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AACE 2017 Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

EXECUTIVE SUMMARY

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American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision-making for specific clinical conditions, but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice.

Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied. These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. Medical professionals are encouraged to use this information in conjunction with, and not as a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual circumstances.

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Abbreviations

ACE = American College of Endocrinology; **ACS** = acute coronary syndrome; **AHA** = American Heart Association; **ASCVD** = atherosclerotic cardiovascular disease; **ATP** = Adult Treatment Panel; **apo** = apolipoprotein; **BEL** = best evidence level; **CAC** = coronary artery calcification; **CKD** = chronic kidney disease; **CIMT** = carotid intimal media thickness; **CPG** = clinical practice guidelines; **CVA** = cerebrovascular accident; **EL** = evidence level; **FH =** familial hypercholesterolemia; **HDL-C** = high-density lipoprotein cholesterol; **HeFH =** heterozygous familial hypercholesterolemia**; HIV =** human immunodeficiency virus; **HoFH** = homozygous familial hypercholesterolemia; **hsCRP** = highly sensitive C-reactive protein; **LDL-C** = low-density lipoprotein cholesterol; **Lp-PLA$_2$** = lipoprotein-associated phospholipase A$_2$**; MESA** = Multi-Ethnic Study of Atherosclerosis; **MetS** = metabolic syndrome; **MI** = myocardial infarction; **NCEP** = National Cholesterol Education Program; **PCOS** = polycystic ovary syndrome**; PCSK9** = Proprotein convertase subtilisin/kexin type 9; **T1DM** = type 1 diabetes mellitus; **T2DM** = type 2 diabetes mellitus; **TG** = triglycerides; **U.S.** = United States; **VLDL-C** = very low-density lipoprotein cholesterol.

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ABSTRACT

Objective: The development of these guidelines is mandated by the American Association of Clinical Endocrinologists (AACE) Board of Directors and American College of Endocrinology (ACE) Board of Trustees and adheres with published AACE protocols for the standardized production of clinical practice guidelines (CPGs).

Methods: Each Recommendation is based on a diligent review of the clinical evidence with transparent incorporation of subjective factors.

Results: The Executive Summary of this document contains 87 Recommendations of which 45 are Grade A (51.7%), 18 are Grade B (20.7%), 15 are Grade C (17.2%), and 9 (10.3%) are Grade D. These detailed, evidence-based recommendations allow for nuance-based clinical decision-making that addresses multiple aspects of real-world medical care. The evidence base presented in the subsequent Appendix provides relevant supporting information for Executive Summary Recommendations. This update contains 695 citations of which 202 (29.1 %) are EL 1 (strong), 137 (19.7%) are EL 2 (intermediate), 119 (17.1%) are EL 3 (weak), and 237 (34.1%) are EL 4 (no clinical evidence).

Conclusions: This CPG is a practical tool that endocrinologists, other healthcare professionals, regulatory bodies and health-related organizations can use to reduce the risks and consequences of dyslipidemia. It provides guidance on screening, risk assessment, and treatment recommendations for a range of patients with various lipid disorders. They emphasize the importance of treating low-density lipoprotein cholesterol (LDL-C) in some individuals to lower goals than previously recommended and support the measurement of coronary artery calcium scores and inflammatory markers to help stratify risk. Special consideration is given to patients with diabetes, familial hypercholesterolemia, women, and pediatric patients with dyslipidemia. Both clinical and cost-effectiveness data are provided to support treatment decision-making.

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1. INTRODUCTION

In 2016, approximately 660,000 United States (U.S.) residents will have a new coronary event (defined as a first hospitalized myocardial infarction [MI] or atherosclerotic cardiovascular disease [ASCVD] death), and approximately 305,000 will have a recurrent event. The estimated annual incidence of MI is 550,000 new and 200,000 recurrent attacks. The average age at first MI is 65.1 years for men and 72.0 years for women (1 [EL 4; NE]). Dyslipidemia is a primary, major risk factor for ASCVD and may even be a prerequisite for ASCVD, occurring before other major risk factors come into play. Epidemiologic data also suggest that hypercholesterolemia and perhaps coronary atherosclerosis itself are risk factors for ischemic cerebrovascular accident (CVA) (2 [EL 4; NE]). According to data from 2009 to 2012, >100 million U.S. adults ≥20 years of age have total cholesterol levels ≥200 mg/dL; almost 31 million have levels ≥240 mg/dL (1 [EL 4; NE]). Increasing evidence also points to insulin resistance— which results in increased levels of plasma triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) and a decreased concentration of high-density lipoprotein cholesterol (HDL-C)— as an important risk factor for peripheral vascular disease (3 [EL 2; PCS]), CVA, and ASCVD (4 [EL 2; PCS]).

Analysis of 30-year national trends in serum lipid levels shows improvements in total cholesterol and LDL-C levels. This may in part be explained by the steady increase in the use of lipid-lowering drug therapy (self-reported rate of lipid-medication use, 38%). However, 69% of U.S. adults have LDL-C concentrations above 100 mg/dL. Furthermore, the doubling in prevalence of individuals who have obesity, the high percentage with elevated TG levels (33%), and the correlation between obesity and elevated TG point to the need for continued vigilance on the part of physicians to reduce ASCVD risk (5 [EL 3; SS]).

This clinical practice guideline (CPG) is for the diagnosis and treatment of dyslipidemia and prevention of atherosclerosis. The mandate for this CPG is to provide a practical guide for endocrinologists, other healthcare professionals, regulatory bodies and health-related organizations to reduce the risks and consequences of dyslipidemia. This CPG extends and updates existing CPGs available in the literature, such as the American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Dyslipidemia and Prevention of Atherosclerosis (6 [EL 4; NE]), and complements the AACE Diabetes Mellitus Comprehensive Care Plan CPG (7 [EL 4; NE]). The landmark National Cholesterol Education Program (NCEP) guidelines (8 [EL 4; NE]) serve as the backbone of these lipid recommendations.

This CPG is unique in that it supports the use of apolipoprotein (apo) B level and/or LDL particle concentration to refine efforts to achieve effective LDL-C lowering, provide screening recommendations

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for individuals of different ages, and identify special issues for children and adolescents. This CPG also discusses the challenges associated with atherosclerosis and heart disease that are specific to women. It continues to emphasize the importance of LDL-C lowering and supports the measurement of inflammatory markers to stratify risk in certain situations. Finally, this CPG presents an evaluation of the cost-effectiveness of lipid-lowering management.

This document is organized based on discrete clinical questions, with an Executive Summary of key recommendations followed by the supporting evidence base. The objectives of this CPG are to provide:

- An overview of the screening recommendations, assessment of risk, and treatment recommendations for various lipid disorders;
- Special consideration for individuals with diabetes, women, and children/adolescents with dyslipidemia; and
- Cost-effectiveness data to support therapeutic decision-making.

2. METHODS

This CPG was developed in accordance with the AACE Protocol for Standardized Production of Clinical Practice Guidelines (9 [EL 4; NE]). Reference citations in the text of this document include the reference number, numerical descriptor (EL 1-4), and semantic descriptor (explained in Table 1) (9 [EL 4; NE]).

