, Annas GJ: Tobacco, the Food and Drug Administration, and Congress. *N Engl J Med* 343:1802, 2000.
 192. True WR, Xian H, Scherrer JF, et al: Common genetic vulnerability for nicotine and alcohol dependence in men. *Arch Gen Psychiatry* 56: 655, 1999.
 - 192a. Chandler MA, Rennard SI: Smoking cessation. *Chest* 137: 428, 2010.
 193. Rosner SA, Stampfer MJ: The heart-breaking news about tobacco: it's all bad. *Lancet* 368: 621, 2006.
 194. Kessler D. *A Question of Intent: A Great American Battle with a Deadly Industry*. New York: Public Affairs, 2001.
 195. Curfman GD, Morrissey S, Drazen JM: Tobacco, public health, and the FDA. *N Engl J Med* 361: 402, 2009.
 196. Leischow SJ: Setting the national tobacco control

- agenda. *JAMA* 301: 1058, 2009.
197. Bayer R, Kelly M: Tobacco control and free speech—an American dilemma. *N Engl J Med* 362: 281, 2010.
198. Gostin LO: FDA regulation of tobacco. Politics, law, and the public's health. *JAMA* 302: 1459, 2009.

References for Chapter 23

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1. Ogden CL, Carroll MD, Curtin LR, et al: Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA* 295:1549,2006.
2. National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity, and health risk. *Arch Intern Med* 160: 898,2000.
3. Parikh NI, Pencina MJ, Wang TJ, et al: Increasing trends in incidence of overweight and obesity over 5 decades. *Am J Med* 120:242,2007.
4. Hedley AA, Ogden CL, Johnson CL, et al: Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA* 291: 2847, 2004.
5. Flegal KM. Epidemiologic aspects of overweight and obesity in the United States. *Physiol Behav* 86:599,2005.
6. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA* 288:1723,2002.
7. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL: Overweight and obesity in the United States: prevalence and trends, 1960-1994. *Int J Obes Relat Metab Disord* 22:39,1998.
8. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL: Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA* 272:205,1994.
9. Supt. of Documents: Healthy People 2000. 017-001-00474-0, 1990. Washington, DC 20402-9325, Government Printing Office.
10. Supt of Documents: Healthy People 2010. 017-001-00547-9, 2000. Washington, DC 20402-9325. Government Printing Office.
11. Visser M, Bouter LM, McQuillan GM, et al: Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 282: 2131,1999.
12. Rea TD, Heckbert SR, Kaplan RC, et al: Body mass index and the risk of recurrent coronary events following acute myocardial infarction. *Am J Cardiol* 88: 467,2001.
13. Pickering TG: Obesity and hypertension: a growing problem. *J Clin Hypertens* 3: 252,2001.
14. Stevens V, Obarzanek E, Cook N, et al: Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, Phase II. *Ann Intern Med* 134:1,2001.
15. Liu S, Manson JE: Dietary carbohydrates, physical inactivity, obesity, and the "metabolic syndrome" as predictors of coronary heart disease. *Curr Opin Lipidol* 12: 395, 2001.
16. Field AE, Coakley EH, Must A, et al: Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med* 161: 1581,2001.
17. Stein PD, Beemath A, Olson RE: Obesity as a risk factor in venous thromboembolism. *Am J Med* 118: 978,2005.
18. Hayashi T, Boyko EJ, Leonetti DL, et al: Visceral adiposity is an independent predictor of incident hypertension in Japanese Americans. *Ann Intern Med* 140: 992,2004.
19. Chinali M, deSimone G, Roman MJ, et al: Impact of obesity on cardiac geometry and function in a population of adolescents. *J Am Coll Cardiol* 47: 2267,2006.
20. Dorbala S, Crugnale S, Yang D, DiCarli MF: Effect of body mass index on left ventricular cavity size and ejection fraction. *Am J Cardiol* 97: 725,2006.
21. Avelar E, Cloward TV, Walker JM, et al: Left ventricular hypertrophy in severe obesity. Interactions among blood pressure, nocturnal hypoxemia and body mass. *Hypertension* 49: 34, 2007.

22. Canoy D, Boekholdt SM, Wareham N, et al: Body fat distribution and risk of coronary heart disease in men and women in the European Prospective Investigation into Cancer and Nutrition in Norfolk Cohort. A population-based prospective study. *Circulation* 116: 2933, 2007.
23. Bogers RP, Bemelmans WJE, Hoogenveen RT, et al for the BMI-CHD Collaboration Investigators: Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels. A meta-analysis of 21 cohort studies including more than 300,000 persons. *Arch Intern Med* 167: 1720, 2007.
24. Wilson PWF, Bozeman SR, Burton TM, et al: Prediction of first events of coronary heart disease and stroke with consideration of adiposity. *Circulation* 118: 124, 2008.
25. Harmancey R, Wilson CR, Taegtmeyer H: Adaptation and maladaptation of the heart in obesity. *Hypertension* 52: 181, 2008.
- 25a. Sui X, LaMonte MJ, Laditka JN, et al: Cardiorespiratory fitness and adiposity as mortality predictors in older adults. *JAMA* 298: 2507, 2007.
26. Zhang C, Rexrode KM, van Dam RM, et al: Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality. Sixteen years of follow-up in US women. *Circulation* 117: 1658, 2008.
27. Burke GL, Bertoni AG, Shea S, et al: The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease. *Arch Intern Med* 168: 928, 2008.
- 27a. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al: Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 363: 2211, 2010.
28. Hill JO, Wyatt HR, Reed GW, Peters JC: Obesity and the environment. Where do we go from here? *Science* 301: 598, 2003.
29. Alley DE, Chang VW: The changing relationship of obesity and disability, 1988-2004. *JAMA* 298: 2020, 2007.
30. Bloomgarden ZT: Diabetes and obesity. *Diabetes Care* 31: 176, 2008.
31. National Institutes of Health, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. *Obes Res* 6(Suppl 2): 51, 1998.
32. Douketis JD, Feightner JW, Attia J, Feldman WF: Periodic health examination, 1999 update: 1. Detection, prevention and treatment of obesity. Canadian Task Force on Preventive Health Care. *Canad Med Assn J* 160:513, 1999.
33. Aronne LJ: Obesity. *Med Clin North Am* 82:161, 1998.
34. Mango V, Frishman WH: Physiologic, psychologic, and metabolic consequences of bariatric surgery. *Cardiol in Rev* 14: 232, 2006.
35. Stunkard AJ: Current views on obesity. *Am J Med* 100:230, 1996.
36. Manson JE, Faich GA: Pharmacotherapy for obesity — do the benefits outweigh the risks? [editorial]. *N Engl J Med* 1996; 335:1996.
37. Bray GA: Evaluation of drugs for treating obesity. *Obes Res* 3 Suppl 4: 425, 1995.
38. Wadden TA, Berkowitz RI, Sarwer DB, et al: Benefits of lifestyle modification in the pharmacologic treatment of obesity. A randomized trial. *Arch Intern Med* 161: 218, 2001.
39. Glazer G: Long-term pharmacotherapy of obesity 2000. A review of efficacy and safety. *Arch Intern Med* 161: 1814, 2001.
40. Andres R, Muller DC, Sorkin JD: Long-term effects of change in body weight on all-cause mortality. A review. *Ann Intern Med* 119(7 Pt 2):737, 1993.
41. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS: The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics* 103(6 Pt 1):1175, 1999.
42. Pi-Sunyer FX: Medical hazards of obesity. *Ann Intern Med* 119(7 Pt 2):655, 1993.
43. Poirier P, Giles TD, Bray GA, et al: Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. An update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 113: 898, 2006.
44. Wong CY, O'Moore-Sullivan T, Leano R, et al: Association of subclinical right ventricular dysfunction with obesity. *J Am Coll Cardiol* 47: 611, 2006.
45. Litwin SE: The growing problem of obesity and the heart. The plot "thickens". Editorial comment. *J Am Coll Cardiol* 47: 617, 2006.
46. Kannel WB, D'Agostino RB, Cobb JL: Effect of weight on cardiovascular disease. *Am J Clin Nutr* 63(3 Suppl):419, 1996.
47. Manson JE, Colditz GA, Stampfer MJ et al: A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med* 322(13):882, 1990.
48. Manson JE, Willett WC, Stampfer MJ et al: Body weight and mortality among women. *N Engl J Med* 333:677, 1995.
49. Lee IM, Paffenbarger-RS J: Change in body weight and longevity. *JAMA* 268:2045, 1992.
50. Lee IM, Manson JE, Hennekens CH, Paffenbarger-RS J: Body weight and mortality. A 27-year follow-

- up of middle-aged men. *JAMA* 270:2823,1993.
51. Colditz GA, Willett WC, Rotnitzky A, Manson JE: Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 122:481,1995.
 52. Stamler R, Stamler J, Riedlinger WF et al: Weight and blood pressure. Findings in hypertension screening of 1 million Americans. *JAMA* 240:1607,1978.
 53. Najarian R, Sullivan L, Kannel W, et al: Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke. *Arch Intern Med*. 166:106,2006.
 54. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 285:2486,2001.
 55. Lee IM, Paffenbarger-RS J: Quetelet's index and risk of colon cancer in college alumni. *J Natl Cancer Inst* 1992; 84:1326,1992.
 56. Wadden TA, Berkowitz RI, Womble LG, et al: Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med* 353: 2111,2006.
 57. Berenson A: A ray of hope for diabetics. This drug helps shed pounds. *New York Times Business Day*, March 2, 2006, C1.
 58. Thompson WG, Cook DA, Clark MM, et al: Treatment of obesity. *Mayo Clin Proc* 82: 93, 2007.
 59. Padwal RS, Majumdar SR: Drug treatments for obesity: orlistat, sibutramine and rimonabant. *Lancet* 369: 71, 2007.
 60. Neff LM, Aronne LJ: Pharmacotherapy for obesity. *Curr Atheroscler Rep* 9: 454, 2007.
 - 60a. Bray GA: Medical therapy for obesity. *Mt. Sinai J Med* 77: 407, 2010.
 61. Blanck HM, Khan LK, Serdula MK: Prescription weight loss pill use among Americans: patterns of pill use and lessons learned from the fen-phen market withdrawal. *Prev Med* 39: 1243, 2004.
 62. Ioannides-Demos L, Proietto J, McNeil J. Pharmacotherapy for obesity. *Drugs* 65:1391,2005.
 63. Carek PJ, Dickerson LM: Current concepts in the pharmacological management of obesity. *Drugs* 57: 883,1999.
 64. Colman, E. Anorectics on trial: A half century of federal regulation of prescription appetite suppressants. *Ann Intern Med* 143:380,2005.
 65. Li Z, Maglione M, Tu W, et al. Meta-analysis: Pharmacologic treatment of obesity. *Ann Intern Med*.142: 532,2005.
 66. Lesses NF, Myerson A: Human autonomic pharmacology: XVI: Benzedrine sulphate as an aid in treatment of obesity. *Obes Res* 2: 286,1994.
 67. Nathanson MH: The central action of beta-amino propylbenzene (Benzedrine): Clinical observations. *JAMA* 108:528,1939.
 68. Frishman WH, Weiser M, Michaelson MD. The pharmacologic approach to the treatment of obesity: past, present and future. In: Frishman WH, Sonnenblick EH (eds). *Cardiovascular Pharmacotherapeutics*. New York: McGraw Hill, 1997: 1093-1114.
 69. Fernandez-Soto ML, Gonzalez-Jimenez A, Barredo-Acedo F et al: Comparison of fluoxetine and placebo in the treatment of obesity. *Ann Nutr Metab* 39:159, 1995.
 70. Sayler ME, Goldstein DJ, Roback PJ, Atkinson RL: Evaluating success of weight loss programs, with an application to fluoxetine weight reduction clinical trial data. *Int J Obes Relat Metab Disord* 18:742,1994.
 71. Goldstein DJ, Rampey-AH J, Enas GG et al: Fluoxetine: a randomized clinical trial in the treatment of obesity. *Int J Obes Relat Metab Disord* 18:129,1994.
 72. Hudson JI, McElroy SL, Raymond NC et al: Fluvoxamine in the treatment of binge-eating disorder: a multicenter placebo-controlled, double-blind trial. *Am J Psychiatry* 1998; 155:1756-62.
 73. Bray GA, Ryan DH, Gordon D et al: A double-blind randomized placebo-controlled trial of sibutramine. *Obes Res* 4:263,1996.
 74. Weintraub M, Rubio A, Golik A et al: Sibutramine in weight control: a dose-ranging, efficacy study. *Clin Pharmacol Ther* 50:330,1991.
 75. Shechter M, Beigel R, Freimark D, et al: Short-term sibutramine therapy is associated with weight loss and improved endothelial function in obese patients with coronary artery disease. *Am J Cardiol* 97: 1650, 2006.
 76. Heusser K, Tank J, Diedrich A, et al: Influence of sibutramine treatment on sympathetic vasomotor tone in obese subjects. *Clin Pharmacol Ther* 79: 500, 2006.
 77. Apfelbaum M, Vague P, Ziegler O et al: Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. *Am J Med* 106:179,1999.
 78. Kaplan L. Pharmacological therapies for obesity. *Gastroenterol Clin N Am* 34:91,2005.
 79. Hauner H, Meier M, Jockel KH, et al: Prediction of successful weight reduction under sibutramine therapy through genotyping of the G-protein $\beta 3$ -subunit gene (GNB3) C825T polymorphism. *Pharmacogenetics* 13: 453,2003.
 80. Wirth A, Krause J: Long-term weight loss with sibutramine: a randomized controlled trial. *JAMA* 286: 1331,2001.
 81. James WPT, Astrup A, Finer N, et al: Effect of

- sibutramine on weight maintenance after weight loss: a randomised trial. *Lancet* 356: 2119,2000.
82. Dujovne CA, Zavoral JH, Rowe E, et al: Effects of sibutramine on body weight and serum lipids: a double-blind, randomized, placebo-controlled study in 322 overweight and obese patients with dyslipidemia. *Am Heart J* 142: 489,2001.
 83. Sánchez-Reyes L, Fanghänel D, Yamamoto J, et al. Use of sibutramine in overweight adult hispanic patients with type 2 diabetes mellitus: a 12-month, randomized, double-blind, placebo-controlled clinical trial. *Clin Therap* 26:1427,2004.
 84. Van Gaal LF, Caterson ID, Coutinho W, et al on behalf of the SCOUT Investigators: Weight and blood pressure response to weight management and sibutramine in diabetic and non-diabetic high-risk patients: an analysis from the 6-week lead-in period of the sibutramine cardiovascular outcomes (SCOUT) trial. *Diabetes Obes Metab* September 16, 2009 (epub ahead of print).
 - 84a. James WPT, Caterson ID, Coutinho W, et al for the SCOUT Investigators: Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 363: 905, 2010.
 - 84b. Sibutramine (Meridia) withdrawn. *The Medical Ltr* 52: 88, 2010.
 85. Scholze J, Grimm E, Herrmann D, et al: Optimal treatment of obesity-related hypertension. The Hypertension-Obesity-Sibutramine (HOS) Study. *Circulation* 115: 1991, 2007.
 86. Davidson MH, Hauptman J, DiGirolamo M et al: Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 1999; 281: 235-42 [published in erratum 281:235,1999.
 87. Richelsen B, Tonstad S, Rössner S, et al: Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients. A 3-year randomized, placebo-controlled trial. *Diabetes Care* 30: 27, 2007.
 88. Heymsfield SB, Segal KR, Hauptman J, et al: Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* 160: 1321,2000.
 89. Lindgärde F. The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: the Swedish Multi-morbidity Study. *J Intern Med* 248: 245,2000.
 90. Swinburn B, Carey D, Hills A, et al. Effect of orlistat on cardiovascular disease risk in obese adults. *Diabetes Obese Meabt*. 7:254,2004.
 91. Ault A: Orlistat gains OTC approval for weight loss. www.cardiologynews.com, March 2007: 7.
 92. Giacobino JP: Beta 3-adrenoceptor: an update. *Eur J Endocrinol* 132:377,1995.
 93. Weyer C, Gautier JF, Danforth E: Development of beta 3-adrenoceptor agonists for the treatment of obesity and diabetes—an update. *Diabetes Metab* 25:11,1999.
 94. Kordik CP, Reitz AB: Pharmacological treatment of obesity: therapeutic strategies. *J Med Chem* 42:181,1999.
 95. Arner P: The beta 3-adrenergic receptor—a cause and cure of obesity? [editorial comment]. *N Engl J Med* 333: 382,1995.
 96. van Marken Lichtenbelt WD, Vanhommelrig JW, Smulders NM, et al: Cold-activated brown adipose tissue in healthy men. *N Engl J Med* 360: 1500,2009.
 97. Cypess AM, Lehman S, Williams G, et al: Identification and importance of brown adipose tissue in adult humans. *N Engl J Med* 360: 1509, 2009.
 98. Virtanen KA, Lidell ME, Orava J, et al: Functional brown adipose tissue in healthy adults. *N Engl J Med* 360: 1518, 2009.
 99. Langin D: Recruitment of brown fat and conversion of white into brown adipocytes: strategies to fight the metabolic complications of obesity? *Biochim Biophys Acta* September 24, 2009 epub ahead of print.
 100. Strosberg AD: Structure and function of the beta 3-adrenergic receptor. *Annu Rev Pharmacol Toxicol* 37:421,1997.
 101. Goldberg DE, Frishman WH. *β₃-Adrenergic Agonism: A New Concept in Human Pharmacotherapy*. New York: Futura, 1995.
 102. Widen E, Lehto M, Kanninen T et al: Association of a polymorphism in the beta 3-adrenergic-receptor gene with features of the insulin resistance syndrome in Finns. *N Engl J Med* 333: 348,1995.
 103. Clement K, Vaisse C, Manning BS et al: Genetic variation in the beta 3-adrenergic receptor and an increased capacity to gain weight in patients with morbid obesity. *N Engl J Med* 333: 352,1995.
 104. Walston J, Silver K, Bogardus C et al: Time of onset of non-insulin-dependent diabetes mellitus and genetic variation in the beta 3-adrenergic-receptor gene. *N Engl J Med* 333: 343,1995.
 105. Mitchell BD, Blangero J, Comuzzie AG et al: A paired sibling analysis of the beta-3 adrenergic receptor and obesity in Mexican Americans. *J Clin Invest* 101:584,1998.
 106. Hsueh W-C, Cole SA, Shuldiner AR, et al: Interactions between variants in the β₃-adrenergic receptor and peroxisome proliferator-activated receptor-γ2 genes and obesity. *Diabetes Care* 24: 672,2001.
 107. Mantzoros CS: The role of leptin in human obesity and disease: A review of current evidence. *Ann In-*

- tern Med* 130:671,1999.
108. Bray GA, York DA: Clinical review 90: Leptin and clinical medicine: a new piece in the puzzle of obesity. *J Clin Endocrinol Metab* 1997; 82:2771-76 [erratum published 82: 2771,1997].
 109. Levin B. Factors promoting and ameliorating the development of obesity. *Physiol Behav* 86: 633,2005.
 110. Jackson M, Ahima R. Neuroendocrine and metabolic effects of adipocyte-derived hormones. *Clin Sci* 110: 143,2006.
 111. Farooqi IS, Jebb SA, Langmack G et al: Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med* 341:879,1999.
 112. Heymsfield SB, Greenberg AS, Fujioka K et al: Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA* 282:1568,1999.
 113. Wang MY, Orci L, Ravazzola M, Unger RH. Fat storage in adipocytes requires inactivation of leptin's paracrine activity: Implications for treatment of human obesity. *Proc Natl Acad Sci* 102: 18011,2005.
 114. Dotsch J, Rascher W, Meissner U. New insights into leptin resistance by modifying cytokine receptor signal transduction. *Eur J Endocrinol.* 152:333,2005.
 115. Howard JK, Cave BJ, Oksanen LJ, et al. Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of Socs3. *Nature Med.* 10:734,2004.
 116. Mori H, Hanada R, Hanada T, et al. Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. *Nature Medicine.* 10:739,2004.
 117. Gadde KM, Allison DB: Cannabinoid-1 receptor antagonist, rimonabant, for management of obesity and related risks. *Circulation* 114: 974, 2006.
 118. Korner J, Aronne L. Pharmacological approaches to weight reduction: Therapeutic targets. *J Clin Endocrinol Metab* 89: 2616,2004.
 119. Després J, Golley A, Sjöström L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med.* 353: 2121,2005.
 120. Van Gaal L, Rissanen A, Scheen A, et al. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 365: 1389, 2005.
 121. Wilding J. Clinical evaluation of anti-obesity drugs. *Curr Drug Targets.* 5: 325,2005.
 122. Carai M, Colombo G, Gessa G. Rimonabant: The first therapeutically relevant cannabinoid antagonist. *Life Sci* 77:2339,2005.
 123. Jbilo O, Ravinet-Trillou C, Arnone M, et al. The CB1 receptor antagonist rimonabant reverses the diet-induced obesity phenotype through the regulation of lipolysis and energy balance. *FASEB J.* 19: 1567,2005.
 124. Gelfand EV, Cannon CP: Rimonabant: a cannabinoid receptor type 1 blocker for management of multiple cardiometabolic risk factors. *J Am Coll Cardiol* 47: 1919,2006.
 125. Bays H. Current and investigational antiobesity agents and obesity therapeutic treatment targets. *Obes Res.* 12: 1197, 2004.
 126. Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al for the RIO-North America Study Group: Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients. RIO-North America: a randomized controlled trial. *JAMA* 295: 761,2006.
 127. Wadman M. Rimonabant adds appetizing choice to slim obesity market. *Nature Med* 12: 27, 2006.
 - 127a. Smith SR, Weissman NJ, Anderson CM, et al: Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 363: 245, 2010.
 128. Davidson MB, Peters AL: An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med* 102: 99,1997.
 129. Garber AJ, Duncan TG, Goodman AM et al: Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med* 103:491,1997.
 130. Turner RC, Cull CA, Frighi V, Holman RR: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 281:2005,1999.
 131. Inzucchi SE, Maggs DG, Spollett GR et al: Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 338:867,1998.
 132. Lee A, Morley JE: Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin-dependent diabetes. *Obes Res* 6:47,1998.
 133. Hoffmann J, Spengler M: Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II Study. *Am J Med* 103: 483,1997.
 134. Giugliano D, De-Rosa N, Di-Marco G et al: Metformin improves glucose, lipid metabolism, and reduces blood pressure in hypertensive, obese women. *Diabetes Care* 16:1387,1993.
 135. Campbell IW, Menzies DG, Chalmers J et al: One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. *Diabete Metab*

- 20:394,1994.
136. Wu R-R, Zhao J-P, Jin H, et al: Lifestyle intervention and metformin for treatment of anti-psychotic-induced weight gain. A randomized controlled trial. *JAMA* 299:185,2008.
 137. Mogul HR, Peterson SJ, Weinstein BI, et al: Metformin and carbohydrate-modified diet, a novel obesity treatment protocol: preliminary findings from a case series of non-diabetic women with midlife weight gain and hyperinsulinemia. *Heart Dis* 3: 285, 2001.
 138. Munro JF, MacCuish AC, Marshall A et al: Weight-reducing effect of diguanides in obese non-diabetic women. *Br Med J* 2: 13,1969.
 139. Fontbonne A, Charles MA, Juhan Vague I et al: The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. BIG-PRO Study Group. *Diabetes Care* 19:920,1996.
 140. Mogul HR, Peterson SJ, Weinstein BI, et al: Long-term (2-4 year) weight reduction with metformin plus carbohydrate-modified diet in euglycemic, hyperinsulinemic, midlife women (Syndrome W). *Heart Dis* 5: 384,2003.
 141. Freemark M, Bursey D: The effects of metformin on Body Mass Index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. *Pediatrics* 107(4):e55,2001.
 142. Hadigan C, Corcoran C, Basgoz N et al: Metformin in the treatment of HIV lipodystrophy syndrome: A randomized controlled trial. *JAMA* 284:472,2000.
 143. Crave JC, Fimbel S, Lejeune H et al: Effects of diet and metformin administration on sex hormone-binding globulin, androgens, and insulin in hirsute and obese women. *J Clin Endocrinol Metab* 80:2057,1995.
 144. Glueck CJ, Wang P, Fontaine R et al: Metformin-induced resumption of normal menses in 39 of 43 (91%) previously amenorrheic women with the polycystic ovary syndrome. *Metabolism* 48:511,1999.
 145. Casimirri F, Biscotti M, Gambineri A: Metformin improves insulin, body fat distribution, and androgens in obese women with and without the polycystic ovary syndrome (abstract). *Int J Obes* 21:S61,1997.
 146. Nestler JE, Jakubowicz DJ: Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med* 335:617,1996.
 147. Moghetti P, Castello R, Negri C et al: Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab* 85:139,2000.
 148. Arslanian SA, Lewy V, Danadian K, Saad R: Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. *J Clin Endocrinol Metab* 87: 1555,2002.
 149. Glueck CJ, Goldenberg N, Wang P, et al: Metformin during pregnancy reduces insulin, insulin resistance, insulin secretion, weight, testosterone and development of gestational diabetes: prospective longitudinal assessment of women with polycystic ovary syndrome from preconception throughout pregnancy. *Human Reprod* 19: 510,2004.
 150. Harborne LR, Sattar N, Norman JE, Fleming R: Metformin and weight loss in obese women with polycystic ovary syndrome: comparison of doses. *J Clin endocrinol Metab* 90: 4593,2005.
 151. Ibanez L, Lopez-Bermejo A, Diaz M, et al: Metformin treatment for four years to reduce total and visceral fat in low birth weight girls with precocious pubarche. *J Clin Endocrinol Metab* 93: 1841, 2008.
 152. Dunn CJ, Peters DH: Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 49:721,1995.
 153. Paolisso G, Amato L, Eccellente R et al: Effect of metformin on food intake in obese subjects. *Eur J Clin Invest* 28:441,1998.
 154. Boden G, Chen X, Ruiz J et al: Mechanisms of fatty acid-induced inhibition of glucose uptake. *J Clin Invest* 93:2438,1994.
 155. Abbasi F, Kamath V, Rizvi AA et al: Results of a placebo-controlled study of the metabolic effects of the addition of metformin to sulfonylurea-treated patients. Evidence for a central role of adipose tissue. *Diabetes Care* 20:1863,1997.
 156. Boden G, Chen X, Iqbal N: Acute lowering of plasma fatty acids lowers basal insulin secretion in diabetic and nondiabetic subjects. *Diabetes* 47:1609,1998.
 157. Boden G, Chen X: Effects of fatty acids and ketone bodies on basal insulin secretion in type 2 diabetes. *Diabetes* 48:577,1999.
 158. Lee ZSK, Chan JCN, Yeung VT et al: Plasma insulin, growth hormone, cortisol, and central obesity among young Chinese Type 2 diabetic patients. *Diabetes Care* 22:1450,1999.
 159. Mather KJ, Verma S, Anderson TJ: Improved endo-

- thelial function with metformin in type 2 diabetes mellitus. *J Am Coll Cardiol* 37:1344,2001.
160. Charles MA, Morange P, Eschwege E et al: Effect of weight change and metformin on fibrinolysis and the von Willebrand factor in obese nondiabetic subjects: the BIGPRO1 Study. Biguanides and the Prevention of the Risk of Obesity. *Diabetes Care* 21:1967,1998.
 161. DeFronzo RA, Ratner RE, Han J, et al: Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28: 1092,2005.
 162. Exenatide (Byetta) for type 2 diabetes. *The Medical Letter* 47: 45,2005.
 163. Lam S, See S: Exenatide. A novel incretin mimetic agent for treating type 2 diabetes mellitus. *Cardiol in Rev* 14: 205,2006.
 - 163a. Astrup A, Rössner S, Van Gaal L, et al: Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 374: 1606, 2009.
 164. Whitehouse F, Kruger DF, Fineman M, et al: A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care* 24: 724,2002.
 165. Hollander PA, Levy P, Fineman MS, et al: Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 26: 784,2003.
 166. Ratner RE, Dickey R, Fineman M, et al: Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in type 1 diabetes mellitus: a one year randomized controlled trial. *Diabetes Med* 21: 1204,2004.
 167. Hollander PA, Maggs DG, Ruggles JA, et al: Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. *Obes Res* 12: 661,2004.
 168. Gordon A, Price LH: Mood stabilization and weight loss with topiramate. *Am J Psychiatry* 156:968,1999.
 169. Ben-Menachem E, Axelsen M, Johanson EH, et al. Predictors of weight loss in adults with topiramate-treated epilepsy. *Obes Res.* 11: 556,2003.
 170. Astrup A, Toubro S. Topiramate: a new potential pharmacological treatment for obesity. *Obes. Res.* 12(12) Suppl: 167S,2004.
 171. Bray GA, Hollander P, Klein S, et al. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obes Res.* 11:722,2003.
 172. Astrup A, Caterson I, Zelissen P, et al. Topiramate: Long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. *Obes. Res.* 12: 1658,2004.
 173. Wilding J, Van Gaal L, Rissanen A, et al. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. *Intl J Obesity* 28: 1399,2004.
 174. Gadde KM, Francis DM, Wagner HR 2nd, Krishman KR. Zonisamide for weight loss in obese adults: a randomized controlled trial. *JAMA.* 289:1820,2003.
 175. Appolinario J, Bueno J, Coutinho W. Psychotropic drugs in the treatment of obesity - What promise? *CNS Drugs* 18: 629,2004.
 176. Gadde KM, Parker CB, Maner LG, et al. Bupropion for weight loss: an investigation of efficacy and tolerability in overweight and obese women. *Obes Res* 9: 544,2001.
 177. Anderson JW, Greenway FL, Fujioka K, et al. Bupropion SR enhances weight loss: a 48-week double-blind, placebo-controlled trial. *Obes Res* 10: 633, 2002.
 - 177a. Greenway FL, Fujioka K, Plodkowski RA, et al: Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 376: 595, 2010.
 - 177b. Pollack A: F.D.A. panel backs drug to treat obesity. *NY Times* December 8, 2010.
 178. Cuneo RC, Judd S, Wallace JD et al: The Australian Multicenter Trial of Growth Hormone (GH) Treatment in GH-Deficient Adults. *J Clin Endocrinol Metab* 83:107,1998.
 179. Gura T: Uncoupling proteins provide new clue to obesity's causes [news]. *Science* 280:1369, 1998.
 180. Gimeno RE, Dembski M, Weng X et al: Cloning and characterization of an uncoupling protein homolog: a potential molecular mediator of human thermogenesis. *Diabetes* 46:900,1997.
 181. Gong DW, He Y, Karas M, Reitman M: Uncoupling protein-3 is a mediator of thermogenesis regulated by thyroid hormone, beta3-adrenergic agonists, and leptin. *J Biol Chem* 272: 24129,1997.
 182. Fleury C, Neverova M, Collins S et al: Uncoupling protein-2: a novel gene linked to obesity and hyperinsulinemia. *Nat Genet* 15:269,1997.
 183. Gura T: Enzyme blocker prompts mice to shed weight. *Science* 288: 2299,2000.
 184. Bouchard C: Inhibition of food intake by inhibitors of fatty acid synthase. *N Engl J Med* 343: 1888, 2000.
 185. Kuhajda F, Landreth L, Ronnett G. The connections between C75 and obesity drug-target pathways. *Trends in Pharmacol Sci.* 26:541,2005.