All primary writers have made disclosures regarding multiplicities of interests and have attested that they are not employed by industry. In addition, all primary writers are AACE members and credentialed experts. Primary writers submitted contributions to specific clinical questions, which were subsequently reviewed, discussed, and integrated into the final document. This valuable input provides the basis for the recommendations herein. The format of this CPG is based on specific and relevant clinical questions (labeled “Q”).

Recommendations (labeled “R”) are assigned Grades that map to the best evidence level (BEL) ratings based on the highest quality supporting evidence level (EL) (Tables 1 and 2; Figure 1) (9 [EL 4; NE]), all of which have also been rated based on scientific substantiation (Table 3) (9 [EL 4; NE]). Recommendation Grades are designated “A”, “B”, or “C” when there is scientific evidence available, or “D” when there is only expert opinion or a lack of conclusive scientific evidence. Technically, the BEL follows the recommendation Grade in the Executive Summary. Briefly, there are 4 intuitive levels of evidence: 1 = strong, 2 = intermediate, 3 = weak, and 4 = no evidence (Table 3). Comments may be

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appended to the recommendation Grade and BEL regarding any relevant subjective factors that may have influenced the grading process (Table 4) (9 [EL 4; NE]). Details regarding each recommendation may be found in the upcoming corresponding section of the CPG Evidence Base Appendix and will include a complete list of supporting References. Thus, the process leading to a final recommendation and grade is not rigid, but rather incorporates complex expert integration of objective and subjective factors meant to reflect optimal real-life clinical decision-making, options, and individualization of care. This document is a guideline, and since individual circumstances and presentations differ, ultimate clinical management is based on what is in the best interest of the individual and involves the individual's input ("patient-centered care") and reasonable clinical judgment by treating clinicians.

This CPG has been reviewed and approved by the primary writers, other invited experts, the AACE Publications Committee, the AACE Board of Directors, and the ACE Board of Trustees before submission for peer review by *Endocrine Practice*. The efforts of all those involved are greatly appreciated.

Table 1
2014 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step I: Evidence Rating[a]

Numerical descriptor (evidence level)[b]	Semantic descriptor
1	Meta-analysis of randomized controlled trials (MRCT)
1	Randomized controlled trials (RCT)
2	Meta-analysis of nonrandomized prospective or case-controlled trials
2	Nonrandomized controlled trial (NRCT)
2	Prospective cohort study (PCS)
2	Retrospective case-control study (RCCS)
3	Cross-sectional study (CSS)
3	Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database)
3	Consecutive case series (CCS)
3	Single case reports (SCR)
4	No evidence (theory, opinion, consensus, review, or preclinical study)

[a] Adapted from: *Endocr Pract*. 2014;20(7):692-702 (9 [EL 4; NE]).
[b] 1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; and 4 = no evidence.

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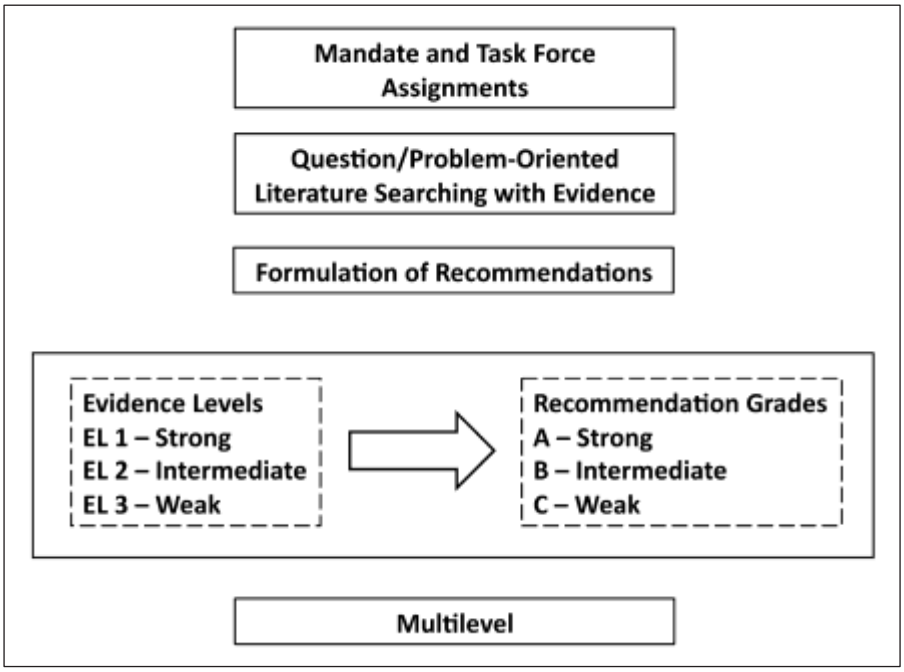

Figure 1. 2014 American Association of Clinical Endocrinologists Clinical Practice Guideline Methodology. Current American Association of Clinical Endocrinologists Clinical Practice Guidelines have a problem-oriented focus that results in a shortened production timeline, middle-range literature searching, emphasis on patient-oriented evidence that matters, greater transparency of intuitive evidence rating and qualifications, incorporation of subjective factors into evidence level to recommendation grade mapping, cascades of alternative approaches, and an expedited multilevel review mechanism (9 [EL 4; NE]).

Table 2
2014 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step II: Evidence Analysis and Subjective Factors[a]

Study design	Data analysis	Interpretation of results
Premise correctness	Intent-to-treat	Generalizability
Allocation concealment (randomization)	Appropriate statistics	Logical
Selection bias		Incompleteness
Appropriate blinding		Validity
Using surrogate endpoints (especially in "first-in-its-class" intervention)		
Sample size (beta error)		
Null hypothesis vs Bayesian statistics		

[a] Reprinted from: *Endocr Pract*. 2014;20(7):692-702 (9 [EL 4; NE]).

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Table 3
2014 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step III: Grading of Recommendations; How Different Evidence Levels Can Be Mapped to the Same Recommendation Grade[a,b]

Best evidence level	Subjective factor impact	Two-thirds consensus	Mapping	Recommendation grade
1	None	Yes	Direct	A
2	Positive	Yes	Adjust up	A
2	None	Yes	Direct	B
1	Negative	Yes	Adjust down	B
3	Positive	Yes	Adjust up	B
3	None	Yes	Direct	C
2	Negative	Yes	Adjust down	C
4	Positive	Yes	Adjust up	C
4	None	Yes	Direct	D
3	Negative	Yes	Adjust down	D
1, 2, 3, 4	NA	No	Adjust down	D

[a] Starting with the left column, best evidence levels (BELs), subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact ("none"), then the BEL is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up ("positive" impact) or down ("negative" impact). If a two-thirds consensus cannot be reached, then the recommendation grade is D. NA, not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation grade D).

[b] Reprinted from *Endocr Pract.* 2014;20(7):692-702 (9 [EL 4; NE]).