186. Leonhardt M, Hrupka B, Langhans W: New approaches in the pharmacological treatment of obesity. *Eur J Nutri* 38:1,1999.
187. Campfield LA, Smith FJ, Burn P: Strategies and potential molecular targets for obesity treatment. *Science* 280:1383,1998.
188. Chaudhri OB, Wynne K, Bloom SR: Can gut hormones control appetite and prevent obesity? *Diabetes Care* 31(Suppl 2): S284,2008.
189. Zimanyi IA, Fathi Z, Poindexter GS: Central control of feeding behavior by neuropeptide Y. *Curr Pharm Des* 4:349,1998.
190. Borowsky B, Walker MW, Bard J et al: Molecular biology and pharmacology of multiple NPY Y5 receptor species homologs. *Regul Pept* 75-76:45,1998.
191. Wisse BE, Schwartz MW: Role of melanocortins in control of obesity. *Lancet* 358: 857,2001.
192. Balasubramaniam A. Clinical potentials of neuropeptide Y family of hormones. *Am J Surg.* 4: 430,2002.
193. Wieland HA, Hamilton BS, Drist B, Doods HN. The role of NPY in metabolic homeostasis: implications for obesity therapy. *Invest Drugs.* 9: 1327,2000.
194. Sherman CB, Peterson SJ, Frishman WH: Apolipoprotein A-I mimetic peptides: a potential new therapy for the prevention of atherosclerosis. *Cardiol in Rev* 18: 141, 2010.
195. Hallschmid M, Benedicta C, Borna J, et al. Manipulating central nervous mechanisms of food intake and body weight regulation by intranasal administration of neuropeptides in man. *Physiol Behav* 83:55,2004.
196. Blüher S, Ziotopoulou M, Bullen J, et al. Responsiveness to peripherally administered melanocortins in lean and obese mice. *Diabetes* 53:82,2004.
197. Batterham RL, Cowley MA, Small CJ, et al. Gut hormone PYY 3-36 physiologically inhibits food intake. *Nature* 418:650,2002.
198. Batterham RL, Cohen MA, Ellis SM, et al. Inhibition of food intake in obese subjects by peptide YY3-36. *N Engl J Med* 349:941,2003.
199. Hansen TK, Dall R, Hosoda H, et al. Weight loss increases circulating levels of ghrelin in human obesity. *Clin Endocrinol* 56:203,2002.
200. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* 346:1623,2002.
201. Christophe J: Is there appetite after GLP-1 and PACAP? *Ann N Y Acad Sci* 865:323,1998.
202. Nakazato M, Murakami N, Date Y et al: A role for ghrelin in the central regulation of feeding. *Nature* 409:194,2001.
203. Shintani M, Ogawa Y, Ebihara K et al: Ghrelin, an endogenous growth hormone secretagogue, is a novel orexigenic peptide that antagonizes leptin action through the activation of hypothalamic neuropeptide Y/Y1 receptor pathway. *Diabetes* 50:227,2001.
204. Cummings DE, Purnell JQ, Frayo RS et al: A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes* 50:1714,2001.
205. Riley E, Dasari V, Frishman WH, Sperber K: Vaccines in development to prevent and treat atherosclerotic disease. *Cardiol in Rev* 16: 288, 2008.
206. Lambert PD, Anderson KD, Sleeman MW et al: Ciliary neurotrophic factor activates leptin-like pathways and reduces body fat, without cachexia or rebound weight gain, even in leptin-resistant obesity. *Proc Natl Acad Sci U S A* 98:4652,2001.
207. Ettinger MP, Littlejohn TW, Schwartz SL, et al. Recombinant ciliary neurotrophic factor for weight loss in obese adults: a randomized dose-ranging study. *JAMA* 289:1826,2003.
208. Coffin S, Konduru C, Schwarcz M, Frishman WH: Surgical approaches for the prevention and treatment of type 2 diabetes mellitus. *Cardiol in Rev* 17: 275, 2009.
209. Palamara KL, Mogul HR, Peterson SJ, Frishman WH: Obesity: new perspectives and pharmacotherapies. *Cardiol in Rev* 14: 238, 2006.
210. McNeely W, Goa KL. Better Than Slim Chances for Orlistat and Sibutramine to Promote Weight Loss. *Drugs & Therapy Perspectives.* 2000;15(12):1-6; 4.

References for Chapter 24

Heart Disease and Treatment of Diabetes Mellitus

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1. 2007 National Diabetes Fact Sheet. [CDC Website] Available at: <http://apps.nccd.cdc.gov/DDTSTRS/default.aspx>. Accessed February 26, 2009.
2. Haffner SM, Lehto S, Ronnema T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 339:229, 1998.
- 2a. Gerstein HC: More insights on the dysglycaemia-cardiovascular connection. *Lancet* 375: 2195, 2010.
3. Fox CS, Coady S, Sorlie PD, et al: Trends in cardiovascular complications of diabetes. *JAMA.* 292:2495, 2004.
- 3a. Laakso M: Cardiovascular disease in type 2 diabetes from population to man to mechanisms. The Kelly West Award Lecture 2008. *Diabetes Care* 33: 442, 2010.
- 3b. Selvin E, Steffes MW, Zhu H, et al: Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 362: 800, 2010.
4. Selvin E, Marinopoulos S, Berkenblit G, et al: Meta-analysis: Glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med.* 141:421, 2004.
5. Khaw KT, Wareham N, Bingham S, et al: Association of hemoglobin A1c with cardiovascular disease and mortality in adults: The European prospective investigation into cancer in Norfolk. *Ann Intern Med.* 141:413, 2004.
6. Selvin E, Coresh J, Golden SH, et al: Glycemic control and coronary heart disease risk in persons with and without diabetes: The atherosclerosis risk in communities study. *Arch Intern Med.* 165:1910, 2005.
7. Selvin E, Coresh J, Golden SH, et al: Glycemic control, atherosclerosis, and risk factors for cardiovascular disease in individuals with diabetes: The atherosclerosis risk in communities study. *Diabetes Care.* 28:1965, 2005.
8. Ravipati G, Aronow WS, Ahn C, et al: Association of diet alone, insulin, sulfonylureas, metformin, and thiazolidinediones with the severity of coronary artery disease in patients with diabetes mellitus. *Am J Ther.* 13:400, 2006.
9. Loubatieres A: The mechanism of action of the hypoglycemic sulfonamides; a concept based on investigations in animals and in man. *Diabetes.* 6:408, 1957.
10. Siconolfi-Baez L, Banerji MA, Lebovitz HE: Characterization and significance of sulfonylurea receptors. *Diabetes Care.* 13 Suppl 3:2, 1990.
11. Aguilar-Bryan L, Nichols CG, Wechsler SW, et al: Cloning of the beta cell high-affinity sulfonylurea receptor: A regulator of insulin secretion. *Science* 268:423, 1995.
12. Groop L, Groop PH, Stenman S, et al: Comparison of pharmacokinetics, metabolic effects and mechanisms of action of glyburide and glipizide during long-term treatment. *Diabetes Care* 10:71, 1987.
13. Simonson DC, Kourides IA, Feinglos M, et al: Efficacy, safety, and dose-response characteristics of glipizide gastrointestinal therapeutic system on glycemic control and insulin secretion in NIDDM. results of two multicenter, randomized, placebo-controlled clinical trials. the glipizide gastrointestinal therapeutic system study group. *Diabetes Care* 20:597, 1997.
14. Shorr RI, Ray WA, Daugherty JR, et al: Individual sulfonylureas and serious hypoglycemia in older people. *J Am Geriatr Soc* 44:751, 1996.
15. Meinert CL, Knatterud GL, Prout TE, et al: A study of the effects of hypoglycemic agents on vascular

- complications in patients with adult-onset diabetes. II. mortality results. *Diabetes* 19:Suppl:789, 1970.
16. Garratt KN, Brady PA, Hassinger NL, et al: Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 33:119, 1999.
 17. Huizar JF, Gonzalez LA, Alderman J, et al: Sulfonylureas attenuate electrocardiographic ST-segment elevation during an acute myocardial infarction in diabetics. *J Am Coll Cardiol* 42:1017, 2003.
 18. Simpson SH, Majumdar SR, Tsuyuki RT, et al: Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: A population-based cohort study. *CMAJ* 174:169, 2006.
 19. Brady PA, Terzic A: The sulfonylurea controversy: More questions from the heart. *J Am Coll Cardiol* 31:950, 1998.
 20. Bell DS: Do sulfonylurea drugs increase the risk of cardiac events? *CMAJ* 174:185, 2006.
 21. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK prospective diabetes study (UKPDS) group. *Lancet* 352:837, 1998.
 22. Selvin E, Bolen S, Yeh HC, et al: Cardiovascular outcomes in trials of oral diabetes medications: A systematic review. *Arch Intern Med* 168:2070, 2008.
 23. Dornhorst A: Insulinotropic meglitinide analogues. *Lancet* 358:1709, 2001.
 24. Sunaga Y, Gonoi T, Shibasaki T, et al: The effects of mitiglinide (KAD-1229), a new anti-diabetic drug, on ATP-sensitive K⁺ channels and insulin secretion: Comparison with the sulfonylureas and nateglinide. *Eur J Pharmacol* 431:119, 2001.
 25. Black C, Donnelly P, McIntyre L et al: Meglitinide Analogues for Type 2 Diabetes Mellitus. *Cochrane database Syst Rev* April 18, 2007.
 26. Esposito K, Giugliano D, Nappo F, et al: Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation*. 110:214, 2004.
 27. Rizzo MR, Barbieri M, Grella R, et al: Repaglinide has more beneficial effect on cardiovascular risk factors than glimepiride: Data from meal-test study. *Diabetes Metab* 31:255,2005.
 - 27a. The NAVIGATOR Study Group: Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med* 362: 1463, 2010.
 - 27b. Nathan DM: Navigating the choices for diabetes prevention. *N Engl J Med* 362: 1533, 2010.
 28. Kawamori R, Tajima A, Iwamoto Y, et al: Voglibose for prevention of type 2 diabetes mellitus: a randomized, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet* 373: 1607, 2009.
 29. Inzucchi SE: Oral antihyperglycemic therapy for type 2 diabetes: Scientific review. *JAMA* 287:360, 2002.
 30. Chiasson JL, Josse RG, Gomis R, et al: Acarbose for prevention of type 2 diabetes mellitus: The STOP-NIDDM randomised trial. *Lancet* 359:2072, 2002.
 31. Chiasson JL, Josse RG, Gomis R, et al: Acarbose for the prevention of type 2 diabetes, hypertension and cardiovascular disease in subjects with impaired glucose tolerance: Facts and interpretations concerning the critical analysis of the STOP-NIDDM trial data. *Diabetologia* 47:969, 2004; discussion 976-7.
 32. Hanefeld M, Chiasson JL, Koehler C, et al: Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance. *Stroke* 35:1073, 2004.
 33. Van de Laar FA, Lucassen PL, Akkermans RP, et al: Alpha-glucosidase inhibitors for patients with type 2 diabetes: Results from a Cochrane systematic review and meta-analysis. *Diabetes Care* 28:154,2005.
 34. Scheen AJ: Clinical efficacy of acarbose in diabetes mellitus: A critical review of controlled trials. *Diabetes Metab* 24:311,1998.
 35. Nathan DM, Buse JB, Davidson MB, et al: Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 29:1963, 2006.
 36. Cusi K, Consoli A, DeFronzo RA: Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 81:4059, 1996.
 37. Hundal RS, Krssak M, Dufour S, et al: Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes* 49:2063, 2000.
 38. Johnson AB, Webster JM, Sum CF, et al: The impact of metformin therapy on hepatic glucose production and skeletal muscle glycogen synthase activity in overweight type II diabetic patients. *Metabolism* 42:1217, 1993.
 39. Razani B, Chakravarthy MV, Semenkovich CF: Insulin resistance and atherosclerosis. *Endocrinol Metab Clin North Am* 37:603, 2008.
 40. Nagi DK, Yudkin JS: Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects. A study of two ethnic groups. *Diabetes* 42:1017, 1993.

- betes Care* 16:621, 1992.
41. Mather KJ, Verma S, Anderson TJ: Improved endothelial function with metformin in type 2 diabetes mellitus. *J Am Coll Cardiol* 37:1344, 2001.
 42. Jadhav S, Ferrell W, Greer IA, et al: Effects of metformin on microvascular function and exercise tolerance in women with angina and normal coronary arteries: A randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 48:956, 2006.
 43. Golay A: Metformin and body weight. *Int J Obes (Lond)*. 32:61, 2008.
 44. Garber AJ, Duncan TG, Goodman AM, et al: Efficacy of metformin in type II diabetes: Results of a double-blind, placebo-controlled, dose-response trial. *Am J Med*. 103:491, 1997.
 45. Bailey CJ, Turner RC: Metformin. *N Engl J Med* 334:574, 1996.
 46. Masoudi FA, Inzucchi SE, Wang Y, et al: Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: An observational study. *Circulation* 111:583, 2005.
 47. Eurich DT, Majumdar SR, McAlister FA, et al: Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care* 28:2345, 2005.
 48. Tahrani AA, Varughese GI, Scarpello JH, et al: Metformin, heart failure, and lactic acidosis: Is metformin absolutely contraindicated? *BMJ* 335:508, 2007.
 49. McCormack J, Johns K, Tildesley H: Metformin's contraindications should be contraindicated. *CMAJ* 173:502, 2005.
 50. Fantus IG: Metformin's contraindications: Needed for now. *CMAJ* 173:505, 2005.
 51. Holstein A, Stumvoll M: Contraindications can damage your health—is metformin a case in point? *Diabetologia* 48:2454, 2005.
 52. Bodmer M, Meier C, Krahenbuhl S, et al: Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: A nested case-control analysis. *Diabetes Care* 31:2086, 2008.
 53. Rachmani R, Slavachevski I, Levi Z, et al: Metformin in patients with type 2 diabetes mellitus: Reconsideration of traditional contraindications. *Eur J Intern Med*. 13:428, 2002.
 54. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK prospective diabetes study (UKPDS) group. *Lancet* 352:854,1998.
 55. vans JM, Ogston SA, Emslie-Smith A, et al: Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: A comparison of patients treated with sulfonylureas and metformin. *Diabetologia* 49:930,2006.
 56. Johnson JA, Majumdar SR, Simpson SH, et al: Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. *Diabetes Care* 25:2244,2002.
 57. Chiarelli F, Di Marzio D: Peroxisome proliferator-activated receptor-gamma agonists and diabetes: Current evidence and future perspectives. *Vasc Health Risk Mgmt* 4:297,2008.
 58. Yki-Jarvinen H: Thiazolidinediones. *N Engl J Med* 351:1106,2004.
 59. McGuire DK, Inzucchi SE: New drugs for the treatment of diabetes mellitus. Part I: Thiazolidinediones and their evolving cardiovascular implications. *Circulation* 117: 440, 2008.
 60. Deeks ED, Keam SJ: Rosiglitazone. A review of its use in type 2 diabetes mellitus. *Drugs* 67: 2747, 2007.
 61. Nakamura T, Funahashi T, Yamashita S, et al: Thiazolidinedione derivative improves fat distribution and multiple risk factors in subjects with visceral fat accumulation—double-blind placebo-controlled trial. *Diabetes Res Clin Pract* 54:181,2001.
 62. Mayerson AB, Hundal RS, Dufour S, et al: The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes* 51:797,2002.
 63. Bajaj M, Suraamornkul S, Pratipanawatr T, et al: Pioglitazone reduces hepatic fat content and augments splanchnic glucose uptake in patients with type 2 diabetes. *Diabetes* 52:1364,2003.
 64. Lebovitz HE, Kreider M, Freed MI: Evaluation of liver function in type 2 diabetic patients during clinical trials: Evidence that rosiglitazone does not cause hepatic dysfunction. *Diabetes Care* 25:815,2002.
 65. Ali AA, Weinstein RS, Stewart SA, et al: Rosiglitazone causes bone loss in mice by suppressing osteoblast differentiation and bone formation. *Endocrinology* 146:1226,2005.
 66. Schwartz AV, Sellmeyer DE, Vittinghoff E, et al: Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab* 91:3349,2006.
 67. Yaturu S, Bryant B, Jain SK: Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men. *Diabetes Care* 30:1574,2007.
 68. Grey A, Bolland M, Gamble G, et al: The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: A randomized, controlled trial. *J Clin Endocrinol Metab* 92:1305,2007.
 69. Guan Y, Hao C, Cha DR, et al: Thiazolidinediones

- expand body fluid volume through PPAR gamma stimulation of ENaC-mediated renal salt absorption. *Nat Med* 11:861, 2005.
70. Delea TE, Edelsberg JS, Hagiwara M, et al: Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: A retrospective cohort study. *Diabetes Care* 26:2983,2003.
71. Inzucchi SE, Masoudi FA, Wang Y, et al: Insulin-sensitizing antihyperglycemic drugs and mortality after acute myocardial infarction: Insights from the National Heart Care Project. *Diabetes Care* 28:1680,2005.
72. Home PD, Pocock SJ, Beck-Nielsen H, et al: Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med* 357:28,2007.
73. Home PD, Pocock SJ, Beck-Nielsen H, et al for the RECORD Study Team: Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 373: 2125, 2009.
74. Lago RM, Singh PP, Nesto RW: Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: A meta-analysis of randomised clinical trials. *Lancet* 370:1129, 2007.
75. Singh S, Loke YK, Furberg CD: Long-term risk of cardiovascular events with rosiglitazone: A meta-analysis. *JAMA* 298:1189,2007.
76. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE: Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. A meta-analysis of randomized trials. *JAMA* 298; 1180, 2007.
77. Dargie HJ, Hildebrandt PR, Riegger GA, et al: A randomized, placebo-controlled trial assessing the effects of rosiglitazone on echocardiographic function and cardiac status in type 2 diabetic patients with New York Heart Association functional class I or II heart failure. *J Am Coll Cardiol* 49:1696,2007.
78. Manufacturers of some diabetes drugs to strengthen warning on heart failure risk. [FDA NEWS website] August 14, 2007 Available at: <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01683.html> Accessed February 12, 2009.
79. Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356:2457,2007.
80. Diamond GA, Bax L, Kaul S: Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death. *Ann Intern Med* 147:578,2007.
81. Lipscombe LL, Gomes T, Levesque LE, et al: Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA* 298:2634,2007.
82. BARI 2D Study Group: A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 360: 2503, 2009.
83. Pop-Busui R, Lombardero M, Lavis V, et al and the BARI 2D Study Group: Relation of severe coronary artery narrowing to insulin or thiazolidinedione use in patients with type 2 diabetes mellitus (from the Bypass Angioplasty Revascularization Investigation 2 Diabetes Study). *Am J Cardiol* 104: 52,2009.
- 83a. Rosiglitazone (*Avandia*) revisited. *The Medical Ltr* 52: 17, 2010.
- 83b. Nissen SE, Wolski K: Rosiglitazone revisited. An updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 170: 1191, 2010.
- 83c. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, et al: Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 304: 411, 2010.
84. Ratner RE, Cannon CP, Gerstein HC, et al: Assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history (APPROACH): Study design and baseline characteristics. *Am Heart J* 156: 1074, 2008.
85. Van der Meer RW, Rijzewijk LJ, de Jong HWAM, et al: Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus. *Circulation* 119: 2069, 2009.
86. Nissen SE, Nicholls SJ, Wolski K, et al: Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: The PERISCOPE randomized controlled trial. *JAMA* 299:1561, 2008.
87. Goldberg RB, Kendall DM, Deeg MA, et al: A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 28:1547, 2005.
88. Dormandy JA, Charbonnel B, Eckland DJ, et al: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAzone clinical trial in macroVascular events): A randomised controlled trial. *Lancet* 366:1279, 2005.
89. Wilcox R, Kupfer S, Erdmann E, et al: Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: Results from PROspective pioglitAzone clinical trial in macro vascular events (PROactive 10). *Am Heart J*

- 155:712, 2008.
90. Erdmann E, Charbonnel B, Wilcox RG, et al: Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: Data from the PROactive study (PROactive 08). *Diabetes Care* 30:2773, 2007.
 91. Takagi T, Yamamuro A, Tamita K, et al: Pioglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with type 2 diabetes mellitus: An intravascular ultrasound scanning study. *Am Heart J* 146:E5, 2003.
 92. Nishio K, Sakurai M, Kusuyama T, et al: A randomized comparison of pioglitazone to inhibit restenosis after coronary stenting in patients with type 2 diabetes. *Diabetes Care* 29:101,2006.
 93. Elrick H, Srimmler L, Hlad CJ,Jr, et al: Plasma insulin response to oral and intravenous glucose administration. *J Clin Endocrinol Metab* 24:1076, 1964.
 94. Nauck MA, Homberger E, Siegel EG, et al: Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab* 63:492,1986.
 - 94a. Deacon CF: Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes, Obesity, Metab* 13: 7, 2011.
 95. Scott R, Wu M, Sanchez M, et al: Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. *Int J Clin Pract* 61:171,2007.
 96. Aschner P, Kipnes MS, Lunceford JK, et al: Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 29:2632,2006.
 - 96a. Dhillon S: Sitagliptin. A review of its use in the management of type 2 diabetes mellitus. *Drugs* 70: 489, 2010.
 - 96b. <http://www.fda.gov/safety/med-watch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm183800.htm>
 - 96c. Garg R, Chen W, Pendergrass M: Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin. A retrospective observational pharmacy claims analysis. *Diabetes Care* 33: 2349, 2010.
 97. Vella A, Bock G, Giesler PD, et al: Effects of dipeptidyl peptidase-4 inhibition on gastrointestinal function, meal appearance, and glucose metabolism in type 2 diabetes. *Diabetes* 56:1475, 2007.
 98. Farilla L, Bulotta A, Hirshberg B, et al: Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. *Endocrinology* 144:5149, 2003.
 99. Ban K, Hui S, Drucker DJ, Husain M: Cardiovascular consequences of drugs used for the treatment of diabetes: potential promise of incretin-based therapies. *J Am Soc Hypertens* 3: 245, 2009.
 100. Chia CW, Egan JM: Incretin-based therapies in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 93:3703, 2008.
 101. Possibility of pancreatitis in patients taking byetta. [FDA Patient Safety News] August 18, 2008. Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=70> Accessed February 12, 2009.
 102. Drucker DJ, Buse JB, Taylor K, et al: Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomized, open-label, non-inferiority study. *Lancet* 372: 1240, 2008.
 - 102a. Bergenstal RM, Wysham C, MacConell L, et al for the DURATION-2 Study Group: Efficacy and safety of enenatide once weekly versus sitagliptin of pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 376: 431, 2010.
 - 102b. Diamant M, Van Gaal L, Stranks S, et al: Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet* 375: 2234, 2010.
 - 102c. Liraglutide (*Victoza*) for type 2 diabetes. *The Medical Ltr* 52: 25, 2010.
 - 102d. Buse JB, Rosenstock J, Sesti G, et al: Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). LEAD-6 Study Group. *Lancet* 374: 39, 2009.
 103. Mafong DD, Henry RR: Exenatide as a treatment for diabetes and obesity: Implications for cardiovascular risk reduction. *Curr Atheroscler Rep* 10:55, 2008.
 104. Blonde L, Klein EJ, Han J, et al: Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab* 8:436, 2006.
 105. Ray JA, Boye KS, Yurgin N, et al: Exenatide versus insulin glargine in patients with type 2 diabetes in the UK: A model of long-term clinical and cost outcomes. *Curr Med Res Opin* 23:609, 2007.
 106. Sonne DP, Engstrom T, Treiman M: Protective effects of GLP-1 analogues exendin-4 and GLP-1(9-36) amide against ischemia-reperfusion injury in rat heart. *Regul Pept* 146:243, 2008.
 107. Zarich SW, Nesto RW: Implications and treatment of acute hyperglycemia in the setting of acute myocardial infarction. *Circulation* 115: e436, 2007.
 108. Ceriello A, Zarich SW, Testa R: Lowering glucose

- to prevent adverse cardiovascular outcomes in a critical care setting. *J Am Coll Cardiol* 53 (Suppl S): S9, 2009.
109. Van den Berghe G: Does tight blood glucose control during cardiac surgery improve patient outcome? Editorial. *An Intern Med* 146: 307, 2007.
 110. Wiener BS, Wiener DC, Larson RJ: Benefits and risks of tight glucose control in critically ill adults. *JAMA* 300: 933, 2008.
 111. Van den Berghe G, Schetz M, Vlasselaers D, et al: Intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? *J Clin Endocrin Metab* 94: 3163, 2009.
 112. Hermansen K, Mortensen LS, Hermansen ML: Combining insulins with oral antidiabetic agents: Effect on hyperglycemic control, markers of cardiovascular risk and disease. *Vasc Health Risk Mgmt*.4:561, 2008.
 113. Hermansen K, Davies M, Derezinski T, et al: A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care* 29:1269, 2006.
 114. Philis-Tsimikas A, Charpentier G, Clauson P, et al: Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 28:1569, 2006.
 115. Holman RR, Thorne KI, Farmer AJ, et al: Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 357:1716, 2007.
 116. Heine RJ, Van Gaal LF, Johns D, et al: Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: A randomized trial. *Ann Intern Med* 143:559, 2005.
 117. Roper NA, Bilous RW, Kelly WF, et al: Excess mortality in a population with diabetes and the impact of material deprivation: Longitudinal, population based study. *BMJ* 322:1389, 2001.
 118. Skyler JS, Bergenstal R, Bonow RO, et al: Intensive glycemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA diabetes trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 32:187, 2009.
 119. Dickey RA, Feld S: A new paradigm for control of diabetes. *Endocr Pract* 8:65, 2002.
 120. American Diabetes Association :Standards of medical care in diabetes—2009. *Diabetes Care* 32:S13, 2009.
 121. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al :Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358:2545, 2008.
 122. Couzin J: Deaths in diabetes trial challenge a long-held theory. *Science* 319: 884, 2008.
 123. ADVANCE Collaborative Group, Patel A, MacMahon S, et al: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 358:2560, 2008.
 124. Duckworth W, Abraira C, Moritz T, et al: Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 360:129, 2009.
 - 124a. Ismail-Beigi F, Craven T, Banerji, MA, et al for the ACCORD Trial Group: Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 376: 419, 2010.
 125. Desouza C, Salazar H, Cheong B, et al: Association of hypoglycemia and cardiac ischemia: A study based on continuous monitoring. *Diabetes Care* 26:1485, 2003.
 126. Kelly TN, Bazzano LA, Fonseca VA, et al: Systematic review: glucose control and cardiovascular disease in type 2 diabetes. *Ann Intern Med* 151: 394, 2009.
 127. Holman RR, Paul SK, Bethel MA, et al: 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359:1577, 2008.
 128. Gaede P, Lund-Andersen H, Parving HH, et al: Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 358:580, 2008.
 129. The ACCORD Study Group: Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 364: 818, 2011.