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Table 4
2014 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step IV: Examples of Qualifiers That May Be Appended to Recommendations[a]

Cost-effectiveness
Risk-benefit analysis
Evidence gaps
Alternative physician preferences (dissenting opinions)
Alternative recommendations ("cascades")
Resource availability
Cultural factors
Relevance (patient-oriented evidence that matters)

[a] Reprinted from *Endocr Pract*. 2014;20(7):692-702 (9 [EL 4; NE]).

3Q1. HOW SHOULD INDIVIDUALS BE SCREENED FOR THE DETECTION OF DYSLIPIDEMIA?

3Q1.1. Global Risk Assessment

- **R1.** Identify risk factors that enable personalized and optimal therapy for dyslipidemia (Table 5) **(Grade A; BEL 1)**.

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Table 5
Major Atherosclerotic Cardiovascular Disease Risk Factors

Major risk factors	Additional risk factors	Nontraditional risk factors
Advancing age [a-d]	Obesity, abdominal obesity[c,d]	⇧Lipoprotein (a)
⇧ Total serum cholesterol level[a,b,d]	Family history of hyperlipidemia[d]	⇧ Clotting factors
⇧ Non–HDL-C[d]	⇧ Small, dense LDL-C[d]	⇧ Inflammation markers (hsCRP; Lp-PLA_2)
⇧ LDL-C[a,d]	⇧ Apo B[d]	⇧Homocysteine levels
Low HDL-C[a,d,e]	⇧LDL particle concentration	Apo E4 isoform
Diabetes mellitus[a,b,c,d]	Fasting/postprandial hypertriglyceridemia[d]	⇧ Uric acid
Hypertension[a,b,c,d]	PCOS[d]	⇧ TG-rich remnants
Chronic kidney disease 3,4[h]	Dyslipidemic triad[f]	
Cigarette smoking[a,b,c,d]		
Family history of ASCVD[a,d,g]		

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, highly sensitive C-reactive protein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA_2, lipoprotein-associated phospholipase; PCOS, polycystic ovary syndrome.

[a] Risk factors identified in the Framingham Heart study.

[b] Risk factors identified in the MRFIT study (Multiple Risk Factor Intervention Trial).

[c] Risk factors identified in the INTERHEART study.

[d] Risk factors identified in guidelines and position statements (National Cholesterol Education Program Adult Treatment Panel III, American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Position Statement, American Association of Clinical Endocrinologists Insulin Resistance Syndrome Position Statement, American Diabetes Association Standards of Care 2009, American Diabetes Association/American College of Cardiology Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk, National Lipid Association, Clinical Utility of Inflammatory Markers and Advanced Lipoprotein Testing).

[e] Elevated HDL-C is a negative risk factor.

[f] Hypertriglyceridemia; low HDL-C; and an excess of small, dense LDL-C.

[g] Definite myocardial infarction or sudden death before age 55 years in father or other male first-degree relative or before age 65 years in mother or other female first-degree relative.

[h] Based on a pooled analysis of community-based studies (N=22,634).

- **R2.** Based on epidemiologic studies, individuals with type 2 diabetes (T2DM) should be considered as high, very high, or extreme risk for ACSVD (Table 6) **(Grade B; BEL 3; upgraded due to high relevance)**.

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Table 6 Atherosclerotic Cardiovascular Disease Risk Categories and Low-Density Lipoprotein Treatment Goals				
Risk category	**Risk factors[a]/10-year risk[b]**	**Treatment goals**		
		LDL-C (mg/dL)	**Non-HDL-C (mg/dL)**	**Apo B (mg/dL)**
Extreme Risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very High Risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High Risk	– ≥2 risk factors and 10-year risk 10%-20% – Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate Risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low Risk	0 risk factors	<130	<160	NR

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; NR, not recommended; UKPDS, United Kingdom Prospective Diabetes Study.

[a] Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C.

[b] Framingham risk scoring is applied to determine 10-year risk.

- **R3.** Based on epidemiologic and prospective cohort studies, individuals with type 1 diabetes (T1DM) and duration more than 20 years or with 2 or more major CV risk factors (e.g., albuminuria, chronic kidney disease (CKD) stage 3/4, initiation of intensive control >5 years after diagnosis), elevation in A1C >10.4%, or insulin resistance with metabolic syndrome should be considered to have risk-equivalence to individuals with T2DM (Table 14) **(Grade B; BEL 2)**.

- **R4.** The 10-year risk of a coronary event (high, intermediate, or low) should be determined by detailed assessment using one or more of the following tools (Table 7) **(Grade C; BEL 4, upgraded due to cost-effectiveness)**:
    - Framingham Risk Assessment Tool (https://www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/hard-10-year-risk.php)

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- Multi-Ethnic Study of Atherosclerosis (MESA) 10-year ASCVD Risk with Coronary Artery Calcification Calculator (https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx)
- Reynolds Risk Score, which includes highly sensitive CRP (hsCRP) and family history of premature ASCVD) (http://www.reynoldsriskscore.org)
- United Kingdom Prospective Diabetes Study (UKPDS) risk engine to calculate ASCVD risk in individuals with T2DM) (https://www.dtu.ox.ac.uk/riskengine)

Table 7
Key Cardiovascular Risk Scoring Tools: Framingham, MESA, Reynolds, and UKPDS

Framingham Global Risk **Risk factors included/questions**	**Risk group/Framingham Global Risk (10-year absolute ASCVD risk)**	**Clinical examples**
Risk assessment tool for calculating 10-year risk of having a heart attack for adults 20 and older who do not have heart disease or diabetes (using data from the Framingham Heart Study): Age: ☐ years Gender: ◯ Female ◯ Male Total Cholesterol: ☐ mg/dL HDL Cholesterol: ☐ mg/dL Smoker (in last month): ◯ No ◯ Yes Systolic blood pressure: ☐ mm/Hg Are you currently on any medication to treat high blood pressure: ◯ No ◯ Yes Calculate	High >20%	• Established coronary artery disease • Cerebrovascular disease • Peripheral arterial disease • Abdominal aortic aneurysm • Diabetes mellitus • Chronic kidney disease
	Intermediate 10%-20%	• Subclinical coronary artery disease • MetS • Multiple risk factors[a] • Markedly elevated levels of a single risk factor[b] • First-degree relative(s) with early onset coronary artery disease
	Lower <10%	• May include women with multiple risk factors, MetS, or 1 or no risk factors
	Optimal <10%	• Optimal levels of risk factors and heart-healthy lifestyle

- **High risk:** A greater than 20% risk that you will develop a heart attack or die from coronary disease in the next 10 years.
- **Intermediate risk:** A 10 to 20% risk that you will develop a heart attack or die from coronary disease in the next 10 years.
- **Low risk:** Less than 10% risk that you will develop a heart attack or die from coronary disease in the next 10 years.

[a] Patients with multiple risk factors can fall into any of the 3 categories by Framingham scoring.
[b] Most women with a single, severe risk factor will have a 10-year risk ≤10%.

Multi-Ethnic Study of Atherosclerosis (MESA) **Risk factors included/questions**	**Risk calculation outcomes**

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MESA 10-Year ASCVD risk with coronary artery calcification: Gender: Male ◯ Female ◯ Age (45-85 years): ☐ Years Coronary Artery Calcification: ☐ Agatston Race/Ethnicity (choose one): ◯ Caucasian ◯ Chinese ◯ African American ◯ Hispanic Diabetes: Yes ◯ No ◯ Currently Smoke: Yes ◯ No ◯ Family History of Heart Attack: Yes ◯ No ◯ Total Cholesterol: ☐ mg/dL HDL Cholesterol: ☐ mg/dL Systolic Blood Pressure: ☐ mmHg Lipid Lowering Medication: Yes ◯ No ◯ Hypertension Medication: Yes ◯ No ◯ Calculate 10-year ASCVD risk	• External validation provided evidence of very good discrimination and calibration • Harrell's C-statistic ranged from 0.779 to 0.816 in validation against existing studies • The difference in estimated 10-year risk between events and nonevents was approximately 8%-9%, indicating excellent discrimination • Mean calibration found average predicted 10-year risk within 1/2 of a percent of the observed event rate • The test predicts 10-year risk of a ASCVD event
Reynolds Risk Score **Risk factors included/questions**	**Risk calculation outcomes**
Reynolds Risk Score predicts 10-year risk of heart attack, CVA, or other major heart diseases in healthy people without diabetes. Age ☐ Years (≤ 80) Currently Smoke? ◯ Yes ◯ No Systolic blood Pressure ☐ mm/Hg Total Cholesterol ☐ mg/dL or ☐ mmol/L HDL Cholesterol ☐ mg/dL or ☐ mmol/L High Sensitivity C-Reactive Protein (hsCRP) ☐ mg/L Mother or Father have heart attack before age 60? ◯ Yes ◯ No Calculate 10-year risk	• Compared to ATP III/ Framingham 10-year risk categorization: o Very little change in categorization of individuals with very low (<5%) risk o 30% reclassification of those classified as 5% to <10% risk according to ATP III o 29% reclassification of those classified as 10% to <20% risk according to ATP III o 25% reclassification of those classified as ≥20% risk according to ATP III • Risk is classified as Low (<5%), Low to Moderate (5% to <10%), Moderate to High (10% to <20%), and High (≥20%) ASCVD Risk
United Kingdom Prospective Diabetes Study (UKDPS) Risk Score **Risk factors included/questions**	**Risk calculation outcomes**

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UK Prospective Diabetes Study (UKPDS) risk engine is a model for estimating risk of ASCVD in persons with type II diabetes (this risk is up to 3x greater than for the general population) Age ☐ Years Weight ☐ kg Height ☐ cm Gender ◯ Male ◯ Female HDL Cholesterol ☐ mmol/L Total Cholesterol ☐ mg/L Systolic Blood Pressure ☐ mm/Hg Smoker ◯ Yes ◯ No Afro-Caribbean ethnicity? ◯ Yes ◯ No A1C ☐ % Time Period (duration of diabetes) ☐ Years: (4, 5, 6, 7, 8, 9, 10, 15, 20) Regular exercise per week: ☐ # of times (1, 2, 3, 4, >5) Calculate risk	• Survival rates predicted by UKPDS Risk Score model were similar to rates observed in the UKPDS trial, well within non-parametric confidence intervals • Predicted survival rates adjust for A1C, blood pressure, and lipid risk factors • The UKPDS Risk Engine provides risk estimates and 95% confidence intervals, in individuals with type 2 diabetes not known to have heart disease, for: -Non-fatal and fatal coronary heart disease -Fatal coronary heart disease -Non-fatal and fatal CVA -Fatal CVA

Abbreviations: ATP III, Adult Treatment Panel III; ASCVD, atherosclerotic cardiovascular disease; A1C, glycated hemoglobin; CVA, cerebrovascular accident; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; ln, natural logarithm; MetS, the metabolic syndrome; MI, myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study.

- **R5.** Special attention should be given to assessing women for ASCVD risk by determining the 10-year risk (high, intermediate, or low) of a coronary event using the Reynolds Risk Score (www.reynoldsriskscore.org) or the Framingham Risk Assessment Tool (www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/hard-10-year-risk.php)(Table 7) **(Grade C; BEL 4, upgraded due to cost-effectiveness)**.

- **R6.** Dyslipidemia in childhood and adolescence should be diagnosed and managed as early as possible to reduce the levels of LDL-C that may eventually increase risk of CV events in adulthood (Table 8) **(Grade A; BEL 1)**.

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Table 8
Classification of Low-Density Lipoprotein Cholesterol Levels in Children and Adolescents

Category	LDL-C, mg/dL
Acceptable	<100
Borderline	100-129
High	≥130

- **R7.** When the HDL-C concentration is greater than 60 mg/dL, 1 risk factor should be subtracted from an individual's overall risk profile **(Grade B; BEL 2)**.

- **R8.** A classification of elevated TG should be incorporated into risk assessments to aid in treatment decisions (Table 9) **(Grade B; BEL 2)**.

Table 9
Classification of Elevated Triglyceride Levels

TG category	TG concentration, mg/dL	Goal
Normal	<150	<150 mg/dL
Borderline-high	150-199	
High	200-499	
Very high	≥500	

3Q1.2. Screening

Familial Hypercholesterolemia

- **R9.** Individuals should be screened for familial hypercholesterolemia (FH) when there is a family history of:
    - Premature ASCVD (definite myocardial infarction [MI] or sudden death before age 55 years in father or other male first-degree relative, or before age 65 years in mother or other female first-degree relative) or
    - Elevated cholesterol levels (total, non-HDL and/or LDL) consistent with FH **(Grade C; BEL 4, upgraded due to cost-effectiveness)**.

Adults With Diabetes

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- **R10.** Annually screen all adult individuals with T1DM or T2DM for dyslipidemia **(Grade B; BEL 2)**.

Young Adults (Men Aged 20-45 Years, Women Aged 20-55 Years)

- **R11.** Evaluate all adults 20 years of age or older for dyslipidemia every 5 years as part of a global risk assessment **(Grade C; BEL 4, upgraded due to cost-effectiveness)**.

Middle-Aged Adults (Men Aged 45-65 Years, Women Aged 55-65 Years)

- **R12.** In the absence of ASCVD risk factors, screen middle-aged individuals for dyslipidemia at least once every 1 to 2 years. More frequent lipid testing is recommended when multiple global ASCVD risk factors are present **(Grade A; BEL 1)**.

- **R13.** The frequency of lipid testing should be based on individual clinical circumstances and the clinician's best judgment **(Grade C; BEL 4, upgraded due to cost-effectiveness)**.

Older Adults (Older Than 65 Years)

- **R14.** Annually screen older adults with 0 to 1 ASCVD risk factor for dyslipidemia **(Grade A; BEL 1)**.

- **R15.** Older adults should undergo lipid assessment if they have multiple ASCVD global risk factors (i.e., other than age) **(Grade C; BEL 4, upgraded due to cost-effectiveness)**.

- **R16.** Screening for this group is based on age and risk, but not gender; therefore, older women should be screened in the same way as older men **(Grade A; BEL 1)**.

Children and Adolescents

- **R17.** In children at risk for FH (e.g., family history of premature cardiovascular disease or elevated cholesterol), screening should be at 3 years of age, again between ages 9 and 11, and again at age 18 **(Grade B; BEL 3, upgraded due to cost-effectiveness)**.