References for Chapter 25

Prostacyclins, Endothelin Inhibitors, and Phosphodiesterase-5 Inhibitors in Pulmonary Hypertension

Warren D. Rosenblum, MD

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1. Proceedings of the 4th World symposium on Pulmonary Hypertension. *J Am Coll Cardiol Suppl S* 54: 2009.
2. Rubin LJ: Pathology and pathophysiology of primary pulmonary hypertension. *Am J Cardiol* 74: 51A, 1995.
3. Lehrman S, Romano P, Frishman W, et al: Primary pulmonary hypertension and cor pulmonale. *Cardiol in Rev* 10: 265, 2002.
4. Rubin LJ, Barst RJ, Kaiser LR, et al: Primary pulmonary hypertension. ACCP Consensus Statement. *Chest* 104: 236, 1993.
- 4a. Abe K, Toba M, Alzoubi A, et al: Formation of plexiform lesions in experimental severe pulmonary arterial hypertension. *Circulation* 121: 2747, 2010.
5. Pietra GG, Edwards WD, Kay JM, Rich S: Histopathology of primary pulmonary hypertension: A qualitative study of pulmonary blood vessels from 58 patients in the National Heart Lung and Blood Institute primary pulmonary hypertension registry. *Circulation* 80: 1198, 1989.
6. Humbert M, Sitbon O, Chaovat A, et al: Pulmonary hypertension in France. Results from a national registry. *Am J Respir Crit Care* 173: 1023, 2006.
7. Humbert M, Sitbon O, Simmoneau G: Treatment of pulmonary arterial hypertension. *N Engl J Med* 351: 1425, 2004.
- 7a. Archer SL, Weir K, Wilkins MR: Basic science of pulmonary arterial hypertension for clinicians: new concepts and experimental therapies. *Circulation* 121: 2045, 2010.
8. Christman BW, McPherson CD, Newman JH, et al: An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 327:70, 1992.
9. Giaid A, Yanagisawa M, Langleben D, et al: Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 328:173, 1993.
10. Stewart DJ, Levy RD, Cernacek P, Langleben D: Increased plasma endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 114:467, 1991.
11. Herve P, Launay JM, Scrobohaci ML, et al: Increased plasma serotonin in primary pulmonary hypertension. *Am J Med* 99:249, 1995.
12. Yuan X-J, Wang J, Juhaszova M, et al: Attenuated K⁺ channel gene transcription in primary pulmonary hypertension. *Lancet* 352:726, 1998.
13. Rich S, Dantzker DR, Ayres SM, et al: Primary pulmonary hypertension: a national prospective study. *Ann Intern Med* 107:236, 1987.
- 13a. Almodovar S, Cicalini S, Petrosillo N, Flores SC: Pulmonary hypertension associated with HIV infection: pulmonary vascular disease: the global perspective. *Chest* 137 Suppl: 6S, 2010
14. D'Alonzo GE, Barst RJ, Ayres SM, et al: Survival in patients with primary pulmonary Hypertension: Results from a national prospective registry. *Ann Intern Med* 115:343, 1991.
15. Rubin LJ: Calcium channel blockers in primary pulmonary hypertension. *Chest* 88:257S, 1985.
16. Alpert MA, Pressly TA, Mukerji V, et al: Acute and long-term effects of nifedipine on pulmonary hypertension associated with diffuse systemic sclerosis, the CREST syndrome and mixed connective tissue diseases. *Am J Cardiol* 68:1687, 1991.
17. Fuster V, Steele PM, Edwards WD, et al: Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 70:580, 1984.

18. Dobkin J, Reichel J: Drug treatment of primary pulmonary hypertension. In: Frishman WH, Sonnenblick EH (eds). *Cardiovascular Pharmacotherapeutics*. New York: McGraw-Hill, 1997:1173–1183.
19. Rubin LJ: Primary pulmonary hypertension: Practical therapeutic recommendations. *Drugs* 43:37, 1992.
20. Rich S: Medical treatment of primary pulmonary hypertension: A bridge to transplantation? *Am J Cardiol* 75:63A, 1995.
21. Pasque MK, Trulock EP, Kaiser LD, Cooper JD: Single lung transplantation for pulmonary hypertension: Three months hemodynamic follow-up. *Circulation* 84:2275, 1991.
22. Doud JR, McCabe MM, Montoya A, Garrity ER: The Loyola University lung transplant experience. *Arch Intern Med* 153:2769, 1993.
23. The Task force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 30: 2493, 2009.
24. McLaughlin W, Archer SL, Badesch DB, et al: ACC/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. A report from the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. *Circulation* 119: 2250, 2009.
25. Von Euler US: Zur Kenntnis der pharmakologischen Wirkungen von Nativsekreten und Extrakten männlicher accessorischer Geschlechtsdrüsen. *Arch Exp Pathol Pharmacol* 75:78, 1934.
26. Moncada S, Gryglewski R, Bunting S, Vane JR: An enzyme isolated from the arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* 263:663, 1976.
27. Whittaker N, Bunting S, Salmon J, et al: The chemical structure of prostaglandin X (prostacyclin). *Prostaglandins* 12:915, 1976.
28. Bunting S, Gryglewski R, Moncada S, Vane JR: Arterial walls generate from prostaglandin endoperoxides a substance (prostaglandin X) which relaxes strips of mesenteric and coeliac arteries and inhibits platelet aggregation. *Prostaglandins* 12:897, 1976.
29. Marcus AJ, Weksler BB, Jaffe EA: Enzymatic conversion of prostaglandin endoperoxide H_2 and arachidonic acid to PGI_2 by cultured human endothelial cells. *Biol Chem* 253:7138, 1978.
30. Weksler BB, Marcus AJ, Jaffe EA: Synthesis of prostaglandin I_2 (prostacyclin) by cultured human bovine endothelial cells. *Proc Natl Acad Sci USA* 74:3922, 1977.
31. MacIntyre DE, Pearson JD, Gordon JL: Localization and stimulation of prostacyclin production in vascular cells. *Nature* 271:549, 1978.
32. Moncada S, Vane JR: Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A₂, and prostacyclin. *Pharmacol Rev* 30:293, 1979.
33. Nakagawa O, Tanaka I, Usui T, et al: Molecular cloning of human prostacyclin receptor cDNA and its gene expression in the cardiovascular system. *Circulation* 90:1643, 1994.
34. Tateson JE, Moncada S, Vane JR: Effects of prostacyclin (PGX) on cyclic AMP concentrations in human platelets. *Prostaglandins* 13:389, 1977.
35. Higgs EA, Moncada S, Vane JR, et al: Effects of prostacyclin (PGI_2) on platelet adhesion to rabbit arterial subendothelium. *Prostaglandins* 16:17, 1978.
36. Cho MJ, Allen MA: Chemical stability of PGI_2 in aqueous solutions. *Prostaglandins* 15:943, 1978.
37. Wong PY, Sun FF, McGiff JC: Metabolism of prostacyclin in blood vessels. *J Biol Chem* 253:5555, 1978.
38. Yui Y, Aoyama T, Morishita H, et al: Serum prostacyclin stabilizing factor is identical to apoprotein A-I (apo-I): A novel function of apo A-I. *J Clin Invest* 82:803, 1988.
39. Rubin LJ, Mendoza J, Hood M, et al: Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol): Results of a randomized trial. *Ann Intern Med* 112:485, 1990.
40. Barst RJ, Rubin LJ, McGoon MD, et al: Survival in primary pulmonary hypertension with long term continuous intravenous prostacyclin. *Ann Intern Med* 121:409, 1994.
41. Barst RJ, Rubin LJ, Long WA, et al: A comparison of continuous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 334:296, 1996.
42. Hinderliter AL, Park WW, Barst RJ, et al: Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension. *Circulation* 95:1479, 1997.
43. McLaughlin VV, Genthner DE, Panella MM, Rich S: Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 338:273, 1998.
44. Higenbottam TW, Spiegelhalter D, Scott JP, et al: Prostacyclin (epoprostenol) and heart-lung transplantation as treatments for severe pulmonary hy-

- pertension. *Br Heart J* 70:366, 1993.
45. Cremona A, Higenbottam T: Role of prostacyclin in the treatment of primary pulmonary hypertension. *Am J Cardiol* 75: 67A, 1995.
 46. Rich S, McLaughlin VV: The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. *J Am Coll Cardiol* 34: 1184, 1999.
 47. Marshall RJ, Helmholz HF, Shepherd JT: Effect of acetylcholine on pulmonary vascular resistance in a patient with idiopathic pulmonary hypertension. *Circulation* 20:391, 1959.
 48. Morgan MJ, McCormack DG, Griffiths MJD, et al: Adenosine as a vasodilator in primary pulmonary hypertension. *Circulation* 84:1145, 1991.
 49. Frostell C, Fratacci MD, Wain JC, et al: Inhaled nitric oxide: A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 83:2038, 1991.
 50. Rozkovec A, Stradling JR, Shepherd G, et al: Prediction of favorable responses to long term vasodilator treatment of pulmonary hypertension by short term administration of epoprostenol (prostacyclin) or nifedipine. *Br Heart J* 59:696, 1988.
 51. Palewsky HI, Long W, Crow J, Fishman AP: Prostacyclin and acetylcholine as screening agents for acute pulmonary vasodilator responsiveness in primary pulmonary hypertension. *Circulation* 82:2018, 1990.
 52. Scradler BJ, Inbar S, Kaufman L, et al: Comparison of the effects of adenosine and nifedipine in pulmonary hypertension. *J Am Coll Cardiol* 19:1060, 1992.
 53. Inbar S, Scradler BJ, Kaufmann E, et al: Effects of adenosine in combination with calcium channel blockers in patients with primary pulmonary hypertension. *J Am Coll Cardiol* 21:413, 1993.
 54. Jolliet P, Bulpa P, Thorens JB, et al: Nitric oxide and prostacyclin as test agents of vasoreactivity in severe precapillary pulmonary hypertension: Predictive ability and consequences on haemodynamics and gas exchange. *Thorax* 52:369, 1997.
 55. Sitbon O, Brenot F, Denjean A, et al: Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension: A dose-response study and comparison with prostacyclin. *Am J Respir Crit Care Med* 151:384, 1995.
 56. Badesch DB, Abman SH, Simonneau G, et al.: Medical therapy for pulmonary arterial hypertension updated ACCP evidence-based clinical practice guidelines. *Chest* 131:1917-1928, 2007.
 57. Shapiro SM, Oudiz RJ, Cao T, et al: Primary pulmonary hypertension: Improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol* 30:343, 1997.
 58. Sakamaki F, Kyotani S, Nagaya N, et al: Increased plasma P-selectin and decrease thrombo-modulin in pulmonary arterial hypertension were improved by continuous prostacyclin therapy. *Circulation* 102:2720, 2000.
 59. Langleben D, Barst RJ, Badesch D, et al: Continuous infusion of epoprostenol improves the net balance between pulmonary endothelin-1 clearance and release in primary pulmonary hypertension. *Circulation* 99:3266, 1999.
 60. Sitbon O, Humbert M, Nunes H, et al: Long-term intravenous epoprostenol infusion in primary pulmonary hypertension. *J Am Coll Cardiol* 40:780, 2002.
 61. Fisher CA, Kappa JR, Sinha AK, et al: Comparison of equimolar concentrations of iloprost, prostacyclin, and prostaglandin E₁ on human platelet function. *J Lab Clin Med* 109:184, 1987.
 62. Saniabadi AR, Belch JFF, Lowe GDO, et al: Comparison of inhibitory actions of prostacyclin and a new prostacyclin analogue on the aggregations of human platelet in whole blood. *Hemostasis* 17:147, 1987.
 63. Schror K, Darius H, Matzky R, Ohlendorf R: The antiplatelet and cardiovascular action of a new carbacyclin derivative (ZK 36 374)-equipotent to PGI₂ in vitro. *Naunyn Schmiedebergs Arch Pharmacol* 316:252, 1981.
 64. Parsons AA, Whalley ET: Effects of prostanoids on human and rabbit basilar arteries precontracted in vitro. *Cephalgia* 9:165, 1989.
 65. Schroder G, Beckman R, Schillinger E: Studies on vasorelaxant effects and mechanisms of iloprost in isolated preparations. In: Gryglewski RJ, Stock G, eds. *Prostacyclin and Its Stable Analogue Iloprost*. Berlin: Springer Verlag, 1987:129.
 66. Belch JJ, Greer I, McLaren M, et al: The effects of intravenous ZK 36-374, a stable prostacyclin analogue, on normal volunteers. *Prostaglandins* 28:67, 1984.
 67. Kaukinen S, Ylitalo P, Pessi T, Vapaatalo H: Hemodynamic effects of iloprost, a prostacyclin analog. *Clin Pharmacol Ther* 36:464, 1984.
 68. Krause W, Humpel M, Hoyer GA: Biotransformation of the stable prostacyclin analogue, iloprost, in the rat. *Drug Metab* 12:645, 1984.
 69. Hildebrand M, Krause W, Fabian H, et al: Pharmacokinetics of iloprost in patients with chronic renal failure and maintenance hemodialysis. *Int J Clin Pharmacol Res* 10:285, 1990.
 70. Hildebrand M, Krause W, Angeli P, et al: Pharmacokinetics of iloprost in patients with hepatic dysfunction. *Int J Clin Pharmacol Ther Toxicol* 28:430,

- 1990.
71. Scott JP, Higenbottam T, Wallwork J: The acute effect of the synthetic prostacyclin analogue iloprost in primary pulmonary hypertension. *Br J Clin Pract* 44:231, 1990.
 72. Olschewski H, Ghofrani H, Walmrath D, et al: Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. *Am J Respir Crit Care Med* 160:600, 1999.
 73. De La Mata J, Gomez-Sanchez MA, Aranzana M, Gomez-Reino JJ: Long-term iloprost infusion therapy for severe pulmonary hypertension in patients with connective tissue diseases. *Arthritis Rheum* 37:1528, 1994.
 74. Olschewski H, Walmrath D, Schermuly R, et al: Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med* 124:820, 1996.
 75. Mikhail G, Gibbs J, Richardson M, et al: An evaluation of nebulized prostacyclin in patients with primary and secondary pulmonary hypertension. *Eur Heart J* 18:1499, 1997.
 76. Olschewski S, Simonneau G, Galié N, et al: Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 347:322, 2002.
 77. Wiedemann R, Ardeschir Ghofrani H, Weissmann N, et al: Atrial natriuretic peptide in severe primary and nonprimary pulmonary hypertension: response to iloprost inhalation. *J Am Coll Cardiol* 38:1130, 2001.
 78. Hoeper M, Schwarze M, Ehlerding S, et al: Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med* 342:1866, 2000.
 79. Olschewski H, Ardeschir H, Schmehl T, et al: Inhaled iloprost to treat severe pulmonary hypertension. *Ann Intern Med* 132:435, 2000.
 80. Wilkens H, Guth A, König J, et al: Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. *Circulation* 104:1218, 2001.
 81. Ghofrani HA, Wiedemann R, Rose F, et al: Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 136:515, 2002.
 82. Schenk P, Petkov V, Madl C, et al: Aerosolized iloprost therapy could not replace long-term intravenous epoprostenol (prostacyclin) administration in severe pulmonary hypertension. *Chest* 119:296, 2000.
 83. Ewert R, Wensel R, Opitz CF: Aerosolized iloprost for primary pulmonary hypertension (correspondence). *N Engl J Med* 343:1421, 2000.
 84. Machherndl S, Kneussl M, Baumgartner H, et al: Long-term treatment of pulmonary hypertension with aerosolized iloprost. *Eur Respir J* 17:8, 2001.
 85. Skoro-Sajer N, Lang I: The role of treprostinil in the management of pulmonary hypertension. *Am J Cardiovasc Drugs* 8: 213, 2008.
 86. Channick RN, Olschewski H, Seeger W et al: Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. *J Am Coll Cardiol* 2006;48:1433-1437.
 87. McLaughlin V, Rubin L, Benza R. TRIUMPH I: efficacy and safety of inhaled treprostinil sodium in patients with pulmonary arterial hypertension (PAH). *Am J Respir Crit Care Med* 2008; 177: A965.
 88. Hildebrand M, Staks T, Nieuweboer B: Pharmacokinetics and pharmacodynamics of cicaprost in healthy volunteers after oral administration of 5 to 20 micrograms. *Eur J Clin Pharmacol* 39:149, 1990.
 89. Melian EB, Goa KL: Beraprost: A review of its pharmacology and therapeutic efficacy in the treatment of peripheral arterial disease and pulmonary arterial hypertension. *Drugs* 62:107, 2002.
 90. Nagaya N, Uematsu M, Okano Y, et al: Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. *J Am Coll Cardiol* 34:1188, 1999.
 91. Galié N, Humbert M, Vachiéry J-L, et al: Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: A randomized, placebo-controlled, double-blind trial. *J Am Coll Cardiol* 30:1496, 2002.
 92. Ichida F, Uese K, Tsubata S, et al: Additive effect of beraprost on pulmonary vasodilation by inhaled nitric oxide in children with pulmonary hypertension. *Am J Cardiol* 80:662, 1997.
 93. Okano Y, Hoshioka T, Shimouchi A, et al: Orally active prostacyclin analogue in primary pulmonary hypertension (letter). *Lancet* 349:1365, 1997.
 94. Hickey KA, Rubanyi GM, Paul RJ, Highsmith RF: Characterization of a coronary vasoconstrictor produced by cultured endothelial cells. *Am J Physiol* 248:550, 1985.
 95. Yanagisawa M, Kurihara H, Kimura S, et al: A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 332:411, 1988.
 96. Kloog Y, Ambar I, Sokolovsky M, et al: Sarafotoxin, a novel vasoconstrictor peptide: Phosphoinositide hydrolysis in rat heart and brain. *Science* 242:268, 1988.
 97. Kramer BK, Nishida M, Kelly RA, Smith TW: Endothelins: Myocardial actions of a new class of cytokines. *Circulation* 85:350, 1992.
 98. Inoue A, Yanagisawa M, Takuwa Y, et al: The human preproendothelin-1 gene. *J Biol Chem* 264:14954,

- 1989.
99. Inoue A, Yanagisawa M, Kimura S, et al: The human endothelin family: Three structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proc Natl Acad Sci U S A* 86:2863, 1989.
 100. Arai H, Hori S, Aramori I, et al: Cloning and expression of a cDNA encoding an endothelial receptor. *Nature* 348:730, 1990.
 101. Lin HY, Kaji EH, Winkel GK, et al: Cloning and functional expression of a vascular smooth muscle endothelin 1 receptor. *Proc Natl Acad Sci U S A* 88:3185, 1991.
 102. Sakurai T, Yanagisawa M, Masaki T: Molecular characterization of the endothelin receptors. *Trends Pharmacol Sci* 13:103, 1992.
 103. Sakamoto A, Yanagisawa M, Sakurai T, et al: Cloning and functional expression of human cDNA for the ETB endothelin receptor. *Biochem Biophys Res Commun* 178:656, 1991.
 104. Webb DJ, Strachan FE: Clinical experience with endothelin antagonists. *Am J Hypertens* 11 (4 Pt 3): 71S, 1998.
 105. Bax WA, Saxena PR: The current endothelin receptor classification: Time for reconsideration? *Trends Pharmacol Sci* 15(10):379, 1994.
 106. Sakurai T, Goto K: Endothelins: Vascular actions and clinical implications. *Drugs* 46(5):795, 1993.
 107. Hosoda K, Nakao K, Hiroshi-Arai, et al: Cloning and expression of human endothelin-1 receptor cDNA. *FEBS Lett* 287(1-2):23, 1991.
 108. Levin ER: Mechanisms of disease: endothelin. *N Engl J Med* 333: 356, 1995.
 109. Yoshimoto S, Ishizaki Y, Sasaki T, Murota SI: Effect of carbon dioxide and oxygen on endothelin production by cultured porcine cerebral endothelial cells. *Stroke* 22:378, 1991.
 110. Nathan C, Sporn M: Cytokines in context. *J Cell Biol* 113:981, 1991.
 111. Chan J, Greenberg DA: Endothelin and calcium signaling in NG 108-15 neuroblastoma X glioma cells. *J Pharmacol Exp Ther* 258:524, 1991.
 112. Ohnishi A, Yamaguchi K, Kusuhara M, et al: Mobilization of intracellular calcium by endothelin in Swiss 3T3 cells. *Biochem Biophys Res Commun* 161:489, 1989.
 113. Takuwa N, Takuwa Y, Yanagisawa M, et al: A novel vasoactive peptide stimulates mitogenesis through inositol lipid turnover in Swiss 3T3 fibroblasts. *J Biol Chem* 264:7856, 1989.
 114. Takuwa Y, Masaki T, Yamashita K: The effects of the endothelin family peptides on cultured osteoblastic cells from rat calvariae. *Biochem Biophys Res Commun* 170:998, 1990.
 115. Miller RC, Pelton JT, Huggins JP: Endothelins—from receptors to medicine. *Trends Pharmacol Sci* 14(2):54, 1993.
 116. Nakaki T, Nakayama M, Yamamoto S, Kato R: Endothelin-mediated stimulation of DNA synthesis in vascular smooth muscle cells. *Biochem Biophys Res Commun* 158:880, 1989.
 117. Nilsson J, Sjolund M, Palmberg L, et al: The calcium antagonist nifedipine inhibits arterial smooth muscle proliferation. *Atherosclerosis* 58:109, 1985.
 118. Battistini B, Chailier P, D'Orleans-Juste P, et al: Growth regulatory properties of endothelins. *Pepptides* 14:385, 1993.
 119. Brown KD, Littlewood CJ: Endothelin stimulates DNA synthesis in Swiss 3T3 cells, synergy with polypeptide growth factors. *Biochem J* 263:977, 1989.
 120. Fabiato A, Fabiato F: Effects of pH on the myofilaments and the sarcoplasmic reticulum of skinned cells from cardiac and skeletal muscles. *J Physiol* 276:233, 1978.
 121. Allen DG, Orchard CH: The effects of changes of pH on intracellular calcium transients in mammalian cardiac muscle. *J Physiol* 335:555, 1983.
 122. Komuro I, Kurihara H, Sugiyama T, et al: Endothelin stimulates c-fos and c-myc expression and proliferation of vascular smooth muscle cells. *FEBS Lett* 238:249, 1988.
 123. Simonson MS, Wann S, Mene P, et al: Endothelin stimulates phospholipase C, Na⁺/H⁺ exchange, c-fos expression, and mitogenesis in rat mesangial cells. *J Clin Invest* 83:708, 1989.
 124. DiNucci G, Thomas R, D'Orleans-Juse P, et al: Pressor effects of circulating endothelin are limited by its removal in the pulmonary *Circulation* and by the release of prostacyclin and endothelin-derived relaxing factor. *Proc Natl Acad Sci USA* 85: 9797, 1988.
 125. Chakravarthy U, Archer DB: Endothelin—a new vasoactive ocular peptide. *Br J Ophthalmol* 76:107, 1992.
 126. Nakami A, Hirata Y, Ishikawa M, et al: ET-1 and ET-3 induce vasorelaxation via common generation of endothelium derived nitric oxide. *Life Sci* 50:677, 1992.
 127. Nakamuta M, Takayanagi R, Sakai Y, et al: Cloning and sequence analysis of cDNA encoding human non-selective type of endothelin receptor. *Biochem Biophys Res Commun* 177:34, 1991.
 128. Vincent R, Hogue M, Clozel M, Thuillez C: In vivo evidence of an endothelin-induced vasopressor tone after inhibition of nitric oxide synthesis in rats (abstr). *Circulation* 90(4 Pt 2):1, 1994.
 129. Haynes WG, Waugh CJ, Dockrell MEC, et al: Mod-

- ulators of calcium and potassium channels: their effects on endothelin-1 binding to cardiac membranes. *J Cardiovasc Pharmacol* 22(Suppl):S154, 1993.
130. Grover GJ, Dzwonczyk S, Parham CS, Sleph PG: The protective effects of cromakalim and pinacidil on reperfusion function and infarct size in anaesthetized dogs. *Cardiovasc Drugs Ther* 4:465, 1990.
 131. Kerr MJ, Wilson R, Shanks RG: Suppression of ventricular arrhythmias after coronary artery ligation by pinacidil, a vasodilator drug. *J Cardiovasc Pharmacol* 7:875, 1985.
 132. Weber MA, Black H, Bakris G, et al: A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. *Lancet* 374: 1423, 2009.
 133. Prasad VS, Palaniswamy C, Frishman WH: Endothelin as a clinical target in the treatment of systemic hypertension. *Cardiol in Rev* 17: 181, 2009.
 134. Benigni A, Remuzzi G: Endothelin antagonists. *Lancet* 353: 133, 1999.
 135. Stewart DJ, Levy RD, Cernacek P, Langleben D: Increased plasma endothelin-1 in pulmonary hypertension: Marker or mediator of disease? *Ann Intern Med* 114:464, 1991.
 136. Snopek G, Pogorzelska H, Rywik TM, et al: Usefulness of endothelin-1 concentration in capillary blood in patients with mitral stenosis as a predictor of regression of pulmonary hypertension after mitral valve replacement or valvuloplasty. *Am J Cardiol* 90:188, 2002.
 137. Li H, Chen SJ, Chen YF, et al: Enhanced endothelin-1 and endothelin receptor gene expression in chronic hypoxia. *J Appl Physiol* 77(3):1451, 1994.
 138. Dupuis J, Cernacek P, Tardif JC, et al: Reduced pulmonary clearance of endothelin-1 in pulmonary hypertension. *Am Heart J* 135(4):614, 1998.
 139. Mikhail G, Chester AH, Gibbs JS, et al: Role of vasoactive mediators in primary and secondary pulmonary hypertension. *Am J Cardiol* 82(2):254, 1998.
 140. Barman SA, Isales CM: Fenfluramine potentiates canine pulmonary vasoreactivity to endothelin-1. *Pulm Pharmacol Ther* 11(2-3):183, 1998.
 141. Reddy VM, Hendricks-Munoz KD, Rajasinghe HA, et al: Post-cardiopulmonary bypass pulmonary hypertension in lambs with increased pulmonary blood flow. A role for endothelin 1. *Circulation* 95(4):1054, 1997.
 142. Akazawa H, Ikeda U, Kuroda T, Shimada K: Plasma endothelin-1 levels in Takayasu's arteritis. *Cardiology* 87(4):303, 1996.
 143. Lutz J, Gorenflo M, Habighorst M, et al: Endothelin-1- and endothelin-receptors in lung biopsies of patients with pulmonary hypertension due to congenital heart disease. *Clin Chem Lab Med* 37(4):423, 1999.
 144. Sartori C, Vollenweider L, Löffler B-M, et al: Exaggerated endothelin release in high-altitude pulmonary edema. *Circulation* 99:2665, 1999.
 145. Chen SJ, Chen YF, Meng QC, et al: Endothelin-receptor antagonist bosentan prevents and reverses hypoxic pulmonary hypertension in rats. *J Appl Physiol* 79(6):2122, 1995.
 146. Itoh H, Yokochi A, Yamauchi-Kohno R, Maruyama K: Effects of the endothelin ET(A) receptor antagonist, TA-0201, on pulmonary arteries isolated from hypoxic rats. *Eur J Pharmacol* 376(3):233, 1999.
 147. Sheedy W, Haleen S, Morice AH: The effect of the ETA receptor antagonist (CI-1020) in rats with established hypoxic pulmonary hypertension. *Pulm Pharmacol Ther* 11(2-3):173, 1998.
 148. Ueno M, Miyauchi T, Sakai S, Goto K: The combined treatment of oral endothelin (ET)-A receptor antagonist and oral prostacyclin (PGI₂) analog is more greatly effective in ameliorating pulmonary hypertension (PH) and right ventricular (RV) hypertrophy than each drug alone in rats (abstr). *Circulation* 100 (Suppl 1):I, 1999.
 149. Jasmin J-F, Lucas M, Cernacek P, Dupuis J: Effectiveness of a nonselective ET_{A/B} and a selective ET_A antagonist in rats with monocrotaline-induced pulmonary hypertension. *Circulation* 103: 314, 2001.
 150. Apostolopoulou SC, Kyriakides Z, Webb DJ, et al: Endothelin A receptor antagonism improves pulmonary and systemic hemodynamics in patients with severe pulmonary hypertension (abstr). *Circulation* 100(Suppl 1):I, 1999.
 151. Goldberg A: Pulmonary arterial hypertension in connective tissue diseases. *Cardiol in Rev* 18: 85, 2010.
 152. Elliott WT, Chan J: Bosentan tablets (Tracleer-Actelion). *Intern Med Alert* 4:13, 2002.
 153. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 346:896-903, 2002.
 154. Galiè N, Rubin LJ, Hoeper MM, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double blind, randomized controlled trial. *Lancet* 371:2093-2100, 2008.
 155. Behr J, Lyseng-Williamson KA: Ambrisentan: a guide to its use in pulmonary arterial hypertension. *Drugs Ther Perspect* 25: 1, 2009.
 156. Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary hypertension:

- Results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circ*. 117:3010-3019, 2008.
157. Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 169:441-447, 2004.
 158. Barst RJ, Langleben D, Badesch D, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *JACC*. 47:2049-2056, 2006.
 159. Krum H, Viskoper RJ, Lacourciere Y, et al—Bosentan Hypertension Investigators: The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. *N Engl J Med* 338(12):784, 1998.
 160. Packer M, Caspi A, Charlon V, et al: Multicenter, double-blind, placebo-controlled study of long-term endothelin blockade with bosentan in chronic heart failure—results of the REACH-1 trial. *Circulation* 98 (Suppl S):12, 1998.
 161. Fattinger K, Funk C, Pantze M, et al: The endothelin export pump: A potential mechanism for hepatic adverse reactions. *Clin Pharmacol Ther* 69:223, 2001.
 162. Stieger B, Fattinger K, Madon J, et al: Drug- and estrogen-induced cholestasis through inhibition of the hepatocellular bile salt export pump of rat liver. *Gastroenterol* 118: 422, 2000.
 163. Moore J: ENABLE 1, 2: Bosentan did not improve HF symptoms. *Today Cardiol* 5:8, 2002.
 164. Archer SL, Michelakis ED: Phosphodiesterase type 5 inhibitors for pulmonary arterial hypertension. *N Engl J Med* 361: 1864, 2009.
 165. Rosenblum WD: Pulmonary arterial hypertension. Pathobiology, diagnosis, treatment and emerging therapies. *Cardiol in Rev* 18: 58, 2010.
 - 165a. Schwartz BG, Kloner RA: Drug interactions with phosphodiesterase 5 inhibitors used for the treatment of erectile dysfunction or pulmonary hypertension. *Circulation* 122: 88, 2010.
 166. Galie N, Ghofrani HA, Torbicki A, et al: Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 353: 2148, 2005.
 167. Rubin LJ, Badesch D, Fleming T, et al: Long-term treatment with sildenafil citrate in pulmonary arterial hypertension. *Chest* 134: 403S, 2008.
 - 167a. The Idiopathic Pulmonary Fibrosis Clinical Research Network: A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 363: 620, 2010.
 168. Galie N, Brudage BH, Ghofrani HA, et al: Tadalafil therapy for pulmonary hypertension. *Circulation* 119: 2894, 2009.
 169. Akagi S, Matsubara H, Miyaji K, et al: Additional effects of bosentan in patients with idiopathic pulmonary arterial hypertension already treated with high-dose epoprostenolol. *Circulation J* 72: 1142, 2008.
 170. Faruqi S, Fathi H, Morice AH: Combination of sitaxsentan and tadalafil for idiopathic pulmonary arterial hypertension following relapse on bosentan. *Intl J Cardiol* 2009 epub/171. Gruenig E, Michelakis E, Vachieri JL, et al: Acute hemodynamic effects of single-dose sildenafil when added to established bosentan therapy in patients with pulmonary arterial hypertension: results of the COMPASS-1 study. *J Clin Pharmacol* 49: 1343, 2009.
 172. Hoeper MM, Leuchte H, Halank H, et al: Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 28: 691, 2006.
 173. Humbert M, Barst RJ, Robbins IM, et al: Combination of bosentan with epoprostenolol in pulmonary arterial hypertension. *Breathe-2*. *Eur Respir J* 24: 353, 2004.
 174. Mathai SC, Girgis RE, Risher MR, et al: Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. *Eur Respir J* 29: 469, 2007.
 175. Murthy SN, Nossaman BD, Kadowitz PJ: New approaches to the treatment of pulmonary hypertension. From bench to bedside. *Cardiol in Rev* 18: 76, 2010.
 - 175a. Hingorany S, Frishman WH: Soluble guanylate cyclase activation with cinaciquat: a new approach to the treatment of decompensated heart failure. *Cardiol in Rev* 19: 2011 in press.
 176. Saji T, Nakayama T, Ishikita T, Matsuura H: Current status and future prospect of prostacyclin therapy for pulmonary hypertension – intravenous, subcutaneous, inhaled and oral PGI₂ derivatives. *Nippon Rinsho* 59: 1132, 2001.

References for Chapter 26

Selective and Nonselective Dopamine-Receptor Agonists

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1. Goldberg LI, Volkman PH, Kohli JD: A comparison of the vascular dopamine receptor with other dopamine receptors. *Annu Rev Pharmacol Toxicol* 18:57, 1978.
2. Goldberg LI, Kohli JD: Peripheral pre- and post-synaptic dopamine receptors: Are they different from dopamine receptors in the central nervous system? *Commun Psychopharmacol* 3:447, 1979.
3. Goldberg LI, Kohli JD: Identification and characterization of dopamine receptors in the cardiovascular system. *Cardiologia* 32:1603, 1987.
4. Berecek KH, Carey RM: Adrenergic and dopaminergic receptors and actions. In Izzo JL Jr., Sica DA, Black HR: *Hypertension Primer 4th ed.* Texas: American Heart Assn 2008: 39.
5. Hampton JR, van Veldhuisen DJ, Kleber FX, et al: Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. *Lancet* 349:971, 1997.
6. Francis GS: Receptor systems involved in norepinephrine release in heart failure: focus on dopaminergic systems. *Clin Cardiol* 18:113, 1995.
7. Lee MR: Dopamine and the kidney. *Clin Sci (Colch)* 62:439, 1982.
8. Lee MR: Dopamine and the kidney: Ten years on. *Clin Sci (Colch)* 84:357, 1993.
9. Bertorello A, Aperia A: Regulation of Na⁺,K⁺-ATPase activity in kidney proximal tubules: Involvement of GTP binding proteins. *Am J Physiol* 256:F57, 1989.
10. Felder CC, Campbell T, Albrecht F, Jose PA: Dopamine inhibits Na(+)-H+ exchanger activity in renal BBMV by stimulation of adenylate cyclase. *Am J Physiol* 259:F297, 1990.
11. Felder CC, Albrecht FE, Campbell T, et al: cAMP-independent, G protein-linked inhibition of Na⁺/H⁺ exchange in renal brush border by D1 dopamine agonists. *Am J Physiol* 264:F1032, 1993.
12. Gesek FA, Schoolwerth AC: Hormonal interactions with the proximal Na(+)-H+ exchanger. *Am J Physiol* 258:F514, 1990.
13. Carey RM: Renal dopamine system. Paracrine regulator of sodium homeostasis and blood pressure. *Hypertension* 38:297, 2001.
14. Jose PA, Eisner GM, Felder RA: Role of dopamine in the pathogenesis of hypertension. *Clin Exp Pharmacol Physiol Suppl* 26:S10, 1999.
15. Zeng C, Felder Ra, Jose PA: A new approach for treatment of hypertension: modifying D1 dopamine receptor function. *Cardiovasc Hematol Agts Med Chem* 4: 369, 2006.
16. Shi Y, Zalewski A, Bravette B, et al: Selective dopamine-1 receptor agonist augments regional myocardial blood flow: Comparison of fenoldopam and dopamine. *Am Heart J* 124:418, 1992.
17. Murphy MB, Vaughn CJ: Dopamine. In: Messerli FH (ed). *Cardiovascular Drug Therapy*. Philadelphia: WB Saunders, 1996:1162–1166.
18. Lokhandwala MF, Barrett RJ: Cardiovascular dopamine receptors: Physiological, pharmacological and therapeutic implications. *J Auton Pharmacol* 2:189, 1982.
19. Lokhandwala MF, Hegde SS: Cardiovascular pharmacology of adrenergic and dopaminergic receptors: Therapeutic significance in congestive heart failure. *Am J Med* 90:2S, 1991.
20. Carey RM: Dopamine, hypertension and the potential for agonist therapy. In: Laragh JG, Brenner BB, eds. *Hypertension Pathophysiology, Diagnosis and Management*, 2nd ed. New York: Raven Press,

- 1995: 2937–2952.
21. Haeusler G, Lues I, Minck KO, et al: Pharmacological basis for antihypertensive therapy with a novel dopamine agonist. *Eur Heart J* 13(Suppl D):129, 1992.
 22. van Veldhuisen DJ, Girbes AR, de Graeff PA, Lie KI: Effects of dopaminergic agents on cardiac and renal function in normal man and in patients with congestive heart failure. *Int J Cardiol* 37:293, 1992.
 23. Kellum JA, Decker JM: Use of dopamine in acute renal failure: A meta-analysis. *Crit Care Med* 29:1526, 2001.
 24. Bellomo R, Chapman M, Finfer S, et al: Low dose dopamine in patients with early renal dysfunction: A placebo-controlled randomized trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 356:2139, 2000.
 25. Lassnigg A, Donner E, Grubhofer G, et al: Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. *J Am Soc Nephrol* 11(1):97, 2000.
 - 25a. Murphy MB, Murray C, Shorten GD: Fenoldopam: A selective peripheral dopamine receptor agonist. *N Engl J Med* 345:1548, 2001.
 26. Pilmer BL, Green JA, Panacek EA, et al: Fenoldopam mesylate versus sodium nitroprusside in the acute management of severe systemic hypertension. *J Clin Pharmacol* 33:549, 1993.
 27. Blanchett DG, Green JA, Nara A, et al: The effect of food on pharmacokinetics and pharmacodynamics of fenoldopam in class III heart failure. *Clin Pharmacol Ther* 49:449, 1991.
 28. Clancy A, Locke-Haydon J, Cregeen RJ, et al: Effect of concomitant food intake on absorption kinetics of fenoldopam (SK&F 82526) in healthy volunteers. *Eur J Clin Pharmacol* 32:103, 1987.
 29. Mansoor GA, Frishman WH: Comprehensive management of hypertensive emergencies and urgencies. *Heart Disease* 4:358, 2002.
 - 29a. Phillips RA, Greenblatt J, Krakoff LR: Hypertensive emergencies: Diagnosis and management. *Prog Cardiovasc Dis* 45:33, 2002.
 30. Abdelwahab W, Frishman W, Landau A: Management of hypertensive urgencies and emergencies. *J Clin Pharmacol* 35:747, 1995.
 31. Rhoney D, Peacock WF: Intravenous therapy for hypertensive emergencies. Part 1. *Am J Health Syst Pharm* 66: 1343, 2009.
 32. Elliott WJ: Clinical features in the management of selected hypertensive emergencies. *Prog Cardiovasc Dis* 48: 316, 2006.
 33. Calhoun DA: Hypertensive crisis. In Oparil S, Weber MA: *Hypertension: a Companion to Brenner and Rector's "The Kidney"*. Philadelphia: Saunders 2000: 715.
 34. Katakam R, Townsend RR: Hypertensive emergencies. In Antman EM: *Cardiovascular Therapeutics 3rd ed.* Philadelphia: Saunders/Elsevier, 2007, 666.
 35. Oparil S, Aronson S, Deeb GM, et al: Fenoldopam: A new parenteral antihypertensive. Consensus round table on the management of perioperative hypertension and hypertensive crises. *Am J Hypertens* 12:653, 1999.
 36. Rodriguez MA, Kumar SK, DeCaro M: Hypertensive crisis. *Cardiol in Rev* 18: 102: 2010.
 37. Munger MA, Rutherford WF, Anderson L, et al: Assessment of intravenous fenoldopam mesylate in the management of severe systemic hypertension. *Crit Care Med* 18:502, 1990.
 38. Panacek EA, Bednarczyk EM, Dunbar LM, et al: Randomized, prospective trial of fenoldopam vs sodium nitroprusside in the treatment of acute severe hypertension. Fenoldopam Study Group. *Acad Emerg Med* 2:959, 1995.
 39. Post JB, Frishman WH: Fenoldopam: a new dopamine agonist for the treatment of hypertensive urgencies and emergencies. *J Clin Pharmacol* 38:2, 1998.
 40. Tumlin JA, Dunbar LM, Oparil S, et al: Fenoldopam, a dopamine agonist, for hypertensive emergency: A multicenter randomized trial. Fenoldopam Study Group. *Acad Emerg Med* 7:653, 2000.
 41. Murphy MB, McCoy CE, Weber RR, et al: Augmentation of renal blood flow and sodium excretion in hypertensive patients during blood pressure reduction by intravenous administration of the dopamine-1 agonist fenoldopam. *Circulation* 76:1312, 1987.
 42. Shusterman NH, Elliott WJ, White WB: Fenoldopam, but not nitroprusside, improves renal function in severely hypertensive patients with impaired renal function. *Am J Med* 95:161, 1993.
 43. Elliott WJ, Karnezis TA, Silverman RA, et al: Intraocular pressure increases with fenoldopam, but not nitroprusside, in hypertensive humans. *Clin Pharmacol Ther* 49:285, 1991.
 44. Everitt DE, Boike SC, Piltz-Seymour JR, et al: Effect of intravenous fenoldopam on intraocular pressure in ocular hypertension. *J Clin Pharmacol* 37:312, 1997.
 45. Kini A, Mitre C, Kamran M, et al: Changing trends in incidence and predictors of radiographic contrast nephropathy after percutaneous coronary intervention with use of fenoldopam. *Am J Cardiol* 89:999, 2002.
 46. Tumlin JA, Wang A, Murray PT, Mathur VS: Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: A pi-

- lot trial in the prevention of contrast nephropathy. *Am Heart J* 143:894, 2002.
47. Teirstein PS, Price MJ, Mathur VS, et al: Differential effects between intravenous and targeted renal delivery of fenoldopam on renal function and blood pressure in patients undergoing cardiac catheterization. *Am J Cardiol* 97: 1076, 2006.
 48. Weisz G, Filby SJ, Cohen MG, et al: Safety and performance of targeted renal therapy: the Be-RITe! Registry. *J Endovasc Ther* 16:1, 2009.
 49. Gilbert TB, Hasnain JU, Flinn WR, et al: Fenoldopam infusion associated with preserving renal function after aortic cross-clamping for aneurysm repair. *J Cardiovasc Pharmacol Ther* 6:31, 2001.
 50. Barr LF, Kolodner K: N-acetylcysteine and fenoldopam protect the renal function of patients with chronic renal insufficiency undergoing cardiac surgery. *Crit Care Med* 36: 1427, 2008.
 51. Roasio A, Lobreglio R, Santin A, et al: Fenoldopam reduces the incidence of renal replacement therapy after cardiac surgery. *J Cardiothorac Vasc Anesth* 22: 23, 2008.
 52. Cogliati AA, Vellutini R, Nardini A, et al: Fenoldopam infusion for renal protection in high-risk cardiac surgery patients: a randomized clinical study. *J Cardiothorac Vasc Anesth* 21: 847, 2007.
 53. Meco M, Cirri S: Effects of fenoldopam mesylate on central hemodynamics and renal flow in patients undergoing cardiac surgery: color Doppler echocardiographic evaluation. *J Cardiothorac Vasc Anesth* 24: 58, 2010.
 54. Bove T, Landoni G, Calabro MG, et al: Renoprotective action of fenoldopam in high-risk patients undergoing cardiac surgery: a prospective, double-blind, randomized clinical trial. *Circulation* 111: 3230, 2005.
 55. Shepherd AMM: Nitrates, dopamine agonists, potassium channel openers, and serotonic-related agents. In Izzo JL Jr, Sica DA, Black HR: *Hypertension Primer 4th ed.* Dallas: American Heart Assn 2008: 472.
 56. Quinn N, Illas A, Lhermitte F, Agid Y: Bromocriptine in Parkinson's disease: A study of cardiovascular effects. *J Neurol Neurosurg Psychiatry* 44:426, 1981.
 57. Walden RJ, Hernandez J, Bhattacharjee P, et al: Bromocriptine in the treatment of hypertension. *Eur J Clin Pharmacol* 30:141, 1986.
 58. Lahlou S, Duarte GP, Demenge P: Central dopaminergic origin of bromocriptine induced tachycardia in normotensive rats. *Cardiovasc Res* 27:2022, 1993.
 59. Eickman FM: Recurrent myocardial infarction in a postpartum patient receiving bromocriptine. *Clin Cardiol* 15:781, 1992.
 60. Kuznar W: Timed dopamine agonist therapy reduced cardiovascular events in type 2 diabetes. *Cardiology Today* September 2007: 20.
 - 60a. Bromocriptine (Cycloset) for type 2 diabetes. *The Med Ltr* 52: 97, 2010.
 - 60b. Scranton R, Cincotta A: Bromocriptine- unique formulation of a dopamine agonist for the treatment of type 2 diabetes. *Expert Opin Pharmacother* 11: 269, 2010.
 - 60c. Gaziano JM, Cincotta AH, O'Connor CM, et al: Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* 33: 1503, 2010.
 61. Carmoxirole. In: Messerli FH, ed. *Cardiovascular Drug Therapy*, 2nd ed. Philadelphia: Saunders, 1996:1189.

References for Chapter 27

Natriuretic Peptides

Nesiritide

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1. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H: A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 28: 89, 1981.
2. de Bold AJ, Raymond JJ, Bencosme SA: Atrial specific granules of the rat heart : light microscopic staining and histochemical reactions. *Histochem Cytochem* 26: 1094, 1978.
3. Garcia R, Cantin M, Thibault G, et al: Relationship of specific granules to the natriuretic and diuretic activity of rat atria. *Experientia* 38: 1071, 1982.
4. Sudoh T, Kangawa K, Minamino N, Matsuo H: A new natriuretic peptide in porcine brain. *Nature* 332: 78, 1988.
5. Hosoda K, Nakao K, Mukoyama M, et al: Expression of brain natriuretic peptide gene in human heart: production in the ventricle. *Hypertension* 17: 1152, 1991.
6. Sudoh I, Minamino N, Kangawa K, Matsuo H: C-type natriuretic peptide (NP): a new member of natriuretic peptide family identified in porcine brain. *Biochem Biophys Res Commun* 168: 863, 1990.
7. Wong SK, Garbers DL. Receptor guanylyl cyclases. *J Clin Invest* 1992;90(2):299-305.
8. Cheng JWM: Nesiritide: a review of clinical pharmacology and role in heart failure management. *Heart Dis* 4: 199, 2002.
9. Achilihu G, Frishman WH, Landau A: Neutral endopeptidase inhibitors and atrial natriuretic peptide. *J Clin Pharmacol* 31: 758, 1991.
10. Tsukamoto O, Fujita M, Kato M, et al: Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. *J Am Coll Cardiol* 53: 2070, 2009.
11. Colucci WS, Elkayam U, Horton SP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. *N Engl J Med* 343:246, 2000.
12. Abraham WT, Cheng ML, Smoluk G for the VMAC Study Group: Clinical and hemodynamic effects of nesiritide (B-type natriuretic peptide) in patients with decompensated heart failure receiving beta blockers. *Congest Heart Fail* 11: 59, 2005.
13. Frishman WH, Nawarskas J, Rajan V, Sica DA: Vasopeptidase inhibitors: neutral endopeptidase inhibitors and dual inhibitors of angiotensin converting enzyme and neutral endopeptidase. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed.* New York: McGraw Hill 2003: 813.
14. Nawarskas J, Anderson JR: Omapatrilat: a unique new agent for the treatment of cardiovascular disease. *Heart Dis* 2: 266, 2000.
15. Cowie MR, Mendez GF: BNP and congestive heart failure. *Prog Cardiovasc Dis* 44: 293, 2002.
16. Rubattu S, Sciarretta S, Valenti V, et al: Natriuretic peptides: an update on bioactivity, potential therapeutic use, and implication in cardiovascular diseases. *Am J Hypertens* 21: 733, 2008.
17. Burger AJ, Horton DP, Elkayam U, et al. Nesiritide is not associated with proarrhythmic effects of dobutamine in the treatment of decompensated CHF: The PRECEDENT study. *J Card Fail* 5 (suppl 1):49, 1995.
18. Burger AJ, Horton DP, Elkayam U, et al. Evidence of ventricular ectopy at baseline is not predictive of the proarrhythmic effects of dobutamine in the treatment of decompensated CHF: The PRECEDENT study. *J Card Fail*;6 (suppl 2):46, 2000.
19. Elkayam U, Silver MA, Burger AJ, Horton DP. The effect of short-term therapy with nesiritide (B-type natriuretic peptide) or dobutamine on long-term

- survival. *J Card Fail* 6 (suppl 2):45, 2000.
- 19a. Abraham WT, Trupp RJ, Jarjoura D: Nesiritide in acute decompensated heart failure: a pooled analysis of randomized controlled trials. *Clin Cardiol* 33: 484, 2010.
 20. Silver MA, Horton DP, Ghali JK, Elkayam U: Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acute decompensated heart failure. *J Am Coll Cardiol* 39: 798, 2002.
 21. Hernandez AF, O'Connor CM, Starling RC, et al: Rationale and design of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial (ASCEND-HF). *Am Heart J* 157: 271, 2009.
 22. Ezekowitz JA, Hernandez AF, Starling RC, et al: Standardizing care for acute decompensated heart failure in a large megatrial: the approach for the Acute Studies of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure (ASCEND-HF). *Am Heart J* 157: 219, 2009.
 - 22a. AHA News Release: Large study of patients with severe heart failure confirms nesiritide safe, but shows no significant benefit on symptoms or mortality. American Heart Association Scientific Sessions, Chicago, Ill., November 14, 2010.
 - 22b. George I, Xydias S, Klotz S, et al: Long-term effects of B-type natriuretic peptide infusion after acute myocardial infarction in a rat model. *J Cardiovasc Pharmacol* 55: 14, 2010.
 23. Sackner-Bernstein JD, Skopicki HA, Aaronson KD: Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 111: 1487, 2005.
 24. Lewicki JA, Protter AA: Physiologic studies of the natriuretic peptide family. In Laragh JH, Brenner BM (eds): *Hypertension: Pathophysiology, Diagnosis and Management 2nd ed.* New York: Raven Press 1995: 1029.
 25. Elkayam U, Silver MA, Burger AJ, et al: Limitations of commonly used titrated doses of intravenous nitroglycerin in patients with acute decompensated heart failure. *J Card Fail* 7:Suppl 2: 12, 2001.
 26. Givertz MM, Stevenson LW, Colucci WS: Strategies for management of decompensated heart failure. In Antman EM (ed) *Cardiovascular Therapeutics. A Companion to Braunwald's Heart Disease 3rd ed.* Philadelphia: Saunders, 2007: 385.
 27. Wang DJ, Dowling TC, Meadows D, et al: Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. *Circulation* 110: 1620, 2004.
 28. Michaels AD, Chatterjee K, DeMarco T: Effects of intravenous nesiritide on pulmonary vascular hemodynamics in pulmonary hypertension. *J Card Fail* 11: 425, 2005.
 29. Leyh RG, Kofidis T, Struber M, et al: Methylene blue: the drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass? *J Thorac Cardiovasc Surg* 125: 1426, 2003.
 30. Yancy CW, Saltzberg MT, Berkowitz RL, et al: Safety and feasibility of using infusions of nesiritide for heart failure in an outpatient setting (from the FUSION 1 Trial). *Am J Cardiol* 94: 595, 2004.
 31. Yancy CW, Singh A: Potential applications of outpatient nesiritide infusions in patients with advanced heart failure and concomitant renal insufficiency (from the Follow-Up Serial Infusions of Nesiritide (FUSION 1) trial). *Am J Cardiol* 98: 226, 2006.
 32. Yancy CW, Krum H, Massie BM, et al for the FUSION II investigators: Safety and efficacy of outpatient nesiritide in patients with advanced heart failure. Results of the Second Follow Up Serial Infusions of Nesiritide (FUSION II) trial. *Circ Heart Fail* 1: 9, 2008.
 33. Peacock WF, Holland R, Gyarmathy R, et al: Observation unit treatment of heart failure with nesiritide: results from the Proaction Trial. *J Emerg Med* 29: 243, 2005.
 34. Kragelund C, Grønning B, Køber L, et al: N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med* 352: 666, 2005.
 35. de Lemos JA, McGuire DK, Drazner MH: B-type natriuretic peptide in cardiovascular disease. *Lancet* 362: 316, 2003.
 36. Wang TJ, Larson MG, Levy D, et al: Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 350: 655, 2004.
 37. Mueller C, Scholer A, Laule-Kilian K, et al: Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 350: 647, 2004.
 38. Shadman R, Allison MA, Criqui MH: Glomerular filtration rate and N-terminal pro-brain natriuretic peptide as predictors of cardiovascular mortality in vascular patients. *J Am Coll Cardiol* 49: 2172, 2007.
 39. Bergler-Klein J, Mundigler G, Pibarot P, et al: B-type natriuretic peptide in low-flow, low-gradient aortic stenosis. Relationship to hemodynamics and clinical outcome: results from the Multicenter Truly or Pseudo-Severe Aortic Stenosis (TOPAS) study. *Circulation* 115: 2848, 2007.
 40. Bibbins-Domingo K, Gupta R, Na B, et al: N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-ProBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. *JAMA* 297: 169, 2007.