- **R18.** Screen adolescents older than 16 years every 5 years or more frequently if they have ASCVD risk factors, have overweight or obesity, have other elements of the insulin resistance syndrome, or have a family history of premature ASCVD **(Grade B; BEL 3, upgraded due to cost-effectiveness)**.

3Q2. WHICH SCREENING TESTS ARE RECOMMENDED FOR THE DETECTION OF CARDIOVASCULAR RISK?

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3Q2.1. Fasting Lipid Profile

- **R19.** Use a fasting lipid profile to ensure the most precise lipid assessment; this should include total cholesterol, LDL-C, TG, and non-HDL-C **(Grade C; BEL 4, upgraded due to cost-effectiveness)**.

- **R20.** Lipids, including TG, can be measured in the non-fasting state if fasting determinations are impractical **(Grade D)**.

3Q2.2. Low-Density Lipoprotein Cholesterol

- **R21.** LDL-C may be estimated using the Friedewald equation: LDL-C = (total cholesterol – HDL-C) – TG/5; however, this method is valid only for values obtained during the fasting state and becomes increasingly inaccurate when TG levels are greater than 200 mg/dL, and becomes invalid when TG levels are greater than 400 mg/dL **(Grade C; BEL 3)**.

- **R22.** LDL-C should be directly measured in certain high-risk individuals, such as those with fasting TG levels greater than 250 mg/dL or those with diabetes or known vascular disease **(Grade C; BEL 3)**.

3Q2.3. High-Density Lipoprotein Cholesterol

- **R23.** Measurement of HDL-C should be included in screening tests for dyslipidemia **(Grade B; BEL 2)**.

3Q2.4. Non–High-Density Lipoprotein Cholesterol

- **R24.** The non-HDL-C (total cholesterol minus HDL-C) should be calculated to assist risk stratification in individuals with moderately elevated TG (200 to 500 mg/dL), diabetes, and/or established ASCVD **(Grade B; BEL 2)**.

- **R25.** If insulin resistance is suspected, the non-HDL-C should be evaluated to gain useful information regarding the individual's total atherogenic lipoprotein burden **(Grade D)**.

3Q2.5. Triglycerides

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- **R26.** TG levels should be part of routine lipid screening: moderate elevations (≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome and levels ≥200 mg/dL may identify individuals at substantially increased ASCVD risk **(Grade B; BEL 2)**.

3Q2.6. Apolipoproteins

- **R27.** Apo B and/or an apo B/apo A1 ratio calculation and evaluation may be useful in at-risk individuals (TG ≥ 150, HDL-C < 40, prior ASCVD event, T2DM, and/or the insulin resistance syndrome [even at target LDL-C levels]) to assess residual risk and guide decision-making **(Grade A; BEL 1)**.

- **R28.** Apo B measurements (reflecting the particle concentration of LDL and all other atherogenic lipoproteins) may be useful to assess the success of LDL-C–lowering therapy **(Grade A; BEL 1)**.

3Q2.7. Secondary Causes of Dyslipidemia

- **R29.** Rule out secondary causes of dyslipidemia (Table 10) **(Grade B; BEL 2)**.

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Table 10
Common Secondary Causes of Dyslipidemia

Affected lipids	Conditions
↑ Total cholesterol and LDL-C	• Hypothyroidism • Nephrosis • Dysgammaglobulinemia (systemic lupus erythematosus, multiple myeloma) • Progestin[a] or anabolic steroid treatment • Cholostatic diseases of the liver due to abnormal lipoproteins, as in primary biliary cirrhosis • Protease inhibitors for treatment of HIV infection[b]
↑ TG and VLDL-C	• Chronic renal failure • Type 2 diabetes mellitus[c] • Obesity • Excessive alcohol intake • Hypothyroidism • Antihypertensive medications (thiazide diuretics and b-adrenergic blocking agents) • Corticosteroid therapy (or severe stress that increases endogenous corticosteroids) • Orally administered estrogens[d], oral contraceptives, pregnancy • Protease inhibitors for treatment of HIV infection[b]

Abbreviation: HIV, human immunodeficiency virus.
a Progestational agents, especially those with androgenic activity, can increase LDL-C and decrease HDL-C.
b Protease inhibitors can induce peripheral lipodystrophy, increased visceral fat, insulin resistance, and diabetes. Protease inhibitor-induced dyslipidemia may include elevated LDL-C and/or the atherogenic dyslipidemia pattern of high TG; small, dense, LDL-C; and low HDL-C. However, newer generation protease inhibitors may have improved lipid profiles.
c Diabetic dyslipidemia is often similar to atherogenic dyslipidemia: high TG, small, dense LDL-C, and low HDL-C.
d Transdermally administered estrogens are not associated with increased TG levels.

3Q2.8. Additional Tests

- **R30.** Use highly sensitive C-reactive protein (hsCRP) to stratify ASCVD risk in individuals with a standard risk assessment that is borderline, or in those with an intermediate or higher risk with an LDL-C concentration less than 130 mg/dL **(Grade B; BEL 2)**.

- **R31.** Measure lipoprotein-associated phospholipase A_2 (Lp-PLA_2), which in some studies has demonstrated more specificity than hsCRP, when it is necessary to further stratify an individual's ASCVD risk, especially in the presence of hsCRP elevations **(Grade A; BEL 1)**.

- **R32.** The routine measurement of homocysteine, uric acid, plasminogen activator inhibitor-1, or other inflammatory markers is not recommended because the benefit of doing so is not sufficiently proven **(Grade D)**.

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- **R33.** Coronary artery calcification (CAC) measurement has been shown to be of high predictive value and is useful in refining risk stratification to determine the need for more aggressive treatment strategies **(Grade B; BEL 2)**.

- **R34.** Carotid intima media thickness (CIMT) may be considered to refine risk stratification to determine the need for more aggressive ASCVD preventive strategies **(Grade B; BEL 2)**.

3Q3. WHAT ARE THE TREATMENT RECOMMENDATIONS IN INDIVIDUALS WITH DYSLIPIDEMIA AND ASCVD RISK?

3Q3.1. Treatment Goals

- **R35.** Treatment goals for dyslipidemia should be personalized according to levels of risk (Tables 6, 11) **(Grade A; BEL 1)**.

Table 11
Lipid Goals for Patients at Risk for Atherosclerotic Cardiovascular Disease

Lipid Parameter	Goal (mg/dL)
TC	<200
LDL-C	<130 (low risk) <100 (moderate risk) <100 (high risk) <70 (very high risk) <55 (extreme risk)
Non-HDL-C	30 above LDL-C goal; 25 above LDL-C goal (extreme risk patients)
TG	<150
Apo B	<90 (patients at high risk of ASCVD, including those with diabetes) <80 (patients at very high risk with established ASCVD or diabetes plus ≥1 additional risk factor) <70 (patients at extreme risk)

See text for references and evidence levels.
Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

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3Q3.1.1. Risk Categories and Low-Density Lipoprotein Cholesterol Goals (Table 6)

- **R36.** For individuals at **low risk** (i.e., with no risk factors), an LDL-C goal of less than 130 mg/dL is recommended **(Grade A; BEL 1)**.