41. Mutlu B, Bayrak F, Kahveci G, et al: Usefulness of N-terminal pro-B-type natriuretic peptide to predict clinical course in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 98: 1504, 2006.
42. Bernus A, Wagner BD, Accurso F, et al: Brain natriuretic peptide levels in managing pediatric patients with pulmonary arterial hypertension. *Chest* 135: 745, 2009.
43. Jarai R, Fellner B, Haoula D, et al: Early assessment of outcome in cardiogenic shock: relevance of plasma N-terminal pro-B-type natriuretic peptide and interleukin-6 levels. *Crit Care Med* 37: 1837, 2009.
44. Sodeck G, Domanovits H, Schillinger M, et al: Preoperative N-terminal pro-brain natriuretic peptide predicts outcome in type A aortic dissection. *J Am Coll Cardiol* 51: 1092, 2008.
45. Battaglia M, Pewsner D, Jüni P, et al: Accuracy of B-type natriuretic peptide tests to exclude congestive heart failure. *Arch Intern Med* 166: 1073, 2006.
46. Shapiro BP, Chen HH, Burnett JC Jr., Redfield MM: Use of plasma brain natriuretic peptide concentration to aid in the diagnosis of heart failure. *Mayo Clin Proc* 78: 481, 2003.
47. Januzzi JL Jr., Camargo CA, Anwaruddin S, et al: The N-terminal pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. *Am J Cardiol* 95: 948, 2005.
48. Maisel AS, McCord J, Nowak RM, et al for the Breathing Not Properly Multinational Study Investigators: Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. *J Am Coll Cardiol* 41: 2010, 2003.
49. Nicholls MG, Obineche EN, Frampton CM, Richards AM: Plasma cardiac natriuretic peptide levels in screening for cardiac disease. *Am J Med* 116: 561, 2004.
50. Wazni OM, Martin DO, Marrouche NE, et al: Plasma B-type natriuretic peptide levels predict postoperative atrial fibrillation in patients undergoing cardiac surgery. *Circulation* 110: 124, 2004.
51. Krüger S, Graf J, Merx MW, et al: Brain natriuretic peptide predicts right heart failure in patients with acute pulmonary embolism. *Am Heart J* 147: 60, 2004.
52. Bhalla MA, Chiang A, Epshteyn VA, et al: Prognostic role of B-type natriuretic peptide levels in patients with type 2 diabetes mellitus. *J Am Coll Cardiol* 44: 1047, 2004.
53. Siriwardena M, Kleffmann T, Ruygrok P, et al: B-type natriuretic peptide signal peptide circulates in human blood. Evaluation as a potential biomarker of cardiac ischemia. *Circulation* 122: 255, 2010.
- 53a. Lam LL, Camerson PA, Schneider HG: Meta analysis: effect of B-type natriuretic peptide testing on clinical outcomes in patients with acute dyspnea in the emergency setting. *Ann Intern Med* 153: 728, 2010.
54. Pfisterer M, Buser P, Rickli H, et al for the TIME-CHF Investigators: BNP-guided vs symptom-guided heart failure therapy. The Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) randomized trial. *JAMA* 301: 383, 2009.

References for Chapter 28

Vasopressin and Vasopressin Receptor Antagonists

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1. Sachs H: Biosynthesis and release of vasopressin. *Am J Med* 1967; 42: 687-700.
2. Cowley JF, Ausello DA: Vasopressin Cellular and Integrative Functions. Raven Press, New York: 1988.
3. Schrier RW: Vasopressin. Raven Press, New York: 1985.
4. Schrier RW, Cadnapaphornchai MA, Umenishi F: Water-losing and water-retaining states: role of water channels and vasopressin receptor antagonists. *Heart Disease* 3: 210, 2001.
5. Manning M, Sawyer W: Discovery, development, and some uses of vasopressin and oxytocin antagonists. *J Lab Clin Med* 1989; 114: 617-32.
6. Robertson GL, Harris A: Clinical use of vasopressin analogues. *Hosp Prac* 1989; 24: 114-133.
7. Maggi M, Fantoni G, Peri A, et al: Steroid modulation of oxytocin/vasopressin receptors in the uterus. *J Steroid Biochem Molec Biol* 1991; 40: 481-91.
8. deKeyser Y, Auzan C, Lenne F, et al: Cloning and characterization of the human V3 pituitary vasopressin receptors. *FEBS Lett* 1994; 345: 215-20.
9. Fahrenholz F, Jurzak M, Gerstberger R, Haase W: Renal and central vasopressin receptors: immunocytochemical localization. *Ann NY Acad Sci* 1993; 689: 194-206.
10. Phillips M: Functions of angiotensin in the central nervous system. *Ann Rev Physiol* 1987; 54: 413-35.
11. McKinley MJ, Congiu M, Denton DA, et al: The anterior wall of the third cerebral ventricle and homeostatic responses to dehydration. *J Physiol-Paris* 1984; 79: 421-27.
12. Zeisberger E: The role of septal peptides in thermoregulation and fever. In Bligh J, Voigt K (eds): *Thermoreception and Temperature Regulation*. Springer Verlag, Berlin: 1990; 273.
13. Stehle J, Reuss S, Riemann R, et al: The role of arginine vasopressin for pineal melatonin synthesis in the rat: involvement of vasopressinergic receptors. *Neurosci Ltrs* 1991; 123: 131-34.
14. Kasting NW: Criteria for establishment of a physiological role for brain peptides. A case in point: the role of vasopressin in thermoregulation during fever and antipyresis. *Brain Res Rev* 1989; 14: 143-53.
15. Meisenberg G, Simmons WH: Hypothermia induced by centrally administered vasopressin in rats. A structure-activity study. *Neuropharmacol* 1984; 23: 1195-1200.
16. Whitnall MH: Stress selectively activates the vasopressin-containing subset of corticotropin-releasing hormone neurons. *Neuroendocrin* 1989; 50: 702-07.
17. Gibbs DM: Vasopressin and oxytocin: hypothalamic modulators of the stress response. A review. *Psychoneuroendocrin* 1986; 11: 131-39.
18. Diamant M, DeWied D: Differential effects of centrally injected AVP on heart rate, core temperature and behavior in rats. *Am J Physiol* 1993; 264: R51-61.
19. Cowley AW, Cushman WC, Quillen EW, et al: Vasopressin elevation in essential hypertension and increased responsiveness to sodium intake. *Hypertension* 1981; 3 (3 Pt 2): 193-100.
20. Mohring J, Glanzer K, Maciel JA Jr, et al: Greatly enhanced pressor response to antidiuretic hormone in patients with impaired cardiovascular reflexes due to idiopathic orthostatic hypotension. *J Cardiovasc Pharmacol* 1980; 2: 367-76.
21. Andrews CE, Brenner BM: Relative contributions of arginine vasopressin and angiotensin II to maintenance of systemic arterial pressure in the an-

- aesthetized water deprived rat. *Circ Res* 1981; 48: 254-58.
22. Woods RL, Johnston CI: Contribution of vasopressin to the maintenance of blood pressure during dehydration. *Am J Physiol* 1983; 245 (5 Pt. 1): F615-21.
 23. McNeill JR, Stark RD, Greenway CV: Intestinal vasoconstriction after hemorrhage: roles of vasopressin and angiotensin. *Am J Physiol* 1970; 219: 1342-47.
 24. Laszlo FA, Laszlo F Jr., deWied D: Pharmacology and clinical perspectives of vasopressin antagonists. *Pharmacol Rev* 1991; 43: 73-108.
 25. Bichet D, Szatalowicz V, Chaimovitz C, Schrier RW: Role of vasopressin in abnormal water excretion in cirrhotic patients. *Ann Intern Med* 1982; 96: 413-17.
 26. Tsuboi Y, Ishikawa S, Fujisawa G, et al: Therapeutic efficacy of the non-peptide AVP antagonist OPC 31260 in cirrhotic rats. *Kidney Intl* 1994; 46: 237-44.
 27. Gueugniaud P-Y, David J-S, Chanzy E, et al: Vasopressin and epinephrine vs epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med* 359: 21, 2008.
 28. Barrett LK, Singer M, Clapp LH: Vasopressin: mechanisms of action on the vasculature in health and in septic shock. *Crit Care Med* 35: 33, 2007.
 29. Annane D: Vasopressin plus corticosteroids: the shock duo!. *Crit Care Med* 37: 1126, 2009.
 30. Oghlakian G, Klapholz M: Vasopressin and vasopressin receptor antagonists in heart failure. *Cardiol in Rev* 17: 10, 2009.
 31. Freeman JG, Cobden I, Lishman AH, Record CO: Controlled trial of terlipressin (glypressin) versus vasopressin in the early treatment of oesophageal varices. *Lancet* 1982; 2: 66-68.
 32. Kelsch T, Kikuchi K, Vahdat S, Frishman WH: Innovative pharmacologic approaches to cardiopulmonary resuscitation. *Heart Disease* 3: 46-54, 2001.
 33. Wenzel V, Lindner KH, Krismer AC, et al: Repeated administration of vasopressin but not epinephrine maintains coronary perfusion pressure after early and later administration during prolonged cardiopulmonary resuscitation in pigs. *Circulation* 99: 1379, 1999.
 34. Scharte M, Meyere J, Vanakin H, et al: Hemodynamic effects of terlipressin (a synthetic analog of vasopressin) in healthy and endotoxemic sheep. *Crit Care Med* 29: 1756, 2001.
 35. Ryckwaert F, Virsolvy A, Fort A, et al: Terlipressin, a provasopressin drug exhibits direct vaso-constrictor properties: consequences on heart perfusion and performance. *Crit Care Med* 37: 876, 2009.
 36. Chase LR, Aurbach GD: Renal adenylyl cyclase: anatomically separate sites for parathyroid hormone and vasopressin. *Science* 1968; 159: 545-47.
 37. Butlen D, Guillon G, Rajerison RM, et al: Structural requirements for activation of vasopressin-sensitive adenylyl cyclase, hormone binding, and anti-diuretic actions: effects of highly potent analogues and competitive inhibitors. *Molec Pharmacol* 1978; 14: 1006-17.
 38. Aiyar N, Nambi P, Stassen FL, Crooke ST: Vascular vasopressin receptors mediate phosphatidylinositol turnover and calcium efflux in an established smooth muscle cell line. *Life Sci* 1986; 39: 37-45.
 39. Kelly JM, Abrahams JM, Phillips PA, et al: [¹²⁵I]-[d(CH₂)₃, Sar⁷] AVP: Selective radioligand for V1 vasopressin receptors. *J Recep Res* 1989; 9: 27-41.
 40. Marchingo AJ, Abrahams JM, Woodcock EA, et al: Properties of [³H] 1-desamino-8-D-arginine vasopressin as a radioligand for vasopressin V2 receptors in rat kidney. *Endocrinol* 1988; 122: 1328.
 41. Antoni FA: Receptors mediating the CRH effects of vasopressin and oxytocin. *Ann NY Acad Sci* 1987; 512: 195-204.
 42. Baertschi AJ, Friedli M: A novel type of vasopressin receptor on anterior pituitary corticotrophs. *Endocrinol* 1985; 116: 499-502.
 43. Nambi P, Whitman M, Gessner G, et al: Vasopressin-mediated inhibition of atrial natriuretic factor-stimulated cGMP accumulation in an established smooth muscle cell line. *Proc Natl Acad Sci USA* 1986; 83: 8492-95.
 44. Jard S, Lombard C, Marie J, Devilliers G: Vasopressin receptors from cultured mesangial cells resemble V1a type. *Am J Physiol* 1987; 253: F41-49.
 45. Morel A, O'Carroll AM, Brownstein MJ, Lolait SJ: Molecular cloning and expression of a rat V1a arginine vasopressin receptor. *Nature* 1992; 356: 523-26.
 46. Thibonnier M: Signal transduction of V1-vascular vasopressin receptors. *Reg Peptides* 1992; 38: 1-11.
 47. Nabika T, Velletri PA, Lovenberg W, Beaven MA: Increase in cytosolic calcium and phosphoinositide metabolism induced by angiotensin II and [arg] vasopressin in vascular smooth muscle cell. *J Biol Chem* 1985; 260: 4661-70.
 48. Tahara A, Tomura Y, Wada K, et al: Effect of YM087, a potent nonpeptide vasopressin antagonist, on vasopressin-induced hyperplasia and hypertrophy of cultured vascular smooth-muscle cells. *J Cardio-vasc Pharmacol* 1997; 30(6):759-66.
 49. Tahara A, Saito M, Tsukada J, et al: Vasopressin increases vascular endothelial growth factor secretion from human vascular smooth muscle cells.

- Eur J Pharmacol 1999; 26: 89-94.
50. Tahara A, Tomura Y, Wada K, et al: Effect of YM087, a potent nonpeptide vasopressin antagonist, on vasopressin-induced protein synthesis in neonatal rat cardiomyocyte. *Cardiovasc Res* 1998; 38(1): 198-205.
 51. Maggi M, Baldi E, Genazzani AD, et al: Vasopressin receptors in human seminal vesicles: identification, pharmacologic characterization, and comparison with the vasopressin receptors present in the human kidney. *J Androl* 1989; 10: 393-400.
 52. Liard JF: Peripheral vasodilatation induced by a vasopressin analogue with selective V2-agonism in dogs. *Am J Physiol* 1989; 256: H1621-26.
 53. Lolait SJ, O'Carroll AM, McBride OW, et al: Cloning and characterization of a vasopressin V2 receptor and possible link to nephrogenic diabetes insipidus. *Nature* 1992; 357: 336-39.
 54. Lolait SJ, O'Carroll AM, Mahan LC, et al: Extrapituitary expression of the rat V1b vasopressin receptor gene. *Proc Natl Acad Sci USA* 1995; 92: 6783-87.
 55. Chang WY, Wo NC, Stoev S, et al: Discovery of novel selective hypotensive vasopressin peptides. A new vasodilating vasopressin receptor? *Adv Exp Med Biol* 1998; 449: 451-53.
 56. Kumar R: Endocytosis of the vasopressin receptor. *Seminars Nephrol* 1994; 14: 357-67.
 57. Cowley AW, Liard JF: Cardiovascular actions of vasopressin. In, Gash DM, Boer GJ (eds): *Vasopressin: Principles and Properties*. Plenum: New York, 1987: 389.
 58. Imaizumi T, Thames MD: Influence of intravenous and intracerebroventricular vasopressin on baroreflex control of renal nerve traffic. *Circ Res* 1986; 58: 17-25.
 59. Masaki H, Imaizumi T, Harada S, et al: Effects of a novel orally effective V1-receptor antagonist OPC 21268, on AVP-induced sympathoinhibition. *Am J Physiol* 1993; 264: R1089-94.
 60. Abboud FM, Aylward PE, Floras JS, Gupta BN: Sensitization of aortic and cardiac baroreceptors by arginine vasopressin in mammals. *J Physiol* 1986; 377: 251-65.
 61. Undesser KP, Hasser EM, Haywood JR, et al: Interactions of vasopressin with the area postrema in arterial baroreflex function in conscious rabbits. *Circ Res* 1985; 56: 410-17.
 62. Hasser EM, Bishop VS: Reflex effect of vasopressin after blockade of V1 receptors in the area postrema. *Circ Res* 1990; 67: 265-71, 1990.
 63. Suzuki S, Takeshita A, Imaizumi T, et al: Central nervous system mechanisms involved in inhibition of renal sympathetic nerve activity induced by arginine vasopressin. *Circ Res* 1989; 65: 1390-99.
 64. Malpas SC, Coote JH: Role of vasopressin in sympathetic response to paraventricular nucleus stimulation in anesthetized rats. *Am J Physiol* 1994; 266: R228-36.
 65. Brooks VL, Osborn JW: Hormonal-sympathetic interactions in long-term regulation of arterial pressure: a hypothesis. *Am J Physiol* 1995; 268: R1343-58.
 66. Luk A, Ajaelo I, Wong V, et al: Role of V1 receptors in the action of vasopressin in the baroreflex control of heart rate. *Am J Physiol* 1993; 265: R524-29.
 67. Ebert TJ, Cowley AW, Skelton M: Vasopressin reduces cardiac function and augments cardiopulmonary baroreflex resistance increases in man. *J Clin Invest* 1986; 77: 1136.
 68. Unger T, Rohmeiss P, Demmert G, et al: Differential modulation of the baroreceptor reflex by brain and plasma vasopressin. *Hypertension* 1986; 8 (Suppl II): II-157-62.
 69. Sampey DB, Burrell LM, Widdop RE: Vasopressin V2 receptor enhances gain of baroreflex in conscious spontaneously hypertensive rats. *Am J Physiol* 1999; 276 (3 Pt 2): R872-79.
 70. Hegarty AA, Felder RB: Antagonism of vasopressin V1 receptors in NTS attenuates baroreflex control of renal nerve activity. *Am J Physiol* 1995; 269: H1080-86.
 71. Sved AF, Imaizumi T, Talman WT, Reis DJ: Vasopressin contributes to hypertension caused by nucleus tractus solitarius lesions. *Hypertension* 1985; 7: 262-67.
 72. Lowes VL, McLean LE, Kasting NW, Ferguson AV: Cardiovascular consequences of microinjection of vasopressin and angiotensin II in the area postrema. *Am J Physiol* 1993; 265: R615.
 73. Zhang X, Abdel-Rahman AR, Woolles WR: Vasopressin receptors in the area postrema differentially modulate baroreceptor responses in rats. *Eur J Pharmacol* 1992; 222: 81-91.
 74. Qu L, Hay M, Bishop VS: Administration of AVP to the area postrema alters response of NTS neurons to afferent inputs. *Am J Physiol* 1997; 272 (2 Pt 2): R519-25.
 75. Stebbins CL, Bonigut S, Liviakis LR, Munch PA: Vasopressin acts in the area postrema to attenuate the exercise pressor reflex in anesthetized cats. *Am J Physiol* 274: H2116, 1998.
 76. Goldsmith SR: Arginine vasopressin and baroreflex function after converting enzyme inhibition in normal humans. *Am J Physiol* 1997; 272 (3 Pt 1): E429-36.
 77. Cowley AW Jr., Michalkiewicz M: Vasopressin and neuropeptide Y. In Izzo JL Jr., Sica DA, Black HR (eds): *Hypertension Primer 4th ed*. Dallas: American

- can Heart Assn, 2008: 70.
78. Tsuneyoshi I, Yamada H, Kakihana Y, et al: Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock. *Crit Care Med* 29: 487, 2001.
 79. Gazmuri RJ, Shakeri SA: Low-dose vasopressin for reversing vasodilation during septic shock. *Crit Care Med* 29: 673, 2001.
 80. Argenziano M, Chen JM, Choudhri AF, et al: Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg* 116: 973, 1998.
 81. 2005 International Consensus on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care ECC Science with Treatment Recommendation. Part 2: Adult basic life support. *Circulation* 112 (Suppl): III-5, 2005.
 82. Wenzel V, Lindner KH, Prengel AW, et al: Vasopressin improves vital organ blood flow after prolonged cardiac arrest with postcountershock pulseless electrical activity in pigs. *Crit Care Med* 27: 486, 1999.
 83. Kornberger E, Prengel AW, Krismer A, et al: Vasopressin-mediated adrenocorticotropin release increases plasma cortisol concentrations during cardiopulmonary resuscitation. *Crit Care Med* 28: 3517, 2000.
 84. Lindner KH, Dirks B, Strohmenger H-U, et al: Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet* 349: 535, 1997.
 85. Callaway CW, Hostler D, Doshi AA, et al: Usefulness of vasopressin administered with epinephrine during out-of-hospital cardiac arrest. *Am J Cardiol* 98: 1316, 2006.
 86. Rosenzweig EB, Starc TJ, Chen JM, et al: Intravenous arginine-vasopressin in children with vasodilatory shock after cardiac surgery. *Circulation* 100 (Suppl II): II-182, 1999.
 87. Luckner G, Mayr VD, Jochberger S, et al: Comparison of two dose regimens of arginine vasopressin in advanced vasodilatory shock. *Crit Care Med* 35: 2280, 2007.
 88. Landry DW, Levin HR, Gallant EM, et al: Vasopressin deficiency contributes to the vasodilatation of septic shock. *Circulation* 95: 1122, 1997.
 89. Sharshar T, Carlier R, Blanchard A, et al: Depletion of neurohypophyseal content of vasopressin septic shock. *Crit Care med* 30: 497, 2002.
 90. Hollenberg SM, Tangora JJ, Piotrowski MJ, et al: Impaired microvascular vasoconstrictive responses to vasopressin in septic rats. *Crit Care Med* 25: 869, 1997.
 91. Argenziano M, Chen M, Choudhri AF, et al: A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. *Circulation* 96 (Suppl II): II-286, 1997.
 92. Russell JA, Walley KR, Single J, et al: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 358: 877, 2008.
 93. Lankhuizen IM, van Veghel R, Saxena PR, Schoemaker RG: [Arg⁸]-vasopressin-induced responses on coronary and mesenteric arteries of rats with myocardial infarction: the effects of V_{1a} and V₂ receptor antagonists. *J Cardiovasc Pharmacol* 36: 38, 2000.
 94. Kraft W, Greenberg HE, Waldman SA: Paradoxical hypotension and bradycardia after intravenous arginine vasopressin. *J Clin Pharmacol* 38: 283, 1998.
 95. Decaux G, Soupart A, Vassart G: Non-peptide arginine-vasopressin antagonists: the vaptans. *Lancet* 371: 1624, 2008.
 96. Wang YX, Crofton JT, Share L: Sex differences in the cardiovascular and renal actions of vasopressin in conscious rats. *Am J Physiol* 272: R370, 1997.
 97. Eatman D, Stallone JN, Rutecki GW, et al: Sex differences in extracellular and intracellular calcium-mediated vascular reactivity to vasopressin in rat aorta. *Eur J Pharmacol* 20: 207, 1998.
 98. Liard JF: L-NAME antagonizes vasopressin V₂-induced vasodilation in dogs. *Am J Physiol* 26: H99, 1994.
 99. Leier CV, Dei Cas L, Metra M: Clinical relevance and management of the major electrolyte abnormalities in congestive heart failure: hyponatremia, hypokalemia and hypomagnesemia. *Am Heart J* 128: 254, 1994.
 100. Francis GS, Benedict C, Johnstone DE, et al: Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: a substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation* 81: 1724, 1990.
 101. Bakris G, Burszty M, Gavras I, et al: Role of vasopressin in essential hypertension: racial differences. *J Hyperten* 15: 545, 1997.
 102. Gavras H: Role of vasopressin in clinical hypertension and congestive cardiac failure: interaction with the sympathetic nervous system. *Clin Chem* 37 (10 Pt 2): 1828, 1991.
 103. Rouleau JL, Packer M, Moye L, et al: Prognostic value of neurohormonal activation in patients with an acute myocardial infarction: effect of captopril. *J Am Coll Cardiol* 24: 583, 1994.
 104. Schrier RW: Water and sodium retention in edematous disorders: role of vasopressin and aldosterone.

- Am J Med* 119 Suppl 1: S47, 2006.
105. Ribeiro A, Mulinari R, Gavras I, et al: Sequential elimination of pressor mechanisms in severe hypertension in humans. *Hypertension* 8 Suppl I: I-169, 1986.
 106. Houck PC, Fiksen-Olsen MJ, Britton SL, Romero JC: Role of angiotensin and vasopressin on blood pressure of ganglionic blocked dogs. *Am J Physiol* 244: H115, 1983.
 107. Yatsu T, Tomura Y, Tahara A, et al: Cardiovascular and renal effects of conivaptan hydrochloride (YM087), a vasopressin V1a and V2 receptor antagonist, in dogs with pacing induced congestive heart failure. *Eur J Pharmacol* 376: 239, 1999.
 108. Walker BR, Childs ME, Adams EM: Direct cardiac effects of vasopressin: role of V1 and V2 vasopressinergic receptors. *Am J Physiol Heart Circ Physiol* 255: H261, 1988.
 109. Gavras I, Hatinoglou S, Gavras H: The adrenergic system and the release and pressor action of vasopressin. *Hypertension* 8 (Suppl II): 163, 1986.
 110. Nishida N, Ogura Y, Yamauchi T, Hosoya M, Ota Z: Treatment with cilazapril, angiotensin converting enzyme inhibitor, changes the affinity of arginine vasopressin receptor in the kidney of the spontaneously hypertensive rat. *Res Commun Chem Pathol & Pharm* 84: 143, 1994.
 111. Khokhar AM, Slater JDH, Ma J, Ramage CM: The cardiovascular effect of vasopressin in relation to its plasma concentration in man and its relevance to high blood pressure. *Clin Endocrin* 13: 259, 1980.
 112. Gavras H, Hatzinikolaou P, North WG, et al: Interaction of the sympathetic nervous system with vasopressin and renin in the maintenance of blood pressure. *Hypertension* 4: 400, 1982.
 113. Domanski M, Norman J, Pitt B, et al: Diuretic use, progressive heart failure and death in patients in the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 42: 705, 2003.
 114. Lee DS, Austin PC, Rouleau JL, et al: Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA* 290: 2581, 2003.
 115. De Luca L, Klein L, Udelson JE, et al: Hyponatremia in patients with heart failure. *Am J Cardiol* 96: 19L, 2005.
 116. Klein L, O'Connor CM, Leimberger JD, et al: Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation* 111: 2454, 2005.
 117. Goldsmith SR, Gheorghiade M: Vasopressin antagonism in heart failure. *J Am Coll Cardiol* 46: 1785, 2005.
 118. Finley JJ IV, Konstam MA, Udelson JE: Arginine vasopressin antagonists for the treatment of heart failure and hyponatremia. *Circulation* 118: 410, 2008.
 119. Shoaf SE, Wang Z, Bricmont P, Mallikaarjun S: Pharmacokinetics, pharmacodynamics, and safety of tolvaptan, a nonpeptide AVP antagonist, during ascending single-dose studies in healthy subjects. *J Clin Pharmacol* 47: 1498, 2007.
 120. Yamamura Y, Nakamura S, Itoh S, et al: OPC-41061 a highly potent human vasopressin V2 receptor antagonist: pharmacologic profile and aquaretic effect by single and multiple oral dosing in rats. *J Pharmacol Exp Ther* 287: 860, 1998.
 121. Veeraveedu PT, Watanabe K, Ma M, et al: Effects of V2 receptor antagonist tolvaptan and the loop diuretic furosemide in rats with heart failure. *Biochem Pharmacol* 75: 1322, 2008.
 122. Hirano T, Yoshitaka Y, Nakamura S, et al: Effects of the V2 receptor antagonist OPC 41061 and the loop diuretic furosemide alone and in combination in rats. *J Pharmacol Exp Ther* 292: 288, 2000.
 123. Gheorghiade M, Gottlieb SS, Udelson JE, et al for the Tolvaptan investigators: Vasopressin V2 receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. *Am J Cardiol* 97: 1064, 2006.
 124. Gheorghiade M, Niazi I, Ouyang J, et al Vasopressin V2 receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind randomized trial. *Circulation* 107: 2690, 2003.
 125. Gheorghiade M, Gattis WA, O'Connor CM, et al: Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA* 291: 1963, 2004.
 126. Gheorghiade M, Konstam MA, Burnett JC Jr., et al: Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: EVEREST clinical status trial. *JAMA* 297: 1332, 2007.
 127. Konstam MA, Gheorghiade M, Burnett JC Jr., et al: Efficacy of vasopressin antagonist in heart failure outcome study with tolvaptan (EVEREST) investigators: effects of oral tolvaptan in patients hospitalized for worsening heart failure. The EVEREST Outcomes Trial. *JAMA* 297: 1319, 2007.
 128. Udelson JE, McGrew FA, Flores E, et al: Multicenter, randomized, double-blind, placebo-controlled study on the effect of tolvaptan on left

- ventricular dilation and function in patients with heart failure and systolic dysfunction. *J Am Coll Cardiol* 49: 2151, 2007.
129. Schrier RW, Gross P, Gheorghide M, et al for the SALT investigators: Tolvaptan, a selective oral vasopressin V2-receptor antagonist for hyponatremia. *N Engl J Med* 355: 2099, 2006.
 130. Tolvaptan (Samsca) for hyponatremia. *The Medical Letter* 51: 95, 2009.
 - 130a. Plosker GL: Tolvaptan. *Drugs* 70: 443, 2010.
 - 130b. Ferguson-Myrthil N: Novel agents for the treatment of hyponatremia. A review of conivaptan and tolvaptan. *Cardiol in Rev* 18: 313, 2010.
 131. Kruszynski M, Lammeck B, Manning M, et al: [1(β -mercapto- β -cyclopentamethyl-enepropionic acid)2-(O-methyl)tyrosine] argin vasopressin and [1-(β -mercapto- β - β -cyclopenta-methylenepropionic acid)] argin vasopressin, two highly potent antagonists of the vasopressor response to arginine-vasopressin. *J Med Chem* 23: 364, 1980.
 132. Lee CR, Watkins M, Patterson JH, et al: Vasopressin: a new target for the treatment of heart failure. *Am Heart J* 146: 9, 2003.
 133. Laszlo FA, Csati S, Balaspiri L: Effect of the vasopressin antagonist d/CH2/5Tyr/Et/VAVP on the antidiuretic action of exogenous and endogenous vasopressin. *Acta Endocrinol* 106: 52, 1984.
 134. Yatsu T, Tomura Y, Tahara A, et al: Pharmacological profile of YM087, a novel nonpeptide dual vasopressin V1a and V2 receptor antagonist in dogs. *Eur J Pharmacol* 321: 225, 1997.
 135. Yamamura Y, Ogawa H, Chihara T, et al: OPC 21268, an orally effective, nonpeptide vasopressin V1 receptor antagonist. *Science* 252: 572, 1991.
 136. Burrell LM, Phillips PA, Stephenson J, et al: Effects of an orally active vasopressin V1 antagonist. *Clin Exp Pharmacol Physiol* 20: 388, 1993.
 137. Burnier M, Fricker AF, Hayoz D, et al: Pharmacokinetic and pharmacodynamic effects of YM087, a combined V1/V2 vasopressin receptor antagonist in normal subjects. *Eur J Clin Pharmacol* 55: 633, 1999.
 138. Udelson JE, Smith WB, Hendrix GH, et al: Acute hemodynamic effects of conivaptan, a dual V1A/V2 vasopressin receptor antagonist in patients with advanced heart failure. *Circulation* 104: 2417, 2001.
 139. Abraham WT, Shamsheer AA, McFann K, et al: Aquaretic effect of lixivaptan, an oral, nonpeptide, selective V2 receptor vasopressin antagonist in NYHA functional class II and III chronic heart failure. *J Am Coll Cardiol* 47: 1615, 2006.