- **R37.** For individuals at **moderate risk** (i.e., with 2 or fewer risk factors and a calculated 10-year risk of less than 10%), an LDL-C goal of less than 100 mg/dL is recommended **(Grade A; BEL 1)**.

- **R38.** For individuals at **high risk** (i.e., with an ASCVD equivalent including diabetes or CKD stage 3 or 4 with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%), an LDL-C goal of less than 100 mg/dL is recommended **(Grade A; BEL 1)**.

- **R39.** For individuals at **very high risk** (i.e., with established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease; diabetes or CKD stage 3 or 4 with 1 or more risk factors; a calculated 10-year risk greater than 20%; or heterozygous familial hypercholesterolemia [HeFH]), an LDL-C goal of less than 70 mg/dL is recommended **(Grade A; BEL 1)**.

- **R40.** For individuals at **extreme risk** (i.e., with progressive ASCVD, including unstable angina that persists after achieving an LDL-C less than 70 mg/dL, or established clinical ASCVD in individuals with diabetes, CKD stage 3 or 4, and/or HeFH, or in individuals with a history of premature ASCVD (<55 years of age for males or <65 years of age for females), an LDL-C goal of less than 55 mg/dL is recommended **(Grade A; BEL 1)**.

- **R41.** An LDL-C goal of <100 mg/dL is considered "acceptable" for children and adolescents, with 100 to 129 mg/dL considered "borderline" and 130 mg/dL or greater considered "high" (based on recommendations from the American Academy of Pediatrics) (Table 8) **(Grade D)**.

3Q3.1.2. High-Density Lipoprotein Cholesterol

- **R42.** HDL-C should be greater than 40 mg/dL, but also as high as possible, primarily through the use of lifestyle interventions (e.g., weight loss, physical activity, and tobacco cessation), and if risk factors are present (e.g., borderline elevated LDL-C levels, a family history of premature

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ASCVD, or a personal history of ASCVD), also through the use of pharmacotherapy primarily focused on reducing LDL-C **(Grade A; BEL 1)**.

3Q3.1.3. Non–High-Density Lipoprotein Cholesterol

- **R43.** For most individuals, a non–HDL-C goal (total cholesterol minus HDL-C) 30 mg/dL higher than the individual's specific LDL-C goal is recommended (Table 11) **(Grade D)**.

- **R44.** For individuals at extreme risk, a non-HDL-C goal 25 mg/dL higher than the individual-specific LDL-C goal is recommended (Table 11) **(Grade A; BEL 1)**.

3Q3.1.4. Apolipoproteins

- **R45.** For individuals at increased risk of ASCVD, including those with diabetes, an optimal apo B goal is less than 90 mg/dL, while for individuals with established ASCVD or diabetes plus 1 or more additional risk factor(s), an optimal apo B goal is less than 80 mg/dL, and for individuals at extreme risk, an optimal apo B goal is less than 70 mg/dL (Table 11) **(Grade A; BEL 1)**.

3Q3.1.5 Triglycerides

R46. TG goals of less than 150mg/dL are recommended (Table 11) **(Grade A; BEL 1)**.

3Q3.2. Treatment Recommendations

- **R47.** A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using lifestyle changes **(Grade A, BEL 1)** and patient education with pharmacotherapy as needed to achieve evidence-based targets **(Grade A, BEL 1)**.

3Q3.2.1. Physical Activity

- **R48.** A reasonable and feasible approach to fitness therapy (i.e., exercise programs that include at least 30 minutes of moderate-intensity physical activity [consuming 4-7 kcal/min] 4 to 6 times weekly, with an expenditure of at least 200 kcal/day) is recommended; suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities **(Grade A; BEL 1)**.

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- **R49.** Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum per session); for some individuals, breaking activity up throughout the day may help improve adherence with physical activity programs **(Grade A; BEL 1)**.

- **R50.** In addition to aerobic activity, muscle-strengthening activity is recommended at least 2 days a week **(Grade A; BEL 1)**.

3Q3.2.2. Medical Nutrition Therapy

- **R51.** For adults, a reduced-calorie diet consisting of fruits and vegetables (combined ≥5 servings/day), grains (primarily whole grains), fish, and lean meats is recommended **(Grade A; BEL 1)**.

- **R52.** For adults, the intake of saturated fats, *trans*-fats, and cholesterol should be limited, while LDL-C-lowering macronutrient intake should include plant stanols/sterols (~2 g/ day) and soluble fiber (10-25 g/day) **(Grade A; BEL 1)**.

- **R53.** Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children **(Grade A; BEL 1)**.

3Q3.2.3. Smoking Cessation

- **R54.** Tobacco cessation should be strongly encouraged and facilitated **(Grade A; BEL 2; upgraded due to potential benefit**).

3Q3.2.4. Pharmacologic Therapy

- **R55.** In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals (Table 13) **(Grade A, BEL 1)**.

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Table 13 Primary Lipid-Lowering Drug Classes		
Drug class	**Metabolic effect**[a]	**Main considerations**[b]
HMG-CoA reductase inhibitors (statins: lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, rosuvastatin, pitavastatin)	Primarily ↓ LDL-C 21%-55% by competitively inhibiting rate-limiting step of cholesterol synthesis in the liver, leading to upregulation of hepatic LDL receptors Effects on TG and HDL-C are less pronounced (↓ TG 6%-30% and ↑ HDL-C 2%-10%)	Liver function test prior to therapy and as clinically indicated thereafter. Myalgias and muscle weakness in some patients Potential for drug-drug interaction between some statins and CYP450 3A4 inhibitors, cyclosporine, warfarin, and protease inhibitors Myopathy/rhabdomyolysis in rare cases; increased risk with coadministration of some drugs (see product labeling) Simvastatin dosages of 80 mg are no longer recommended. Do not exceed 20 mg simvastatin daily with amlodipine or ranolazine. Plasma elevations of rosuvastatin may be higher among Asian persons than other ethnic groups. New-onset diabetes is increased in patients treated with statins; however, it is dose-related, occurs primarily in patients with MetS, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in ASCVD.
Cholesterol absorption inhibitors (ezetimibe)	Primarily ↓ LDL-C 10%-18% by inhibiting intestinal absorption of cholesterol and decreasing delivery to the liver, leading to upregulation of hepatic LDL receptors ↓ Apo B 11%-16% In combination with statins, additional ↓ LDL-C 25%, total ↓ LDL-C 34%-61% In combination with fenofibrate, ↓ LDL-C 20%-22% and ↓ apo B 25%-26% without reducing ↑ HDL-C	Myopathy/rhabdomyolysis (rare) Myopathy/rhabdomyolysis (rare) When coadministered with statins or fenofibrate, risks associated with those drugs remain (e.g., myopathy/ rhabdomyolysis, cholelithiasis)
PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors (alirocumab, evolocumab)	↓LDL-C 48%-71%, ↓ non-HDL-C 49%-58%, ↓Total-C 36%-42%, ↓Apo B 42%-55% by inhibiting PCSK9 binding with LDLRs, increasing the number of LDLRs available to clear LDL, and lowering LDL-C levels	Requires subcutaneous self-injection, and refrigeration is generally needed. Adverse reactions resulted in discontinuation in 2.2% overall, 1.2% more than placebo for evolocumab, and 5.3% overall, 0.2% more than placebo for alirocumab. Overall levels of adverse reactions and discontinuation very low.