References for Chapter 29

Drug-Eluting Stents

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1. Hoff HE, Geddes LA, McCrady JD. The contributions of the horse to knowledge of the heart and *Circulation*. 1. Stephen Hales and the measurement of blood pressure. *Conn Med* 29:795, 1965.
2. Grüntzig AR. Transluminal dilation of coronary-artery stenosis [letter]. *Lancet* 311:263, 1978.
3. Hurst JW. The first coronary angioplasty as described by Andreas Gruentzig. *Am J Cardiol* 57:185, 1986.
4. Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. *N Engl J Med* 354:483, 2006.
5. Sigwart U, Puel J, Mirkovitch V, et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 316:701, 1987.
6. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 331:496, 1994.
- 6a. Frishman WH, Landzberg BR, Weiss M: Pharmacologic therapies for the prevention of restenosis following percutaneous coronary artery interventions. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed*. New York: McGraw Hill 2003: 741.
7. Palmaz JC, Sibbitt RR, Reuter S, et al. Expandable intraluminal graft: a preliminary study. Work in progress. *Radiology* 156:73, 1985.
8. Schatz RA, Palmaz JC, Tio FO, et al. Balloon-expandable intracoronary stents in the adult dog. *Circulation* 76:450, 1987.
9. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 331:489, 1994.
10. Bertrand ME, Rupprecht HJ, Urban P, et al. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 102:624, 2000.
11. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med* 339:1665, 1998.
12. Steinhubl SR, Berger PB, Mann III JT, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention. A randomized controlled trial. *JAMA* 288:2411, 2002.
13. Kushner FG, Hand M, Smith SC Jr, et al. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 120:2271, 2009.
14. Byrne RA, Sarafoff N, Kastrati A, et al. Drug-eluting stents in percutaneous coronary intervention. A benefit-risk assessment. *Drug Safety* 32:749, 2009.
15. Bennett MR. In-stent restenosis: pathology and implications for the development of drug-eluting stents. *Heart* 2003;89:218-24.
16. Moses JW, Leon MG, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 349:1315, 2003.
17. Maluenda G, Lemesle G, Waksman R. A critical

- appraisal of the safety and efficacy of drug-eluting stents. *Clin Pharm Ther* 85:474, 2009.
18. Chatterjee S, Pandey A. Drug-eluting stents: friend or foe? A review of cellular mechanisms behind the effects of paclitaxel and sirolimus eluting stents. *Curr Drug Metab* 9:554, 2008.
 19. Sehgal SN. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc* 35(suppl. 3):7S, 2003.
 20. Gregory CR, Huie P, Billingham ME, et al. Rapamycin inhibits arterial intimal thickening caused by both alloimmune and mechanical injury. Its effect on cellular, growth factor, and cytokine response in injured vessels. *Transplantation* 55:1409, 1993.
 21. Marx SO, Jayaraman T, Go LO, et al. Rapamycin-FKBP inhibits cell cycle regulators of proliferation in vascular smooth muscle cells. *Circ Res* 76:412, 1995.
 22. Poon M, Marx SO, Gallo R, et al. Rapamycin inhibits vascular smooth muscle cell migration. *J Clin Invest* 98:2277, 1996.
 23. Chen J, Fang Y. A novel pathway regulating the mammalian target of rapamycin (mTOR) signaling. *Biochem Pharmacol* 64:1071, 2002.
 24. Imanishi T, Kobayashi K, Kuki S, et al. Sirolimus accelerates senescence of endothelial progenitor cells through telomerase inactivation. *Atherosclerosis* 189:288, 2006.
 25. Deconinck E, Sohler J, De Scheerder I, et al. Pharmaceutical aspects of drug eluting stents. *J Pharm Sci* 97:5047, 2008.
 26. Nakazawa G, Finn AV, Kolodgie FD, et al. A review of current devices and a look at new technology: drug-eluting stents. *Expert Rev Med Devices* 6:33, 2009.
 27. Grube E, Buellesfeld L. Everolimus for stent-based intracoronary applications. *Rev Cardiovasc Med* 5(Suppl. 2):S3, 2004.
 28. Wani MC, Taylor HL, Wall ME, et al. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. *J Am Chem Soc* 93:2325, 1971.
 29. Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by taxol. *Nature* 277:665, 1979.
 30. Rowsinsky EK, Cazenave LA, Donehower RC. Taxol: a novel investigational antimicrotubule agent. *J Natl Cancer Inst* 82:1247, 1990.
 31. Dustin P. Microtubules. *Sci Am* 243:66, 1980.
 32. Rowsinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med* 332:1004, 1995.
 33. Schiff PB, Horwitz SB. Taxol stabilizes microtubules in mouse fibroblast cells. *Proc Natl Acad Sci USA* 77:1561, 1980.
 34. Axel DI, Kunert W, Goggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation* 96:636, 1997.
 35. Wiskirchen J, Schober W, Scharf N, et al. The effects of paclitaxel on the three phases of restenosis: smooth muscle cell proliferation, migration, and matrix formation: an in vitro study. *Invest Radiol* 39:565, 2004.
 36. Farb A, Heller PF, Shroff S, et al. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. *Circulation* 104:479, 2001.
 37. Sollott SJ, Cheng L, Pauly RR, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. *J Clin Invest* 95:1869, 1995.
 38. Heldman AW, Cheng L, Jenkins GM, et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. *Circulation* 103:2289, 2001.
 39. Parry TJ, Brosius R, Thyagarajan R, et al. Drug-eluting stents: sirolimus and paclitaxel differentially affect cultured cells and injured arteries. *Eur J Pharmacol* 524:19, 2005.
 40. Kastrati A, Mehilli J, Dirschniger J, et al. Restenosis after coronary placements of various stent types. *Am J Cardiol* 87:34, 2001.
 41. Shedden L, Oldroyd K, Connolly P. Current issues in coronary stent technology. *Proc Inst Mech Eng H* 223:515, 2009.
 42. Escaned J, Goicolea J, Alfonso F, et al. Propensity and mechanisms of restenosis in different coronary stent designs. Complementary value of the analysis of the luminal gain-loss relationship. *J Am Coll Cardiol* 34:1490, 1999.
 43. Palmaz JC, Bailey S, Marton D, et al. Influence of stent design and material composition on procedure outcome. *J Vascular Surg* 36:1031, 2002.
 44. Lau K-W, Mak K-H, Hung J-S, et al. Clinical impact of stent construction and design in percutaneous coronary intervention. *Am Heart J* 147:764, 2004.
 45. Hara H, Nakamura M, Palmaz JC, et al. Role of stent design and coatings on restenosis and thrombosis. *Adv Drug Delivery Rev* 58:377, 2006.
 46. Kastrati A, Mehilli J, Dirschniger J, et al. Intracoronary stenting and angiographic results: Strut thickness effect on restenosis outcome. (ISAR-STERO) trial. *Circulation* 103:2816, 2001.
 47. Pendyala L, Jabara R, Robinson K, et al. Passive and active polymer coatings for intracoronary stents. *J Interv Cardiol* 22:37, 2009.
 48. Wykrzykowska JJ, Onuma Y, Serruys P. Advances in stent drug delivery: the future is in bioabsorb-

- able stents. *Expert Opin Drug Deliv* 6:113, 2009.
49. Kamath KR, Barry JJ, Miller KM. The Taxus drug-eluting stent: a new paradigm in controlled drug delivery. *Adv Drug Deliv Rev* 58:412, 2006.
 50. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: Delayed healing and late thrombotic risk. *J Am Coll Cardiol* 48:193, 2006.
 51. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: A review of available cases from the research on adverse drug events and reports (RADAR) project. *J Am Coll Cardiol* 47:175, 2006.
 52. Guagliumi G, Farb A, Musumeci G, et al. Images in cardiovascular medicine. Sirolimus-eluting stent implanted in human coronary artery for 16 months: Pathological findings. *Circulation* 107:1340, 2003.
 53. Newsome LT, Kutcher MA, Royster RL. Coronary artery stents: Part I. Evolution of percutaneous coronary intervention. *Anesth Analg* 107:552, 2008.
 54. Carter AJ, Brodeur A, Collingwood R, et al. Tal efficacy of an everolimus eluting cobalt chromium stent. *Catheter Cardiovasc Interv* 68:97, 2006.
 55. Serruys P, Ong A, Pick JJ, et al. A randomized comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent. The SPIRIT first trial. *Eurointervention* 1:58, 2005.
 56. Sheiban I, Villata G, Bollati M, et al. Next-generation drug-eluting stents in coronary artery disease: focus on everolimus-eluting stent (Xience V). *Vasc Health Risk Management* 4:31, 2008.
 - 56a. Kaiser C, Galatius S, Erne P, et al: Drug-eluting versus bare-metal stents in large coronary arteries. *N Engl J Med* November 16, 2010 (epub).
 57. Butt M, Connolly D, Lip GYH. Drug-eluting stents: a comprehensive appraisal. *Future Cardiol* 5:141, 2009.
 - 57a. Garg S, Serruys PW: Coronary stents. Current status. *J Am Coll Cardiol* 56 (Suppl S): S1, 2010.
 58. Indolfi C, Pavia M, Angelillo IF. Drug-eluting stents versus bare metal stents in percutaneous coronary interventions (a meta-analysis). *Am J Cardiol* 95:1146, 2005.
 59. Roiron C, Sanchez P, Bouzamondo A, et al. Drug eluting stents: an updated meta-analysis of randomised controlled trials. *Heart* 92: 641, 2006.
 60. Schampaert E, Moses JW, Schofer J, et al. Sirolimus eluting stents at two years: a pooled analysis of SIRIUS, E-SIRIUS, and C-SIRIUS with emphasis on late revascularizations and stent thromboses. *Am J Cardiol* 98:36, 2006.
 61. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* 27:2784, 2006.
 62. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 370:937, 2007.
 63. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 356:1030, 2007.
 64. Spaulding C, Daemen J, Boersma E, et al. A pooled analysis of data comparing sirolimus-eluting stents with baremetal stents. *N Engl J Med* 356:989, 2007.
 65. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 356:998, 2007.
 66. Pasceri V, Patti G, Speciale G, et al. Meta-analysis of clinical trials on use of drug-eluting stents for treatment of acute myocardial infarction. *Am Heart J* 153:749, 2007.
 67. Boyden TF, Nallamothu BK, Moscucci M, et al. Metaanalysis of randomized trials of drug-eluting stents versus bare metal stents in patients with diabetes mellitus. *Am J Cardiol* 99:1399, 2007.
 68. Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs bare-metal stents in patients with acute myocardial infarction. *Eur Heart J* 28:2706, 2007.
 69. Kumbhani DJ, Bavry AA, Kamdar AR, et al. The effect of drug-eluting stents on intermediate angiographic and clinical outcomes in diabetic patients: insights from randomized clinical trials. *Am Heart J* 155:640, 2008.
 70. Stettler C, Allemann S, Wandel S, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ* 337:a1331, 2008.
 71. Brar SS, Leon MB, Stone GW, et al. Use of drug-eluting stents in acute myocardial infarction: a systematic review and meta-analysis. *J Am Coll Cardiol* 53:1677, 2009.
 72. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation* 119:3198, 2009.
 73. Fajadet J, Wijns W, Laarman GJ, et al. for the ENDEAVOR II Investigators. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 114:798, 2006.
 74. Grube E, Sonoda S, Ikeno F, et al. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. *Circulation* 109:2168, 2004.
 75. Kastrati A, Dibra A, Eberle S, et al. Sirolimus-elut-

- ing stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. *JAMA* 294:819, 2005.
76. Stettler C, Allemann S, Egger M, et al. Efficacy of drug eluting stents in patients with and without diabetes mellitus: indirect comparison of controlled trials. *Heart* 92:650, 2006.
 77. Schömig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J Am Coll Cardiol* 50:1373, 2007.
 78. Gurm HS, Boyden T, Welch KB. Comparative safety and efficacy of a sirolimus-eluting versus paclitaxel-eluting stent: a meta-analysis. *Am Heart J* 155:630, 2008.
 79. Kandzari DE, Leon MB, Popma JJ, et al. for the ENDEAVOR III Investigators. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol* 48:2440, 2006.
 80. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 353:653, 2005.
 81. Galløe AM, Thuesen L, Kelback H, et al. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA* 299:409, 2008.
 82. Morice MC, Colombo A, Meier B, et al. Sirolimus vs paclitaxel-eluting stents in de novo coronary artery lesions. The REALITY trial: a randomized controlled trial. *JAMA* 295:895, 2006.
 83. Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 353:663, 2005.
 84. Leon MB, Mauri L, Popma JJ, et al. for the ENDEAVOR IV Investigators. A randomized comparison of the Endeavor zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions. 12-month outcomes from the ENDEAVOR IV trial. *J Am Coll Cardiol* 55:543, 2010.
 85. Stone GW, Midei M, Newman W, et al. for the SPIRIT III Investigators. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. *Circulation* 119:680, 2009.
 - 85a. Stone GW, Rizvi A, Newman W, et al for the SPIRIT IV Investigators: Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 362: 1663, 2010.
 - 85b. Holmes DR, Kereiakes DJ, Garg S, et al: Stent thrombosis. *J Am Coll Cardiol* 56: 1357, 2010.
 86. Urao N, Okigaki M, Yamada H, et al. Erythropoietin-mobilized endothelial progenitors enhance re-endothelialization via Akt-endothelial nitric oxide synthase activation and prevent neointimal hyperplasia. *Circ Res* 98:1405, 2006.
 87. Butzal M, Loges S, Schweizer M, et al. Rapamycin inhibits proliferation and differentiation of human endothelial progenitor cells *in vitro*. *Exp Cell Res* 300:65, 2004.
 88. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 364:1519, 2004.
 89. Joner M, Finn AV, Frab A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 48:193, 2006.
 90. Luscher TF, Steffel J, Eberli FR, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation* 115:1051, 2007.
 91. Kastrati A. Drug for a while, polymer for life: is it a good solution? *Catheter Cardiovasc Interv* 71:340, 2008.
 92. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 293:2126, 2005.
 93. Eisenstein EL, Anstrom KJ, Fong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 297:159, 2007.
 94. Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 356:1009, 2007.
 95. Steg PG, Fox KA, Eagle KA, et al. Mortality following placement of drug-eluting and bare-metal stents for ST-segment elevation acute myocardial infarction in the Global Registry of Acute Coronary Events. *Eur Heart J* 30:321, 2009.
 96. Buch AN, Javaid A, Steinberg DH, et al. Outcomes after sirolimus- and paclitaxel-eluting stent implantation in patients with insulin-treated diabetes mellitus. *Am J Cardiol* 101:1253, 2008.
 97. Stankovic G, Cosgrave J, Chieffo A, et al. Impact of sirolimus-eluting and paclitaxel-eluting stents on outcome in patients with diabetes mellitus and stenting in more than one coronary artery. *Am J Cardiol* 98:326, 2006.
 98. Daemen J, Garcia-Garcia HM, Kukreja N, et al. The long-term value of sirolimus- and paclitaxel-elut-

- ing stents over bare metal stents in patients with diabetes mellitus. *Eur Heart J* 28:26, 2007.
99. Mauri L, Silbaugh TS, Garg O, et al. Drug-eluting or bare-metal stents for acute myocardial infarction. *N Engl J Med* 359:1330, 2008.
 100. Garg P, Normand SL, Silbaugh TS, et al. Drug-eluting or bare-metal stenting in patients with diabetes mellitus: results from the Massachusetts Data Analysis Center Registry. *Circulation* 118:2277, 2008.
 - 100a. Garg S, Serruys PW: Coronary stents. Looking forward. *J Am Coll Cardiol* 56 Suppl S: S43, 2010.
 - 100b. Serruys PW, Onuma Y, Ormiston JA, et al: Evaluation of the second generation of a bioresorbable everolimus drug-eluting vascular scaffold for treatment of de novo coronary artery stenosis. Six-month clinical and imaging outcomes. *Circulation* 122: 2301, 2010.
 - 100c. Bittl JA: Bioresorbable stents. The next revolution. *Circulation* 122: 2236, 2010.
 101. Joyal D, Fillion KB, Eisenberg MJ: Effectiveness and safety of drug-eluting stents in vein grafts: a meta-analysis. *Am Heart J* 159: 159, 2010.
 102. Abualsaud AO, Eisenberg MJ: Perioperative management of patients with drug-eluting stents. *J Am Coll Cardiol: Cardiovasc Intervent* 3: 131, 2010.
 103. El-Menyar AA, Suwaidi JA, Holmes DR Jr.: Use of drug-eluting stents in patients with coronary artery disease and renal insufficiency. *Mayo Clin Proc* 85: 165, 2010.
 104. Jabara R, Chronos N, Conway D, et al. Evaluation of a novel slow-release paclitaxel-eluting stent with a bioabsorbable polymeric surface coating. *J Am Coll Cardiol Interv* 1:81, 2008.
 105. Hamilos MI, Ostojic M, Beleslin B, et al. Differential effects of drug-eluting stents on local endothelium-dependent coronary vasomotion. *J Am Coll Cardiol* 51:2123, 2008.
 106. Inoue T, Sata M, Hikichi Y, et al. Mobilization of CD34-positive bone marrow-derived cells after coronary stent implantation : Impact on restenosis. *Circulation* 115:553, 2007.
 107. Aoki J, Serruys PW, van Beusekom H, et al. Endothelial progenitor cell capture by stents coated with antibody against CD34. The HEALING-FIM (healthy endothelial accelerated lining inhibits neointimal growth – first in man) registry. *J Am Coll Cardiol* 45:1574, 2005.
 108. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* 94:1690, 1996.
 109. Jabara R, Chronos N, Tondato F, et al. Toxic vessel reaction to an absorbable polymer-based paclitaxel-eluting stent in pig coronary arteries. *J Invasive Cardiol* 18:383, 2006.
 110. Kedhi E, Joesoef KS, McFadden E, et al: Second generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet* 375: 201, 2010.

References for Chapter 30

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1. Eisenberg DM, Kessler RC, Foster C, et al: Unconventional medicine in the United States. *N Engl J Med* 328: 246, 1993.
2. Pearson NI, Chesney MA: The CAM education program of the National Center for Complementary and Alternative Medicine: an overview. *Acad Med* 82: 921, 2007.
3. Krucoff MW, Liebowitz R, Vogel JHK, Mark D: Complementary and alternative medicine therapy in cardiovascular care. In Fuster V, Alexander RW, O'Rourke RA, Roberts R, King SB, Prystowsky E, Nash IS: *Hurst's The Heart 11th ed.* New York: McGraw Hill 2004; 2463.
4. Frishman WH, Lee W-N, Glasser SP, et al: The placebo effect in cardiovascular disease. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed.* New York: McGraw Hill 2003: 15.
5. Matter-Walstra K, Schoeni-Affolter F, Widmer M, et al: Patient-based evaluations of primary care for cardiovascular diseases: a comparison between conventional and complementary medicine. *J Eval Clin Pract* 14:75, 2008.
6. Miller KL, Liebowitz RS, Newby LK. Complementary and alternative medicine in cardiovascular disease: a review of biologically based approaches. *Am Heart J* 147:401, 2004.
7. Morris CD, Carson S: Routine vitamin supplementation to prevent cardiovascular disease: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 139: 56, 2003.
8. Frishman WH, Sinatra ST, Kruger N: Nutraceuticals and cardiovascular illness. In Frishman WH, Weintraub MI, Micozzi M: *Complementary & Integrative Therapies for Cardiovascular Disease.* St. Louis: Elsevier 2005: 58.
9. Ridinger MHT: Nutraceuticals: miracle or meme? *Nature* 82: 352-56, 2007.
- 9a. Haller CA: Nutraceuticals: has there been any progress? *Clin Pharmacol Therap* 87: 137, 2010.
10. Riccioni G, Mancini B, Di Ilio E, et al: Protective effect of lycopene in cardiovascular disease. *Eur Rev Med Pharmacol Sci* 12:183, 2008.
11. Frishman WH, Kruger NA, Nayak DU, Vakili BA: Antioxidant vitamins and enzymatic and synthetic oxygen-derived free-radical scavengers in the prevention and treatment of cardiovascular disease. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed.* New York: McGraw-Hill 2003: 407.
12. Saremi A, Arora R: Vitamin E and cardiovascular disease. *Am J Therap* 17: e56, 2010.
13. Rapola JM, Virtamo J, Ripatti S, et al: Randomized trial of alpha-tocopherol and beta carotene supplements on incidence of major coronary events in men with previous myocardial infarction. *Lancet* 349:1715, 1997.
14. Stephens NG, Parsons A, Schofield PM, et al: Randomized controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study. *Lancet* 347:781, 1996.
15. Yusuf S, Sleight P, Pogue J, et al: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 342:145, 2000.
16. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI Prevenzione trial. *Lancet* 354:447, 1999.
17. Jialal I, Traber M, Deveraj S: Is there a vitamin E paradox? *Curr Opin Lipidol* 12:49, 2001.

18. Vivekananthan DP, Penn MS, Sapp SK, et al: Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomized trials. *Lancet* 361: 2017, 2003.
19. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of antioxidant vitamin supplement in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 360: 23, 2002
20. Rasool AH, Rahman AR, Yuen KH, et al: Arterial compliance and vitamin E blood levels with a self emulsifying preparation of tocotrienol rich vitamin E. *Arch Pharm Res* 31: 1212 2008.
21. Glynn RJ, Ridker PM, Goldhaber SZ, Zee RYL, Buring JE: Effects of random allocation of vitamin E supplementation on the occurrence of venous thromboembolism. Report from the Women's Health Study. *Circulation* 116: 1497, 2007.
22. Cook NR, Albert CM, Gaziano JM, et al: A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. *Arch Intern Med* 168:773, 2008.
- 22a. Roberts JM, Myatt L, Spong CY, et al: Vitamins C and E to prevent complications of pregnancy-associated hypertension. *N Engl J Med* 362: 1282, 2010.
23. Sesso HD, Buring JE, Christen WG, et al: Vitamins E and C in the prevention of cardiovascular disease in men. The Physicians' Health Study II randomized controlled trial. *JAMA* 300: 2123, 2008.
24. Hatzigeorgiou C, Taylor AJ, Feuerstein IM, Bautista L, O'Malley PG: Antioxidant vitamin intake and subclinical coronary atherosclerosis. *Prevent Cardiol* 9: 75, 2006.
25. Kritchevsky SB, Shimakawa T, Tell GS, et al: Dietary antioxidants and carotid artery wall thickness: The ARIC Study. *Circulation* 92:2142, 1995.
26. Osganian SK, Stampfer MJ, Rimm E, et al: Vitamin C and risk of coronary heart disease in women. *J Am Coll Cardiol* 42: 246, 2003.
27. Kaw KT, Bingham S, Welch A, et al: Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk Prospective Study: A prospective population study. *Lancet* 357:657, 2001.
28. Mikirova NA, Thomas IE, Riordan NH: Anti-angiogenic effect of high doses of ascorbic acid. *J Transl Med* 6:50, 2008.
29. Kruger NA, Frishman WH, Hussain J: Fish oils, the B vitamins and folic acid as cardiovascular protective agents. In Frishman WH, Sonnenblick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed*. New York: McGraw Hill 2003: 381.
30. Chan P, Huang TY, Chen YJ, et al: Randomized, double-blind, placebo-controlled study of the safety and efficacy of vitamin B complex in the treatment of nocturnal leg cramps in elderly patients with hypertension. *J Clin Pharmacol* 38:1151, 1998.
31. McCully KS: Vascular pathology of homocysteinemia: Implications for the pathogenesis of arteriosclerosis. *Am J Pathol* 56: 111, 1969.
32. Selhub J, Jacques PF, Bostom AG, et al: Association between plasma homocysteine concentrations and extracranial carotid artery disease. *N Engl J Med* 332:286, 1995.
33. Ridker PM, Manson JE, Buring JE, et al: Homocysteine and risk of cardiovascular disease among post-menopausal women. *JAMA* 281:1817, 1999.
34. Hankey GJ, Eikeboom JW: Homocysteine and vascular disease. *Lancet* 354:407, 1999.
35. Lonn E: Homocysteine-lowering B vitamin therapy in cardiovascular prevention. Wrong Again? *JAMA* 299:2086, 2008.
36. Toole JF, Malinow MR, Chambless LE, et al: Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* 291: 565, 2004.
37. Spence JD, Bang H, Chambless LE, Stampfer MJ: Vitamin Intervention for Stroke Prevention trial: an efficacy analysis. *Stroke* 36: 2404, 2005.
38. Ray JG, Kearon C, Yi Q, et al: Homocysteine-lowering therapy and risk for venous thromboembolism: a randomized trial. *Ann Intern Med* 146: 761, 2007.
39. Bønaa KH, Njølstad I, Ueland PM, et al: Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 354: 1578, 2006.
40. Bleie O, Semb AG, Grundt H, et al: Homocysteine-lowering therapy does not affect inflammatory markers of atherosclerosis in patients with stable coronary artery disease. *J Intern Med* 262: 244, 2007.
- 40a. Miller ER III, Juraschek S, Pastor-Barriuso R, et al: Meta-analysis of folic acid supplementation trials on risk of cardiovascular disease and risk interaction with baseline homocysteine levels. *Am J Cardiol* 106: 517, 2010.
- 40b. Ebbing M, Bønaa KH, Nygård O, et al: Cancer incidence and mortality after treatment with folic acid and vitamin B₁₂. *JAMA* 302: 2119, 2009.
41. Albert CM, Cook NR, Gaziano JM, et al: Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial.

- JAMA* 299:2027, 2008.
42. Jamison RL, Hartigan P, Kaulman JS, Goldfarb DS, Warren SR, Guarino PD, Gaziano JM for the Veterans Affairs Site Investigators: Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease. A randomized controlled trial. *JAMA* 298: 1163, 2007.
 43. Kamanna VS, Kashyap ML: Mechanism of action of niacin. *Am J Cardiol* 101(8A): 20B, 2008.
 44. Meyers CD, Carr MC, Park S, Brunzell JD: Varying cost and free nicotinic acid content in over-the-counter niacin preparations for dyslipidemia. *Ann Intern Med* 139: 996, 2003.
 45. Morgan JM, Capuzzi DM, Guyton JR: A new extended-release niacin (Niaspan):Efficacy, tolerability, and safety in hypercholesterolemic patients. *Am J Cardiol* 82:29U, 1998.
 46. Goldberg A, Alagona P Jr, Capuzzi DM, et al: Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. *Am J Cardiol* 85: 1100, 2000.
 47. Cefali EA, Simmons PD, Stanek EJ, Shamp TR: Improved control of niacin-induced flushing using an optimized once-daily, extended-release niacin formulation. *Int J Clin Pharmacol Ther* 44:633, 2006.
 48. Paolini JF, Mitchel YB, Reyes R, Kheru U, Lai E, Watson DJ, et al: Effects of laropiprant on nicotinic acid-induced flushing in patients with dyslipidemia. *Am J Cardiol* 101:625, 2008.
 49. Lai E, Lepeleire I, Crumley TM, Liu F, Wenning LA, Michiels N, et al: Suppression of niacin-induced vasodilation with an antagonist to prostaglandin D2 receptor subtype 1. *Clin Pharmacol Therap* 81:849, 2007.
 50. Somjen D, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, et al: 25-Hydroxyvitamin D3-1 α -hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. *Circulation* 111: 1666, 2005.
 51. Merke J, Milde P, Lewicka S, Hugel U, Klaus G, Mangelsdorf DJ, et al: Identification and regulation of 1,25-hydroxyvitamin D3 receptor activity and biosynthesis of 1,25-dihydroxyvitamin D3: studies in cultured bovine aortic endothelial cells and human dermal capillaries. *J Clin Invest* 83: 1903, 1989.
 52. Holick MF: High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 81: 353, 2006.
 53. Wallis DE, Penckofer S, Sizemore GW: The "Sunshine Deficit" and cardiovascular disease. *Circulation* 118: 1476, 2008.
 54. Zitterman A, Schleithoff SS, Koerfer R: Putting cardiovascular disease and vitamin D deficiency into perspective. *Br J Nutri* 94: 483, 2005.
 55. Giovannucci E, Liu Y, Hollis W, et al: 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med* 168: 1174, 2008.
 56. Resnick LM, Muller FB, Laragh JH: Calcium-regulating hormones in essential hypertension: relation to plasma renin activity and sodium metabolism. *Ann Intern Med* 105: 649, 1986.
 57. Zittermann A, Schleithoff SS, Koerfer R: Vitamin D and vascular calcification. *Curr Opin Lipidol* 18: 41, 2007.
 58. Wang TJ, Pencina MJ, Booth SL, et al: Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 117: 503, 2008.
 59. Pilz S, Dobnig H, Fischer JE, et al: Low vitamin D levels predict stroke in patients referred to coronary angiography. *Stroke* 39: 2611, 2008
 60. Pilz S, Marz W, Wellnitz B, et al: Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *J Clin Endocrinol Metab* 93: 3927, 2008.
 61. Fleck A: Latitude and ischaemic heart disease. *Lancet* 1: 613, 1989.
 62. Zittermann A, Koerfer R: Vitamin D in the prevention and treatment of coronary heart disease. *Curr Opin Clin Nutri Metab Care* 11: 752, 2008.
 - 62a. Pittas AG, Chung M, Trikalinos T, et al: Systematic review: vitamin D and cardiometabolic outcomes. *Ann Intern Med* 152: 307, 2010.
 - 62b. Wang L, Manson JE, Song Y, Sesso HD: Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 152: 315, 2010.
 63. Erkkila AT, Booth SL: Vitamin K intake and atherosclerosis. *Curr Opin Lipidol* 19: 39, 2008.
 64. Greenberg ER, Baron JA, Karagas MR, et al: Mortality associated with low plasma concentration of beta carotene and the effect of oral supplementation. *JAMA* 275:699, 1996.
 65. Gey FK, Puska P: Plasma vitamin E and A inversely correlated to mortality from ischemic heart disease in cross-cultural epidemiology. *Ann NY Acad Sci* 570:268, 1989.
 66. Kardinaal AF, Kok FJ, Ringstad J, et al: Antioxidants in adipose tissue and risk of myocardial infarction: The EURAMIC Study. *Lancet* 342:1379, 1993.
 67. Gitenay D, Lyan B, Ramebeau M, et al: Comparison of lycopene and tomato effects on biomarkers of oxidative stress in vitamin E deficient rats. *Eur J Nat* 46:468, 2008.
 68. Ullah MF, Khan MW: Food as medicine: potential

- therapeutic tendencies of plant derived polyphenolic compounds. *Asian Pac J Cancer Prev* 9:187, 2008.
69. Maxwell S, Cruickshank A, Thorpe D: Red wine and antioxidant activity in serum. *Lancet* 344:193, 1994.
 70. Hertog MC, Feskens EJ, Hollman PC, et al: Dietary antioxidant flavonoids and risk of coronary heart disease: The Zutphen Elderly Study. *Lancet* 342:1007, 1993.
 71. Duffy SJ, Keaney JF, Holbrook M, et al: Short- and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. *Circulation* 104:151, 2001.
 72. Gresele P, Pignatelli P, Guglielmini G, et al: Resveratrol, at concentrations attainable with moderate wine consumption, stimulates human platelet nitric oxide production. *J Nutr* 138:1602, 2008.
 73. Clinical Trial: Trial to assess bioavailability of flavonoids and phenolic acids. www.clinicaltrials.gov/ct.
 74. Rimm EB, Katan MB, Ascherio A, et al: Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. *Ann Intern Med* 125:384, 1996.
 75. Clinical Trial: Trial to assess Concord Grape Juice. www.clinicaltrials.gov/ct.
 76. Frishman WH, DelVecchio A, Sanal S, Ismail A: Cardiovascular manifestations of substance abuse. Part 2: Alcohol, amphetamines, heroin, cannabis, caffeine. *Heart Dis* 5: 253, 2003.
 77. Mehrinfar R, Frishman WH: Flavonol-rich cocoa. A cardioprotective nutraceutical. *Cardiol in Rev* 16: 109, 2008.
 78. Hollenberg NK, Fisher NDL: Is it the dark in dark chocolate? *Circulation* 116: 2360, 2007.
 79. Houston MC, Harper KJ: Potassium, magnesium, and calcium: their role in both the cause and treatment of hypertension. *J Clin Hypertens (Greenwich)* 10(7 Suppl 2):3, 2008.
 80. Cojocaru IM, Cojocaru M, Burcin C, et al: Serum magnesium in patients with acute ischemic stroke. *Rom J Intern Med* 45:269, 2008.
 81. McLean RM: Magnesium and its therapeutic uses: A review. *Am J Med* 96:63, 1994.
 82. Shechter M: Oral magnesium in coronary artery disease: Fresh insight on thrombus inhibition. *Magn Rep* 1-4, 1999.
 83. Ho KM: Intravenous magnesium for cardiac arrhythmias: jack of all trades. *Magnes Res* 21:65, 2008.
 84. Lichodziejewska B, Klos J, Rezler J, et al: Clinical symptoms of mitral valve prolapse are related to hypomagnesemia and attenuated by magnesium supplementation. *Am J Cardiol* 79:768, 1997.
 85. Preuss HG, Wallerstedt D, Talpur N, et al: Effects of niacin-bound chromium and grape seed proanthocyanidins extract on the lipid profile of hypercholesterolemic subjects: A pilot study. *J Med* 31:227, 2000.
 86. Grundy SM: Cholesterol management in the era of managed care. *Am J Cardiol* 85:3A, 2000.
 87. McLaren DS: Vitamin deficiency, toxicity and dependency. In Berkow R, Fletcher AJ, Bondy PK, et al (eds): *The Merck Manual 16th ed.* Rahway NJ: Merck Research Labs., 1992.
 88. Salvini S, Hennekens CH, Morris JS, et al: Plasma levels of the antioxidant selenium and risk of myocardial infarction among US physicians. *Am J Cardiol* 76:1218, 1995.
 89. Kok FJ, Hofman A, Witteman JCM, et al: Decreased selenium levels in acute myocardial infarction. *JAMA* 261:1161, 1989.
 90. Hercberg S, Galan P, Preziosi P, et al: The SU.VI. MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med* 164:2335, 2004.
 91. Salonen JT, Salonen R, Seppanen K, et al: Interactions of serum copper, selenium, and low density lipoprotein cholesterol in atherosclerosis. *BMJ* 302:756, 1991.
 92. Kuklinski B, Weissenbacher E, Fahnrich A, et al: Coenzyme Q10 and antioxidants in acute myocardial infarction. *Mol Aspects Med* 15: S143, 1994.
 93. Molyneux SL, Young JM, Florkowski CM, et al: Coenzyme q10: is there a clinical role and a case for measurement? *Clin Biochem Rev* 29:71, 2008.
 94. Langsjoen PH, Langsjoen AM: Overview of the use of CoQ10 in cardiovascular disease. *Biofactors* 9: 273, 1999.
 95. Miguel-Carrasco JL, Mate A, Monserrat MT, et al: The role of inflammatory markers in the cardioprotective effect of L-carnitine in L-NAME-induced hypertension. *Am J Hypertens* 21: 1231,2008.
 96. Wierzbicki AS: A fishy business: omega-3 fatty acids and cardiovascular disease. *Int J Clin Pract* 62:1142, 2008.
 - 96a. Weitz D, Weintraub H, Fisher E, Schwartzbard AZ: Fish oil for the treatment of cardiovascular disease. *Cardiol in Rev* 18: 258, 2010.
 97. Brouwer IA, Zock PL, Camm AJ, et al: Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *JAMA* 295:2613, 2006.
 - 97a. deLeiris J, deLorgeril M, Boucher F: Fish oil and heart health. *J Cardiovasc Pharmacol* 54: 378, 2009.
 98. O'Keefe J, Harris W: Omega-3 fatty acids: Time

- for clinical implementation? *Am J Cardiol* 85:1239, 2000.
99. GISSI-HF Investigators: Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 372: 1223, 2008.
 100. Fonarow GC: Statins and n-3 fatty acid supplementation in heart failure. *Lancet* 372: 1195, 2008.
 101. Albert CM, Hennekens CH, O'Donnell CJ, et al: Fish consumption and risk of sudden cardiac death. *JAMA* 279: 23, 1998.
 102. Yokoyama M, Origasa H, Matsuzaki M, et al: Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 369: 1090, 2007.
 103. Kromhout D, Giltay EJ, Geleijnse JM for the Alpha Omega Trial Group: n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med* 363: 2015, 2010.
 - 103a. Saravanan P, Davidson NC, Schmidt EB, Calder PC: Cardiovascular effects of marine omega-3 fatty acids. *Lancet* 375: 540, 2010.
 104. Siani A, Pagano E, Iacone R, et al: Blood pressure and metabolic changes during dietary L-arginine supplementation in humans. *Am J Hypertens* 13:547, 2000.
 105. Candipan RC, Wang B, Buitrago R, et al: Regression or progression. Dependency on vascular nitric oxide. *Arteriothromb Vasc Biol* 16:44, 1996.
 106. Drexler H, Zeiher AM, Meinzer K, Just H: Correction of endothelial dysfunction in coronary microcirculation of hypercholesterolemic patients by L-arginine. *Lancet* 338:1546, 1991.
 107. Egashira K, Hirooka Y, Kuga T, et al: Effects of L-arginine supplementation on endothelium-dependent coronary vasodilation in patients with angina pectoris and normal coronary angiograms. *Circulation* 94:130, 1996.
 108. Quyyumi A, Dakak N, Diodati J, et al: Effect of L-arginine on human coronary endothelium-dependent and physiologic vasodilation. *J Am Coll Cardiol* 30:1220, 1997.
 109. Lerman A, Burnett JC Jr, Higano ST, et al: Long-term L-arginine supplementation improves small-vessel coronary endothelial function in humans. *Circulation* 97:2123, 1998.
 110. Blum A, Hathaway L, Mincemoyer R, et al: Oral L-arginine in patients with coronary artery disease on medical management. *Circulation* 101:2160, 2000.
 111. Loscalzo J, Welch G: Nitric oxide and its role in the cardiovascular system. *Prog Cardiovasc Dis* 38:87, 1995.
 112. Quyyumi A: Does acute improvement of endothelial dysfunction in coronary artery disease improve myocardial ischemia? A double-blind comparison of parenteral D- and L-arginine. *J Am Coll Cardiol* 32:904, 1998.
 113. Ito T, Kimura Y, Uozumi Y, et al: Taurine depletion caused by knocking out the taurine transporter gene leads to cardiomyopathy with cardiac atrophy. *J Mol Cell Cardiol* 44:927, 2008.
 114. Oudit GY, Trivieri MG, Khaper N, et al: Taurine supplementation reduces oxidative stress and improves cardiovascular function in an iron-overload murine model. *Circulation* 109: 1877, 2004.
 - 114a. Stamler J, Brown IJ, Daviglius ML, et al for the INTERMAP Research Group: Glutamic acid, the main dietary amino acid, and blood pressure. The INTERMAP study (International Collaborative Study of Macronutrients, Micronutrients and Blood Pressure). *Circulation* 120: 221, 2009.
 115. Solerte SB, Fioravanti M, Locatelli E, et al: Improvement of blood glucose control and insulin sensitivity during a long-term (60 weeks) randomized study with amino acid dietary supplements in elderly subjects with type 2 diabetes mellitus. *Am J Cardiol* 101 Suppl 11A: 82EE, 2008.
 116. Kalantar-Zadeh K, Anker SD, Horwich TB, Fonarow GC: Nutritional and anti-inflammatory interventions in chronic heart failure. *Am J Cardiol* 101 Suppl 11A: 89E, 2008.
 117. Aquilani R, Viglio S, Iadarola P, et al: Oral amino acid supplements improve exercise capacities in elderly patients with chronic heart failure. *Am J Cardiol* 101 Suppl 11A:104E, 2008.
 118. Corsetti G, Pasini E, D'Antona G, et al: Morphometric changes induced by amino acid supplementation in skeletal and cardiac muscles of old mice. *Am J Cardiol* 101 Suppl 11A:26E, 2008.
 119. Scarabelli TM, Pasini E, Stephanou A, et al: Nutritional supplementation with mixed essential amino acids enhances myocyte survival, preserving mitochondrial functional capacity during ischemia-reperfusion injury. *Am J Cardiol* 93 (8A): 35A, 2004.
 120. Frishman WH, Sinatra ST, Moizuddin M: Herbal approach to cardiac disease. In Frishman WH, Weintraub MI, Micozzi M: *Complementary & Integrative Therapies for Cardiovascular Disease*. St. Louis: Elsevier, 2005: 86.
 121. Goldman P: Herbal medicines today and the roots of modern pharmacology. *Ann Intern Med* 135:594, 2001.
 122. Sinatra ST, Frishman WH, Peterson SJ, Lin G: Use of alternative/complementary medicine in treating cardiovascular disease. In Frishman WH, Sonnen-

- blick EH, Sica DA (eds): *Cardiovascular Pharmacotherapeutics 2nd ed.* New York: McGraw Hill 2003:857.
123. Marcus DM, Grollman AP: Botanical medicine—the need for new regulations (sounding board). *N Engl J Med* 347: 2073, 2002.
 124. Slifman NR, Obermeyer WR, Musser SM, et al: Contamination of botanical dietary supplements by *Digitalis lanata*. *N Engl J Med* 339: 806, 1998.
 125. Radford DJ, Gillies AD, Hinds JA, et al: Naturally occurring cardiac glycosides. *Med J Aust* 144: 540, 1986.
 126. Dasgupta A, Tso G, Wells A: Effect of Asian ginseng, Siberian ginseng, and Indian ayurvedic medicine Ashwagandha on serum digoxin measurement by Digoxin III, a new digoxin immunoassay. *J Clin Lab Anal* 22: 295, 2008.
 127. Aaronson K: HERB CHF (Hawthorn Extract Randomized Blinded Chronic HF Study) presented at the 8th Annual Scientific Meeting of the Heart Failure Society of America. September 12-15, 2004, Toronto, Canada.
 128. Zick SM, Gillespie B, Aaronson KD: The effect of *Crataegus oxycantha* Special Extract WS 1442 on clinical progression in patients with mild to moderate symptoms of heart failure. *Eur J Heart Fail* 10: 587, 2008.
 129. Sutter MC, Wang YX: Recent cardiovascular drugs from Chinese medicinal plants. *Cardiovasc Res* 27: 1891, 1993.
 130. Kawashima K, Hayakawa T, Miwa Y, et al: Structure and hypotensive activity relationships of tetrandrine derivatives in stroke-prone spontaneously hypertensive rats. *Gen Pharmacol* 21:343, 1990.
 131. Ody P: *The Complete Medicinal Herbal*. New York: Dorling Kindersley, 1993.
 132. Ma G, Ding S, Feng Y, et al: Tetramethylpyrazine-eluting stents prevented in-stent restenosis in a porcine model. *J Cardiovasc Pharmacol* 50:201, 2007.
 133. Kuramochi T, Chu J, Suga T: Gou-teng (from *Uncaria rhynchophylla* Miquel) induced endothelium-dependent and independent relaxations in the isolated rat aorta. *Life Sci* 54:2061, 1994.
 134. Wang L, Li W, Liu Y: Hypotensive effect and toxicology of total alkaloids and veratramine from roots and rhizomes of *Veratrum nigrum* L. in spontaneously hypertensive rats. *Pharmazie* 63: 606, 2008.
 135. Chang Q, Zuo Z, Harrison F, Chow MSS: Hawthorn. *J Clin Pharmacol* 42: 605-12, 2002.
 136. Vibes J, Lasserre B, Gleye J, et al: Inhibition of thromboxane A2 biosynthesis in vitro by the main components of *Crataegus oxyacantha* (hawthorn) flower heads. *Prostaglandins Leukot Essent Fatty Acids* 50:173, 1994.
 137. Shanthi S, Parasakthy K, Deepalakshmi PD, et al: Hypolipidemic activity of tincture of *Crataegus* in rats. *Indian J Biochem Biophys* 31:143, 1994.
 138. Nasa Y, Hashizume H, Hoque AN, et al: Protective effect of *Crataegus* extract on the cardiac mechanical dysfunction in isolated perfused working rat heart. *Arzneimittelforschung* 43:945, 1993.
 139. Roddewig C, Hensel H: Reaction of local myocardial blood flow in non-anesthetized dogs and anesthetized cats to the oral and parenteral administration of a *Crataegus* fraction (oligomere procyanidines) [German] *Arzneimittelforschung* 27:1407, 1977.
 140. Baughman KL, Bradley DJ: Hawthorn extract: is it time to turn over a new leaf? *Am J Med* 114: 700, 2003.
 141. Pittler MH, Schmidt K, Ernst E: Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials. *Am J Med* 114: 665, 2003.
 142. Schussler M, Holz J, Fricke U: Myocardial effects of flavonoids from *Crataegus* species. *Arzneim Forsch* 45:842, 1995.
 143. Zhang W, Wojta J, Binder BR: Effect of notoginsenoside R1 on the synthesis of tissue-type plasminogen activator and plasminogen activator inhibitor-1 in cultured human umbilical vein endothelial cells. *Arterioscler Thromb* 14:1040, 1994.
 144. Lin SG, Zheng XL, Chen QY, et al: Effect of *Panax notoginseng* saponins on increased proliferation of cultured aortic smooth muscle cells stimulated by hypercholesterolemic serum. *Chung Kuo Yao Li Hsueh Pao* 14:314, 1993.
 145. Zhang YG, Zhang HG, Zhang GY, et al: *Panax* Notoginseng saponins attenuate atherosclerosis in rats by regulating the blood lipid profile and an anti-inflammatory action. *Clin Exp Pharmacol Physiol* 35: 1238, 2008.
 146. Lam FF, Yeung JH, Chan KM, et al: Dihydrotanshinone, a lipophilic component of *Salvia Miltiorrhiza* (danshen), relaxes rat coronary artery by inhibition of calcium channels. *J Ethnopharmacol* 119: 318, 2008.
 147. Ried K, Frank OR, Stocks NP, et al: Effect of garlic on blood pressure: A systematic review and meta-analysis. *BMC Cardiovascular Disord* 8:13, 2008.
 148. Lau BH: Suppression of LDL oxidation by garlic compounds is a possible mechanism of cardiovascular health benefit. *J Nutr* 136: 765S, 2006.
 149. Gardner CD, Lawson LD, Block E, et al: Effect of raw garlic vs commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia: a randomized clinical trial. *Arch Intern Med* 167:325, 2007.

150. Ackermann RT, Mulrow CD, Ramirez G, et al: Garlic shows promise for improving some cardiovascular risk factors. *Arch Intern Med* 161: 813, 2001.
151. Silagy CA, Neil HA: A meta-analysis of the effect of garlic on blood pressure. *J Hypertens* 12:463, 1994.
152. Silagy C, Neil A: Garlic as a lipid lowering agent—a meta-analysis. *J R Coll Physicians Lond* 28:39, 1994.
153. Clinical Trial: Trial to identify the anti-blood-clotting compounds in garlic. www.clinicaltrials.gov/ct.
154. Kong WJ, Wei J, Zuo ZY, et al: Combination of simvastatin with berberine improves the lipid-lowering efficacy. *Metabolism* 57: 1029, 2008.
155. Low Dog T: Herbs in cardiovascular diseases. *Botanical Medicine in Modern Clinical Practice 8th Annual Course*. Columbia University, New York, June 9-13, 2003.
156. Saper RB, Phillips RS, Sehgal A, et al: Lead, mercury and arsenic in US- and Indian-manufactured ayurvedic medicines sold via the internet. *JAMA* 300: 915, 2008.
157. Clinical Trials: Safety of an herbal treatment for high cholesterol in individuals with statin intolerance. www.clinicaltrials.gov/ct.
158. Clinical Trials: Statin therapy vs. therapeutic lifestyle changes and supplements. www.clinicaltrials.gov/ct.
- 158a. Becker DJ, Gordon RY, Halbert SC, et al: Red yeast rice for dyslipidemia in statin-intolerant patients. *Ann Intern Med* 150: 830, 2009.
159. Gardner CD, Taylor-Piliae RE, Kiazand A, et al: Effect of Ginkgo biloba (EGb 761) on treadmill walking time among adults with peripheral artery disease: a randomized clinical trial. *J Cardiopulm Rehabil Prev* 28: 258, 2008.
160. Stevermer JJ, Lindbloom EJ: Ginkgo biloba for dementia. *J Fam Pract* 46:20, 1998.
161. Solomon PR, Adams F, Silver A, et al: Ginkgo for memory enhancement. A randomized controlled trial. *JAMA* 288:835, 2002.
162. Matthews MK: Association of Ginkgo biloba with intracerebral hemorrhage. *Neurology* 50:1933, 1998.
163. Gianni L, Dreitlein WB: Some popular OTC herbals can interact with anticoagulant therapy. *US Pharm* 23: 80, 1998.
164. Haraguchi H, Saito T, Okamura N, et al: Inhibition of lipid peroxidation and superoxide generation by diterpenoids from *Rosmarinus officinalis*. *Planta Med* 61:333, 1995.
165. al-Hader AA, Hasan ZA, Aqel MB: Hyperglycemic and insulin release inhibiting effects of *Rosmarinus officinalis*. *J Ethnopharmacol* 43:217, 1994.
166. Tyler VE: *The Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies 3rd ed*. New York: Pharmaceutical Product Press, 1993.
167. Diehm C, Vollbrecht D, Amendt K, et al: Medical edema protection—clinical benefit in patients with chronic deep vein incompetence: A placebo controlled double blind study. *Vasa* 21:188, 1992.
168. Lang W: Studies on the percutaneous absorption of 3H-aescin in pigs. *Res Exp Med* 169:175, 1977.
169. Berg D: Venous constriction by local administration of ruscus extract (German). *Fortschr Med* 108:473, 1990.
170. Berg D: Venous tonicity in pregnancy varicose veins (German). *Fortschr Med* 110:67, 1992.
171. Li YP, Wang YM: Evaluation of tussilagone: A cardiovascular respiratory stimulant isolated from Chinese herbal medicine. *Gen Pharmacol* 19: 261, 1988.
172. Flanagan CM, Kaesberg JL, Mitchell ES, et al: Coronary artery aneurysm and thrombosis following chronic ephedra use. *Int J Cardiol* 139: e11, 2010.
173. Chan TYK, Chan JCN, Tomlinson B, et al: Chinese herbal medicines revisited: the Hong Kong perspective. *Lancet* 342: 1532, 1993.
174. Horowitz RS, Feldhaus K, Dart RC, et al: The clinical spectrum of *Jin Bu Huan* toxicity. *Arch Intern Med* 156: 899, 1996.
175. Frishman WH, Opie LH, Sica DA: Adverse cardiovascular drug interactions and complications. In Fuster V, Alexander RW, O'Rourke RA, Roberts R, King SB, Prystowsky E, Nash IS: *Hurst's The Heart 11th ed*. New York: McGraw Hill 2004; 2169.
176. Wang Z, Gorski C, Hamman MA, et al: The effects of St. John's Wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* 70: 317, 2001.
177. Mueller SC, Uehleke B, Woehling H, et al: Effect of St. John's wort dose and preparations on the pharmacokinetics of digoxin. *Clin Pharmacol Ther* 75: 546, 2004.
178. Ernst E: The risk-benefit profile of commonly used herbal therapies: ginkgo, St. John's wort, ginseng, Echinacea, saw palmetto and kava. *Ann Intern Med* 136: 42, 2002.
179. Yuan C-S, Wei G, Dey L, et al: Brief communications: American ginseng reduces warfarin's effect in healthy patients. *Ann Intern Med* 141: 23, 2004.
180. Clauson KA, Santamarina ML, Rutledge JC: Clinically relevant safety issues associated with St. John's wort product labels. *BMC Complement Altern Med* 8:42, 2008.
- 180a. Cohen PA: American roulette – contaminated dietary supplements. *N Engl J Med* 361: 1523, 2009.
181. Whitmont RD, Mamtani R: Homeopathy with a special focus on treatment of cardiovascular dis-

- ease. In Frishman WH, Weintraub MI, Micozzi M: *Complementary & Integrative Therapies in Cardiovascular Disease*. St. Louis: Elsevier 2005: 232.
182. Shang A, Huwiler-Muntener K, Nartey L, et al: Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet* 366: 726, 2005.
183. Goldacre B: Benefits and risks of homeopathy. *Lancet* 370(9600): 1672, 2007.
184. Prasad R: Homeopathy booming in india. *Lancet* 370(9600): 1679, 2007.
185. Diagnostic and therapeutic technology assessment: chelation therapy. *JAMA* 250: 672, 1983.
186. Clarke NE, Clarke CN, Mosher RF: The "in vivo" dissolution of metastatic calcium: an approach to atherosclerosis. *Am J Med Sci* 229: 142, 1955.
187. Eisenberg DM, Davis RB, Ettner SL, et al: Trends in alternative medicine use in the United States, 1990-1997; results of a follow-up national survey. *JAMA* 280: 1569, 1998.
188. Chappell LT, Stahl JP: The correlation between EDTA chelation therapy and improvement in cardiovascular function: a meta-analysis. *J Adv Med* 6: 139, 1993.
189. Gibbons RJ, Abrams J, Chatterjee K, et al: ACC/AHA 2002 guidelines for the management of patients with chronic stable angina. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 41: 159, 2003.
190. Cranton EM: Laguna Hills: American College of Advancement in Medicine, 1989.
191. Frishman WH, Wolff AI: Chelation therapy. In Frishman WH, Weintraub MI, Micozzi M: *Complementary & Integrative Therapies in Cardiovascular Disease*. St. Louis: Elsevier 2005: 288.
192. Mitka M: Chelation therapy trials halted (medical news and perspectives). *JAMA* 300: 2236, 2008.