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		Adverse reactions with significantly different rates between drug and placebo were: local injection site reactions (1.9% greater for alirocumab vs placebo, 0.7% greater for evolocumab vs placebo) and influenza (1.2% greater for alirocumab vs placebo, 0.2% for evolocumab vs. placebo). The most common adverse reactions with similar rates for drug vs. placebo were for: Alirocumab (4%-12%; most common to least common): nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia. Evolocumab (2%-4%; most common to least common): Nasopharyngitis, back pain, and upper respiratory tract infection.
Fibric acid derivatives (gemfibrozil, fenofibrate, fenofibric acid)	Primarily ↓ TG 20%-35%, ↑ HDL-C 6%-18% by stimulating lipoprotein lipase activity Fenofibrate may ↓ TC and LDL-C 20%-25% Lower VLDL-C and LDL-C; reciprocal rise in LDL-C transforms the profile into a less atherogenic form by shifting fewer LDL particles to larger size Fenofibrate ↓ fibrinogen level	Gemfibrozil may ↑ LDL-C 10%-15% GI symptoms, possible cholelithiasis May potentiate effects of orally administered anticoagulants Gemfibrozil may ↑ fibrinogen level[c] Gemfibrozil and fenofibrate can ↑ homocysteine independent of vitamin concentrations[d] Myopathy/rhabdomyolysis when used with statin (uncommon with gemfibrozil, but increased risk with all statins except fluvastatin); interaction less likely with fenofibrate or fenofibric acid (no apparent difference by statin) Fibrates are associated with increased serum creatinine levels, which may not reflect renal dysfunction. Fenofibrate dose should be cut by two-thirds and gemofibrozil by one-half when eGFR is 15-60, and fibrates should be avoided when eGFR is <15. May cause muscle disorders Can improve diabetic retinopathy
Niacin (nicotinic acid)	↓ LDL-C 10%-25%, ↓ TG 20%-30%, ↑ HDL-C 10%-35% by decreasing hepatic synthesis of LDL-C and VLDL-C ↓ Lipoprotein (a) Transforms LDL-C to less atherogenic form by increasing average particle size and also decreases LDL particle concentration	Potential for frequent skin flushing, pruritus, abdominal discomfort, hepatoxicity (rare but may be severe), nausea, peptic ulcer, atrial fibrillation Deleterious effect on serum glucose at higher dosages Increases uric acid levels; may lead to gout

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Bile acid sequestrants (cholestyramine, colestipol, colesevelam hydrochloride)	Primarily ↓ LDL-C 15%-25% by binding bile acids and preventing their reabsorption in the ileum (causing hepatic cholesterol depletion and LDL-Receptor upregulation) Colesevelam ↓ glucose and hemoglobin A1C (~0.5%) – FDA approved to treat T2DM	May ↑ serum TG Frequent constipation and/or bloating, which can reduce adherence Many potential drug interactions (decreased drug absorption), less so with colesevelam (see product labeling) May reduce absorption of folic acid and fat-soluble vitamins such as vitamins A, D, and K
Microsomal Transfer Triglyceride Protein (MTP) inhibitor (lomitapide)	↓ Up to LDL-C 40%, TC 36%, apo B 39%, TG 45%, and non-HDL-C 40% (depending on dose) in patients with HoFH by binding and inhibiting MTP, which inhibits synthesis of chylomicrons and VLDL	Can cause increases in transminases (ALT, AST). Monitoring of ALT, AST, alkaline phosphatase, and total bilirubin prior to initiation, and of ALT and AST during treatment, is required per FDA REMS. Causes increases in hepatic fat (steatosis) with or without concomitant elevated transminases, which may be a risk for progressive liver diseases. Also causes steatosis of the small intestine with resulting abdominal pain and steatorrhea unless a very-low-fat diet is followed. May also cause fat-soluble vitamin deficiency unless vitamin supplements are taken. Caution should be exercised when used with other drugs with potential hepatoxicity. Because of hepatoxicity risk, only available through REMS program.
Anti-sense Apolipoprotein B oligonucleotide (mipomersen - subQ injection)	↓ LDL-C 21%, TC 19%, apo B 24%, and non-HDL-C 22% in patients with HoFH by degrading mRNA for apo B-100, the principal apolipoprotein needed for hepatic synthesis of VLDL (and subsequent intra-plasma production of IDL and LDL)	Can cause increases in transminases (ALT, AST). Monitoring of ALT, AST, alkaline phosphatase, and total bilirubin prior to initiation, and of ALT and AST during treatment is recommended. Causes increases in hepatic fat (steatosis) with or without concomitant elevated transminases, which may be a risk for progressive liver diseases. Caution should be exercised when used with other drugs with potential hepatoxicity. Because of hepatoxicity risk, only available through REMS program.
Omega-3 fatty acids (icosapent ethyl, omega-3-acid ethyl esters)	↓ TG 27%-45%, TC 7%-10%, VLDL-C 20%-42%, apo B 4%, and non-HDL-C 8%-14% in individuals with severe hypertriglyceridemia, most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles. Other potential mechanisms of	TG levels should be carefully assessed prior to initiating therapy and periodically during therapy. Omega-3-acid ethyl esters can increase LDL-C levels. Monitoring of LDL-C levels during treatment is recommended. May prolong bleeding time. Periodic monitoring of coagulation status should be undertaken in patients receiving treatment with omega-3 fatty

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	action include: increased ß-oxiadation; inhibition of acyl-CoA; 1,2-diacylglyceral acyltransferase; decreased hepatic lipogenesis; and increased plasma lipoprotein activity. Icosapent ethyl ↓ LDL-C 5%, whereas omega-3-acid ethyl esters ↑ LDL-C 45%.	acids and other drugs affecting coagulation. Periodic monitoring of ALT and AST levels during treatment is recommended for patients with hepatic impairment. Some patients may experience increases in ALT levels only. Caution should be exercised when treating patients with a known hypersensitivity to fish and/or shellfish. The effect of omega-3 fatty acids on cardiovascular morbidity and mortality and the risk of pancreatitis has not been determined in patients with severe hypertriglyceridemia. In patients with paroxsysmal or persistent AF, therapy with omega-3-acid ethyl esters may be associated with increased frequency of symptomatic AF or flutter, especially within the first 2 to 3 months after initiation. The most common adverse events in patients receiving omega-3 fatty acids included arthralgia (2.3%), eructation (4%), dyspepsia (3%), and taste perversion (4%). Patients may also experience constipation, gastrointestinal disorders, vomiting, rash, or pruritus**.** Omega-3 fatty acids should be used with caution in nursing mothers and should only be used in pregnant women if the benefits of treatment outweigh the potential risk of fetal harm.