References for Chapter 31

Cardiovascular Drug–Drug Interactions

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1. In sour economy, some scale back on medications. *New York Times* article dated October 21, 2008. Available at <http://www.nytimes.com/2008/10/22/business/22drug.html>. Accessed January 31, 2010.
2. IMS Health press release dated March 12, 2008. Available at: <http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnnextoid=280c1d3be7a29110VgnVCM10000071812ca2RCRD&vgnnextfmt=default>. Accessed January 31, 2010.
3. Lipitor prescribing information. Pfizer Ireland Pharmaceuticals. Dublin, Ireland. June 2009.
4. Hansten P, Horn J. Drug-drug interaction mechanisms. Available at: <http://hanstenandhorn.com/article-d-i.html>. Accessed January 31, 2010.
5. Chang GW, Kam PC. The physiological and pharmacological roles of cytochrome P450 isoenzymes. *Anaesthesia* 54:42, 1999.
6. Michalets EL. Update: Clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy* 18:84, 1998.
7. Horn JR, Hansten PD. Get to know an enzyme: CYP3A4. *Pharmacy Times* 2008;9:40. Available at: <http://www.pharmacytimes.com/issue/pharmacy/2008/2008-09/2008-09-8687>. Accessed January 31, 2010.
8. Horn JR, Hansten PD. Get to know an enzyme: CYP1A2. *Pharmacy Times* 2007;11:76. Available at: <http://www.pharmacytimes.com/issue/pharmacy/2007/2007-11/2007-11-8279>. Accessed January 31, 2010.
9. Horn JR, Hansten PD. Get to know an enzyme: CYP2C19. *Pharmacy Times* 2008;5:32. Available at: <http://www.pharmacytimes.com/issue/pharmacy/2008/2008-05/2008-05-8538>. Accessed January 31, 2010.
10. Horn JR, Hansten PD. Get to know an enzyme: CYP2C9. *Pharmacy Times* 2008;3:37. Available at: <http://www.pharmacytimes.com/issue/pharmacy/2008/2008-03/2008-03-8462>. Accessed January 31, 2010.
11. Horn JR, Hansten PD. Get to know an enzyme: CYP2D6. *Pharmacy Times* 2008;7:32. Available at: <http://www.pharmacytimes.com/issue/pharmacy/2008/2008-07/2008-07-8624>. Accessed January 31, 2010.
12. Anderson JR, Nawarskas JJ. Cardiovascular drug-drug interactions. *Cardiology Clinics* 19:215, 2001.
13. Hansten PD, Horn JR, eds. *Hansten and Horn's Drug Interactions Analysis and Management*. St. Louis, MO, Facts & Comparisons, 2009.
14. Bigger JT Jr, Leahey EB Jr. Quinidine and digoxin: an important interaction. *Drugs* 24:229, 1982.
15. Schenck-Gustafsson K, Juhlin-Dannfelt A, Dahlqvist R. Renal function and digoxin clearance during quinidine therapy. *Clinical Physiology* 2:401, 1982.
16. Horn JR, Hansten PD. Drug transporters: the final frontier for drug interactions. *Pharmacy Times* 12:28, 2008.
17. Horn JR, Hansten PD. Drug transporters: the final frontier for drug interactions – part 2. *Pharmacy Times* 2:33, 2009.
18. Eberl S, Renner B, Neubert A, et al. Role of P-glycoprotein inhibition for drug interactions. *Clin Pharmacokinet*. 46:1039, 2007.
19. Rengelshausen J, Goggelmann C, Burhenne J, et al. Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin-clarithromycin interaction. *Br J Clin Pharmacol*. 56:32, 2003.
20. Gurley BJ, Swain A, Williams DK, et al. Gauging

- the clinical significance of P-glycoprotein-mediated herb-drug interactions: comparative effects of St. John's wort, Echinacea, clarithromycin, and rifampin on digoxin pharmacokinetics. *Mol Nutr Food Res*. 52:772, 2008.
21. Regazzi MB, Iacona I, Campana C, et al. Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant Proc*. 25:2732, 1993.
 22. Somogyi A, McLean A, Heinzow B. Cimetidine-procainamide pharmacokinetic interaction in man: evidence of competition for tubular secretion of basic drugs. *Eur J Clin Pharmacol*. 25:339, 1983.
 23. Micromedex Healthcare series, (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. Available at: <http://www.thomson-hc.com>. Assessed: 1/30/2010.
 24. Quinn DI, Day RO. Drug interactions of clinical importance. An updated guide. *Drug Safety* 12: 393, 1995.
 25. Mignat C, Unger T. ACE inhibitors. Drug interactions of clinical significance. *Drug Safety* 12: 334, 1995.
 26. Salvetti A, Abdel-Haq B, Magagna A, et al. Indomethacin reduces the antihypertensive action of enalapril. *Clin Exp Hypertens A*. 9:559, 1987.
 27. Abdel-Haq B, Magagna A, Favilla S, et al. Hemodynamic and humoral interactions between perindopril and indomethacin in essential hypertensive subjects. *J Cardiovasc Pharmacol*. 18 (Suppl 7):S33, 1991.
 28. Seelig CB, Maloley PA, Campbell JR, et al. Nephrotoxicity associated with concomitant ACE inhibitor and NSAID therapy. *South Med J*. 83:1144, 1990.
 29. Stys T, Lawson WE, Smaldone GC, et al. Does aspirin attenuate the beneficial effects of angiotensin-converting enzyme inhibition in heart failure? *Arch Intern Med*. 160:1409, 2000.
 30. Nguyen KN, Aursnes I, Kjekshus J. Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *Am J Cardiol*. 79:115, 1997.
 31. Al-Khadra AS, Salem DN, Rand WM, et al. Antiplatelet agents and survival: a cohort analysis from the studies of left ventricular dysfunction (SOLVD) trial. *J Am Coll Cardiol*. 31:419, 1998.
 32. Oosterga M, Anthonio RL, de Kam PJ, et al. Effects of aspirin on angiotensin-converting enzyme inhibition and left ventricular dilation one year after acute myocardial infarction. *Am J Cardiol*. 81:1178, 1998.
 33. Weksler BB, Pett SB, Alonso D, et al. Differential inhibition by aspirin of vascular and platelet prostaglandin synthesis in atherosclerotic patients. *N Engl J Med*. 308:800, 1983.
 34. Arauz-Pacheco C, Ramirez LC, Rios JM, et al. Hypoglycemia induced by angiotensin-converting enzyme inhibitors in patients with non-insulin-dependent diabetes receiving sulfonylurea therapy. *The American Journal of Medicine*. 89:811, 1990.
 35. Ahmad S. Drug interaction induces hypoglycemia. *J Fam Pract*. 40:540, 1995.
 36. Page RL II, Miller GG, Lindenfeld J. Drug therapy in the heart transplant recipient. Part IV: Drug-Drug interactions. *Circulation*. 111:230, 2005.
 37. Gossmann J, Thürmann P, Bachmann T, et al. Mechanism of angiotensin converting enzyme inhibitor-related anemia in renal transplant recipients. *Kidney Int*. 50:973, 1996.
 38. Gossmann J, Kachel HG, Schoeppe W, et al. Anemia in renal transplant recipients caused by concomitant therapy with azathioprine and angiotensin-converting enzyme inhibitors. *Transplantation*. 56:585, 1993.
 39. Ahmad S. Allopurinol and enalapril. Drug induced anaphylactic coronary spasm and acute myocardial infarction. *Chest*. 108:586, 1995.
 40. Pennell DJ, Nunan TO, O'Doherty MJ, et al. Fatal Stevens-Johnson syndrome in a patient on captopril and allopurinol. *Lancet*. 1:463, 1984.
 41. Samanta A, Burden AC. Fever, myalgia, and arthralgia in a patient on captopril and allopurinol. *Lancet*. 1:679, 1984.
 42. Murray BM, Venuto RC, Kohli R, et al. Enalapril-associated acute renal failure in renal transplants: possible role of cyclosporine. *Am J Kidney Dis*. 16:66, 1990.
 43. Douste-Blazy P, Rostin M, Livarek B, et al. Angiotensin converting enzyme inhibitors and lithium treatment. *Lancet*. 1:1448, 1986.
 44. Correa FJ, Eiser AR. Angiotensin-converting enzyme inhibitors and lithium toxicity. *Am J Med*. 93:108, 1992.
 45. Baldwin CM, Safferman AZ. A case of lisinopril-induced lithium toxicity. *DICP*. 24:946, 1990.
 46. Unger T, Kaschina E. Drug interactions with angiotensin receptor blockers: A comparison with other antihypertensives. *Drug Safety* 26:707, 2003.
 47. Böhler S, Pittrow D, Bramlage P, et al. Drug interactions with angiotensin receptor blockers. *Expert Opin. Drug Saf*. 4:7, 2005.
 48. Kazierad DJ, Martin DE, Blum RA, et al. Effect of fluconazole on the pharmacokinetics of eprosartan and losartan in healthy male volunteers. *Clin Pharmacol Ther*. 62:417, 1997.
 49. Williamson KM, Patterson JH, McQueen RH, et

- al. Effects of erythromycin or rifampin on losartan pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther.* 63:316, 1998.
50. Marino MR, Vachharajani NN. Drug interactions with irbesartan. *Clin Pharmacokinet.* 40:605, 2001.
 51. Mangold B, Gielsdorf W, Marino MR. Irbesartan does not affect the steady-state pharmacodynamics and pharmacokinetics of warfarin. *Eur J Clin Pharmacol.* 55:593, 1999.
 52. Trujillo TC, Nolan PE. Antiarrhythmic agents. Drug interactions of clinical significance. *Drug Safety* 23:509, 2000.
 53. Spinler SA, Cheng JW, Kindwall KE, et al. Possible inhibition of hepatic metabolism of quinidine by erythromycin. *Clin Pharmacol Ther.* 57:89, 1995.
 54. Yamreudeewong W, DeBisschop M, Martin LG, et al. Potentially significant drug interactions of class III antiarrhythmic drugs. *Drug Safety* 26:421, 2003.
 55. Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. *Am J Cardiovasc Drugs* 4:281, 2004.
 56. Kappenberger TR, Steinbrunn W, Meyer UA. Dangerous interactions between amiodarone and quinidine. *Lancet.* 1:1327, 1982.
 57. Baker BJ, Gammill J, Massengill J, et al. Concurrent use of quinidine and disopyramide: evaluation of serum concentrations and electrocardiographic effects. *Am Heart J.* 105:12, 1983.
 58. Hughes B, Dyer JE, Schwartz AB. Increased procainamide plasma concentrations caused by quinidine: a new drug interaction. *Am Heart J.* 114(4 Pt 1):908, 1987.
 59. Saal AK, Werner JA, Greene HL, et al. Effect of amiodarone on serum quinidine and procainamide levels. *Am J Cardiol.* 53:1264, 1984.
 60. Mörike KE, Roden DM. Quinidine-enhanced beta-blockade during treatment with propafenone in extensive metabolizer human subjects. *Clin Pharmacol Ther.* 55:28, 1994.
 61. Cooke CE, Sklar GE, Nappi JM. Possible pharmacokinetic interaction with quinidine: ciprofloxacin or metronidazole? *Ann Pharmacother.* 30:364, 1996.
 62. Lin JC, Quasny HA. QT prolongation and development of torsades de pointes with the concomitant administration of oral erythromycin base and quinidine. *Pharmacotherapy.* 17:626, 1997.
 63. Kaukonen KM, Olkkola KT, Neuvonen PJ. Itraconazole increases plasma concentrations of quinidine. *Clin Pharmacol Ther.* 62:510, 1997.
 64. Farringer JA, Green JA, O'Rourke RA, et al. Nifedipine-induced alterations in serum quinidine concentrations. *Am Heart J.* 108:1570, 1984.
 65. Data JL, Wilkinson GR, Nies AS. Interaction of quinidine with anticonvulsant drugs. *N Engl J Med.* 294:699, 1976.
 66. Koch-Weser J. Quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic warfarin therapy. *Ann Intern Med.* 68:511, 1968.
 67. Vlases PH, Kosoglou T, Chase SL, et al. Trimethoprim inhibition of the renal clearance of procainamide and N-acetylprocainamide. *Arch Intern Med.* 149:1350, 1989.
 68. Rocci ML Jr, Kosoglou T, Ferguson RK, et al. Ranitidine-induced changes in the renal and hepatic clearances of procainamide are correlated. *J Pharmacol Exp Ther.* 248:923, 1989.
 69. Martin DE, Shen J, Griener J. Effects of ofloxacin on the pharmacokinetics and pharmacodynamics of procainamide. *J Clin Pharmacol.* 36:85, 1996.
 70. Bonde J, Bødtker S, Angelo HR, et al. Atenolol inhibits the elimination of disopyramide. *Eur J Clin Pharmacol.* 28:41, 1985.
 71. Kapil RP, Axelson JE, Mansfield IL, et al. Disopyramide pharmacokinetics and metabolism: effect of inducers. *Br J Clin Pharmacol.* 24:781, 1987.
 72. Ragosta M, Wehl AC, Rosenfeld LE. Potentially fatal interaction between erythromycin and disopyramide. *Am J Med.* 86:465, 1989.
 73. Siegmund JB, Wilson JH, Imhoff TE. Amiodarone interaction with lidocaine. *J Cardiovasc Pharmacol.* 21:513, 1993.
 74. Conrad KA, Byers JM 3rd, Finley PR, et al. Lidocaine elimination: effects of metoprolol and of propranolol. *Clin Pharmacol Ther.* 33:133, 1983.
 75. Feely J, Wilkinson GR, McAllister CB, et al. Increased toxicity and reduced clearance of lidocaine by cimetidine. *Ann Intern Med.* 96:592, 1982.
 76. Katz A, Buskila D, Sukenik S. Oral mexiletine-theophylline interaction. *Int J Cardiol.* 17:227, 1987.
 77. Tjandra-Maga TB, Van Hecken A, Van Melle P, et al. Altered pharmacokinetics of oral flecainide by cimetidine. *Br. J. Clin. Pharmacol.* 22:108, 1986.
 78. Spinler SA, Gammaitoni A, Charland SL. Propafenone-theophylline interaction. *Pharmacotherapy.* 13:68, 1993.
 79. Kates RE, Yee YG, Kirsten EB. Interaction between warfarin and propafenone in healthy volunteer subjects. *Clin Pharmacol Ther.* 42:305, 1987.
 80. Rees A, Dalal JJ, Reid PG, et al. Dangers of amiodarone and anticoagulant treatment. *Br Med J (Clin Res Ed).* 282:1756, 1981.
 81. Hamer A, Peter T, Mandel WJ, et al. The potentiation of warfarin anticoagulation by amiodarone. *Circulation.* 65:1025, 1982.
 82. Leor J, Levartowsky D, Sharon C, et al. Amiodarone and beta-adrenergic blockers: an interaction with metoprolol but not with atenolol. *Am Heart J.*

- 116(1 Pt 1):206, 1988.
83. Nicolau DP, Uber WE, Crumbley AJ 3rd, et al. Amiodarone-cyclosporine interaction in a heart transplant patient. *J Heart Lung Transplant*. 11(3 Pt 1):564, 1992.
 84. Nademanee K, Kannan R, Hendrickson J, et al. Amiodarone-digoxin interaction: clinical significance, time course of development, potential pharmacokinetic mechanisms and therapeutic implications. *J Am Coll Cardiol*. 4:111, 1984.
 85. Nolan PE Jr, Marcus FI, Karol MD, et al. Effect of phenytoin on the clinical pharmacokinetics of amiodarone. *J Clin Pharmacol*. 30:1112, 1990.
 86. Windle J, Prystowsky EN, Miles WM, et al. Pharmacokinetic and electrophysiologic interactions of amiodarone and procainamide. *Clin Pharmacol Ther*. 41:603, 1987.
 87. Lohman JJ, Reichert LJ, Degen LP. Antiretroviral therapy increases serum concentrations of amiodarone. *Ann Pharmacother* 33:645, 1999.
 88. Kerin NZ, Blevins RD, Goldman L, et al. The incidence, magnitude, and time course of the amiodarone-warfarin interaction. *Arch Intern Med*. 148:1779, 1988.
 89. Abel S, Nichols DJ, Brearley CJ, et al. Effect of cimetidine and ranitidine on pharmacokinetics and pharmacodynamics of a single dose of dofetilide. *Br J Clin Pharmacol*. 49:64, 2000.
 90. Garcia D, Cheng-Lai A. Dronedarone. A new antiarrhythmic agent for the treatment of atrial fibrillation. *Cardiology in Review* 17:230, 2009.
 91. Elliott HL, McLean K, Summer DJ, et al. Immediate cardiovascular responses to oral prazosin-effects of concurrent beta-blockers. *Clin Pharmacol Ther*. 29:303, 1981.
 92. Singh S, Saini RK, DiMarco J, et al. Efficacy and safety of sotalol in digitalized patients with chronic atrial fibrillation. The sotalol study group. *Am J Cardiol*. 68:1227, 1991.
 93. Frishman WH, Cheng-Lai A, Nawarska J (eds): *Current Cardiovascular Drugs*, 4th ed. Philadelphia: Current Medicine, 2005.
 94. Harder S, Thürmann P. Clinically important drug interactions with anticoagulants. An update. *Clin Pharmacokinet*. 30:416, 1996.
 95. Chesebro JH, Fuster V, Elveback LR, et al. Trial of combined warfarin plus dipyridamole or aspirin therapy in prosthetic heart valve replacement: danger of aspirin compared with dipyridamole. *Am J Cardiol*. 51:1537, 1983.
 96. Jähnchen E, Meinertz T, Gilfrich HJ, et al. Enhanced elimination of warfarin during treatment with cholestyramine. *Br J Clin Pharmacol*. 5:437, 1978.
 97. Rindone JP, Keng HC. Gemfibrozil-warfarin drug interaction resulting in profound hypoprothrombinemia. *Chest*. 114:641, 1998.
 98. O'Reilly RA. Interaction of chronic daily warfarin therapy and rifampin. *Ann Intern Med*. 83:506, 1975.
 99. Bachmann K, Schwartz JI, Forney R Jr, et al. The effect of erythromycin on the disposition kinetics of warfarin. *Pharmacology*. 28:171-6, 1984.
 100. Kazmier FJ. A significant interaction between metronidazole and warfarin. *Mayo Clin Proc*. 51:782, 1976.
 101. O'Reilly RA. The stereoselective interaction of warfarin and metronidazole in man. *N Engl J Med*. 295:354, 1976.
 102. Gericke KR. Possible interaction between warfarin and fluconazole. *Pharmacotherapy*. 13:508, 1993.
 103. Smith AG. Potentiation of oral anticoagulants by ketoconazole. *Br Med J (Clin Res Ed)*. 288:188, 1984.
 104. Hassall C, Feetam CL, Leach RH, et al. Letter: Potentiation of warfarin by co-trimoxazole. *Lancet*. 2:1155, 1975.
 105. Singleton JD, Conyers L. Warfarin and azathioprine: an important drug interactions. *Am J Med*. 92:217, 1992.
 106. Levine M, Sheppard I. Biphasic interaction of phenytoin with warfarin. *Clin Pharm*. 3:200, 1984.
 107. Khaliq SC, Cheng-Lai A. Drug interaction between clopidogrel and proton pump inhibitors. *Cardiology in Review* 17:198, 2009.
 108. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 301:937, 2009.
 109. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 180:713, 2009.
 110. Stanek EJ, Aubert RE, Flockhart DA, et al. A national study of the effect of individual proton pump inhibitors on cardiovascular outcomes in patients treated with clopidogrel following coronary stenting: The Clopidogrel Medco Outcomes Study. <http://www.scai.org/pdf/20090506Medcoabstract.pdf> (Abstract).
 111. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomized trials. *Lancet*. 374:989, 2009.
 112. Rassen JA, Choudhry NK, Avorn J, et al. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after per-

- cutaneous coronary intervention or acute coronary syndrome. *Circulation*. 120:2322, 2009.
113. Information for Healthcare Professionals: Update to the labeling of clopidogrel bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafety-InformationforPatientsandPrescribers> Assessed: 1/18/2010.
 114. Juurlink DN. Proton pump inhibitors and clopidogrel. Putting the interaction in perspective. *Circulation*. 120:2310, 2009.
 115. Laine L, Hennekens C. Proton pump inhibitor and clopidogrel interaction: fact or fiction? *Am J Gastroenterol* 105:34, 2010.
 116. Blaufarb I, Pfeifer TM, Frishman WH. β -Blockers. Drug interactions of clinical significance. *Drug Safety* 13:359, 1995.
 117. Findlay IN, McInnes GT, Dargie HJ. Beta blockers and verapamil: a cautionary tale. *Br Med J (Clin Res Ed)*. 289:1074, 1984.
 118. Benaim ME. Asystole after verapamil. *Br Med J*. 2:169, 1972.
 119. Hunt BA, Bottorff MB, Herring VL, et al. Effects of calcium channel blockers on the pharmacokinetics of propranolol stereoisomers. *Clin Pharmacol Ther*. 47(5):584, 1990.
 120. Bailey RR, Neale TJ. Rapid clonidine withdrawal with blood pressure overshoot exaggerated by beta-blockade. *Br Med J*. 1:942, 1976.
 121. Deacon CS, Bax LNDS, Woods HF, et al. Inhibition of oxidative drug metabolism by β -adrenoceptor antagonists is related to their lipid solubility. *Br J Clin Pharmacol* 12:429, 1981.
 122. Silver JM, Yudofsky SC, Kogan M, et al. Elevation of thioridazine plasma levels by propranolol. *Am J Psychiatry*. 143:1290, 1986.
 123. Wagner F, Kalusche D, Trenk D, et al. Drug interaction between propafenone and metoprolol. *Br J Clin Pharmacol*. 24:213, 1987.
 124. Kowey PR, Kirsten EB, Fu CH, et al. Interaction between propranolol and propafenone in healthy volunteers. *J Clin Pharmacol*. 29:512, 1989.
 125. Schneck DW, Luderer JR, Davis D, et al. Effects of nadolol and propranolol on plasma lidocaine clearance. *Clin Pharmacol Ther*. 36:584, 1984.
 126. Walley T, Pirmohamed M, Proudlove C, et al. Interaction of metoprolol and fluoxetine. *Lancet*. 341:967, 1993.
 127. Miners JO, Wing LM, Lillywhite KJ, et al. Selectivity and dose-dependency of the inhibitory effect of propranolol on theophylline metabolism in man. *Br J Clin Pharmacol*. 20:219, 1985.
 128. Rosenthal T, Ezra D. Calcium antagonists. Drug interactions of clinical significance. *Drug Safety* 13:157, 1995.
 129. Ahmad S. Nifedipine-phenytoin interaction. *J Am Coll Cardiol*. 3:1582, 1984.
 130. Bahls FH, Ozuna J, Ritchie DE. Interactions between calcium channel blockers and the anticonvulsants carbamazepine and phenytoin. *Neurology*. 41:740, 1991.
 131. Sica DA. Interaction of grapefruit juice and calcium channel blockers. *Am J Hypertens* 19:768, 2006.
 132. Jalava KM, Olkkola KT, Neuvonen PJ. Itraconazole greatly increases plasma concentrations and effects of felodipine. *Clin Pharmacol Ther*. 61:410, 1997.
 133. Azie NE, Brater DC, Becker PA, et al. The interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Ther*. 64:369, 1998.
 134. Kantola T, Kivistö KT, Neuvonen PJ. Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther*. 64:177, 1998.
 135. Kohlhaw K, Wonigeit K, Frei U, et al. Effect of the calcium channel blocker diltiazem on cyclosporine A blood levels and dose requirements. *Transplant Proc*. 20(2 Suppl 2):572, 1988.
 136. Lindholm A, Henricsson S. Verapamil inhibits cyclosporine metabolism. *Lancet* 1:1262, 1987.
 137. Pesavento TE, Jones PA, Julian BA, et al. Amlodipine increases cyclosporine levels in hypertensive renal transplant patients: results of a prospective study. *J Am Soc Nephrol*. 7:831, 1996.
 138. Madsen JK, Jensen JD, Jensen LW, et al. Pharmacokinetic interaction between cyclosporine and the dihydropyridine calcium antagonist felodipine. *Eur J Clin Pharmacol*. 50:203, 1996.
 139. Bourbigot B, Guiserix J, Airiau J, et al. Nicardipine increases cyclosporine blood levels. *Lancet*. 1:1447, 1986.
 140. Verschaagen M, Koks CHW, Schellens JHM, et al. P-glycoprotein system as a determinant of drug interactions: The case of digoxin-verapamil. *PharmacoRes* 40:301, 1999.
 141. Rameis H, Magometschnigg D, Ganzinger U, et al. The diltiazem-digoxin interaction. *Clin Pharmacol Ther*. 36:183, 1984.
 142. Winship LC, McKenney JM, Wright JT Jr, et al. The effect of ranitidine and cimetidine on single-dose diltiazem pharmacokinetics. *Pharmacotherapy*. 5:16, 1985.
 143. Smith SR, Kendall MJ, Lobo J, et al. Ranitidine and cimetidine; drug interactions with single dose and steady-state nifedipine administration. *Br J Clin Pharmacol*. 23:311, 1987.
 144. Smith MS, Benyunes MC, Bjornsson TD, et al. In-

- fluence of cimetidine on verapamil kinetics and dynamics. *Clin Pharmacol Ther.* 36:551, 1984.
145. Laganière S, Davies RF, Carignan G, et al. Pharmacokinetic and pharmacodynamic interactions between diltiazem and quinidine. *Clin Pharmacol Ther.* 60:255, 1996.
 146. Van Lith RM, Appleby DH. Quinidine-nifedipine interaction. *Drug Intell Clin Pharm.* 19:829, 1985.
 147. Trohman RG, Estes DM, Castellanos A, et al. Increased quinidine plasma concentrations during administration of verapamil: a new quinidine-verapamil interaction. *Am J Cardiol.* 57:706, 1986.
 148. Klein HO, Beker B, DiSegni E, et al. Asystole produced by the combination of amiodarone and digoxin. *Am Heart J.* 113:399, 1987.
 149. Kounis NG. Asystole after verapamil and digoxin. *Br J Clin Pract.* 34:57, 1980.
 150. Steiness E, Olesen KH. Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy. *Br Heart J.* 38:167, 1976.
 151. Seller RH, Cangiano J, Kim KE, et al. Digitalis toxicity and hypomagnesemia. *Am Heart J.* 79:57, 1970.
 152. Lindenbaum J, Rund DG, Butler VP Jr, et al. Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *N Engl J Med.* 305:789, 1981.
 153. Magnani B, Malini PL. Cardiac Glycosides. Drug interactions of clinical significance. *Drug Safety* 12:97, 1995.
 154. Robinson K, Johnston A, Walker S, et al. The digoxin-amiodarone interaction. *Cardiovasc Drugs Ther.* 3:25, 1989.
 155. Calvo MV, Martin-Suarez A, Martin Luengo C, et al. Interaction between digoxin and propafenone. *Ther Drug Monit.* 11:10, 1989.
 156. Guven H, Tuncok Y, Guneri S, et al. Age-related digoxin-alprazolam interaction. *Clin Pharmacol Ther.* 54:42, 1993.
 157. Nola GT, Pope S, Harrison DC. Assessment of the synergistic relationship between serum calcium and digitalis. *Am Heart J.* 79:499, 1970.
 158. Weeks CE, Conard GJ, Kvam DC, et al. The effect of flecainide acetate, a new antiarrhythmic, on plasma digoxin levels. *J Clin Pharmacol.* 26:27, 1986.
 159. Sachs MK, Blanchard LM, Green PJ. Interaction of itraconazole and digoxin. *Clin Infect Dis.* 16:400, 1993.
 160. Waldorff S, Andersen JD, Heebøll-Nielsen N, et al. Spironolactone-induced changes in digoxin kinetics. *Clin Pharmacol Ther.* 24:162, 1978.
 161. Davis A, Day RO, Begg EJ. Interactions between non-steroidal anti-inflammatory drugs and antihypertensives and diuretics. *Aust N Z J Med.* 16:537, 1986.
 162. Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet.* 29:172, 1995.
 163. Cheitlin MD, Hutter AM Jr, Brindis RG, et al. The ACC/AHA expert consensus document: Use of sildenafil (Viagra) in patients with cardiovascular disease. *J Am Coll Cardiol* 33:273, 1999.
 164. Cialis (tadalafil) Tablet [prescribing information]. Indianapolis, Indiana: Eli Lilly and Company; 2010.
 165. Levitra (vardenafil) Tablet [prescribing information]. Wayne, NJ: Bayer Health Care Pharmaceuticals Inc; 2008.
 166. Brown DD, Juhl RP, Warner SL. Decreased bioavailability of digoxin due to hypocholesterolemic interventions. *Circulation.* 58:164, 1978.
 167. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *JAMA.* 264:71, 1990.
 168. Tal A, Rajeshwari M, Isley W. Rhabdomyolysis associated with simvastatin-gemfibrozil therapy. *South Med J.* 90:546, 1997.
 169. Jacobson TA. Myopathy with statin-fibrate combination therapy: clinical considerations. *Nat Rev Endocrinol.* 5:507, 2009.
 170. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol.* 95:120, 2005.
 171. Drug interactions with simvastatin. *The Medical Letter* 50:83, 2008.
 172. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol.* 94:1140, 2004.
 173. Frishman WH, Horn J: Statin drug interactions: not a class effect. *Cardiol in Rev* 16: 205, 2008.