Abbreviations: AF: atrial fibrillation; ALT, alanine aminotransferase; AR, adverse reaction; AST, aspartate amino transferase; apo, apolipoprotein; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, hydroxymethylglutaryl-coenzyme A; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; REMS, Risk Evaluation and Mitigation Strategies; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol; TC, total cholesterol.

[a] Percentage of change varies depending on baseline lipid variables and dosages. Statin potency and dosages vary.

[b] Most frequent or serious. See prescribing information for complete contraindications, warnings, precautions, and side effects.

[c] Results vary. Gemfibrozil has been shown to decrease, have no effect on, or increase fibrinogen depending on the study.

[d] Results vary. Gemfibrozil has been shown to have no effect on or increase homocysteine.

Statins

- **R56.** Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials **(Grade A; BEL 1)**.

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- **R57.** For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2DM associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction **(Grade A, BEL 1)**.

- **R58.** In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered **(Grade A, BEL 1)**.

- **R59.** Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes, who also have at least 1 additional risk factor, should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL **(Grade A, BEL 1)**.

- **R60.** Extreme risk individuals should be treated with statins to target an even lower LDL-C treatment goal of <55 mg/dL (Table 6) **(Grade A, BEL 1)**.

Fibrates

- **R61.** Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL) (Table 13) **(Grade A; BEL 1)**.

- **R62.** Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations <40 mg/dL **(Grade A; BEL 1)**.

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Omega-3 Fish Oil

- **R63.** Prescription omega-3 oil, 2 to 4 g daily, should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose. **(Grade A, BEL 1)**.

Niacin

- **R64.** Niacin therapy is recommended principally as an adjunct for reducing TG **(Grade A, BEL 1)**.

- **R65.** Niacin therapy should not be used in individuals aggressively treated with statin due to absence of additional benefits with well-controlled LDL-C **(Grade A; BEL 1)**.

Bile Acid Sequestrants

- **R66.** Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG **(Grade A; BEL 1)**.

Cholesterol Absorption Inhibitors

- **R67.** Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals **(Grade B, BEL 2)**.

- **R68.** Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk **(Grade A; BEL 1)**.

PCSK9 Inhibitors

- **R69.** Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH **(Grade A; BEL 1)**.

- **R70.** PCSK9 inhibitors should be considered in patients with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals **(Grade A; BEL 1)**.

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Combination Therapy

- **R71.** Combination therapy of lipid-lowering agents should be considered when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal **(Grade A; BEL 1)**.

Special Considerations: Women

- **R72.** Women should be evaluated for their ASCVD risk and be treated with pharmacotherapy if lifestyle intervention is insufficient **(Grade C; BEL 4; upgraded due to potential benefit)**.
- **R73.** Hormone replacement therapy for the treatment of dyslipidemia in postmenopausal women is not recommended **(Grade A; BEL 1)**.

Special Considerations: Children and Adolescents

- **R74.** Pharmacotherapy is recommended for children and adolescents older than 10 years who do not respond sufficiently to lifestyle modification, and particularly for those satisfying the following criteria **(Grade D; BEL 4)**:
    - LDL-C ≥190 mg/dL
    - LDL-C ≥160 mg/dL and the presence of 2 or more cardiovascular risk factors, even after vigorous intervention
    - Family history of premature ASCVD (before 55 years of age), or
    - Having overweight, obesity, or other elements of the insulin resistance syndrome

3Q3.3. Follow-up and Monitoring

- **R75.** Reassess individuals' lipid status 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved **(Grade D; BEL 4)**.

- **R76.** While on stable lipid therapy, individuals should be tested at 6- to 12-month intervals **(Grade D; BEL 4)**.

- **R77.** While on stable lipid therapy, the specific interval of testing should depend on individual adherence to therapy and lipid profile consistency; if adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment **(Grade C; BEL 4; upgraded due to potential benefit)**.

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- **R78.** More frequent lipid status evaluation is recommended in situations such as deterioration of diabetes control, use of a new drug known to affect lipid levels, progression of atherothrombotic disease, considerable weight gain, unexpected adverse change in any lipid parameter, development of a new ASCVD risk factor, or convincing new clinical trial evidence or guidelines that suggest stricter lipid goals **(Grade C; BEL 4; upgraded due to potential benefit)**.

- **R79.** Liver transaminase levels should be measured before and 3 months after niacin or fibric acid treatment initiation because most liver abnormalities occur within 3 months of treatment initiation. Liver transaminase levels should be measured periodically thereafter (e.g. semiannually or annually) **(Grade C; BEL 4; upgraded due to potential benefit)**.

- **R80.** Creatine kinase levels should be assessed and the statin discontinued, at least temporarily, when an individual reports clinically significant myalgias or muscle weakness on statin therapy **(Grade C; BEL 4; upgraded due to potential benefit)**.

3Q4. IS TREATMENT OF DYSLIPIDEMIA AND PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE COST-EFFECTIVE?

- **R81.** Nonpharmacologic interventions, such as dietary management **(Grade A; BEL 1)** and smoking cessation, are the most cost-effective options available for ASCVD prevention **(Grade A; BEL 2, upgraded due to potential health benefit)**.

- **R82.** When nonpharmacologic interventions fail, pharmacologic intervention is a recommended cost-effective option for primary and secondary intervention among individuals at moderate to high risk **(Grade B; BEL 2)**.

- **R83.** Among otherwise healthy individuals at lower risk, the cost-effectiveness of primary pharmacologic intervention varies on the basis of age and sex (with this approach being least cost-effective among women at low risk) **(Grade C; BEL 3)**.

- **R84.** Statins have proven cost-effective in both secondary and primary prevention of ASCVD events in individuals at moderate to high risk, or in individuals at low risk whose LDL-C levels are very high (≥190 mg/dL) **(Grade B; BEL 2)**.

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- **R85.** Treatment with fibrates has been found to be cost-effective as both monotherapy and combination therapy for lowering TG and raising HDL-C **(Grade D; BEL 4)**, but not in reducing cardiovascular events, except in individuals with TG concentrations greater than 200 mg/dL and HDL-C concentrations less than 40 mg/dL **(Grade D; BEL 4)**.

- **R86.** Ezetimibe, co-administered with statin therapy in individuals unable to meet target LDL-C levels, has not been evaluated for cost-effectiveness in the U.S. Based on studies from Canada and the United Kingdom, ezetimibe may be a cost-effective strategy to achieve LDL-C goals, especially with price decreases for generic ezetimibe **(Grade A; BEL 1)**.

- **R87.** Bile acid sequestrants are generally not cost-effective alternatives to statin therapy despite generic availability; this is due to their low LDL-C lowering efficacy compared to statins **(Grade B; BEL 2)**.

A complete list of references will be published with the upcoming Evidence Base Appendix.

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Additional Figures and Tables

Table 14
Components of the Insulin Resistance Syndrome

1. Some degree of glucose intolerance
   - Impaired fasting glucose
   - Impaired glucose tolerance
2. Abnormal uric acid metabolism
   - Plasma uric acid concentration
   - Renal uric acid clearance
3. Dyslipidemia
   - Triglycerides
   - HDL-C
   - LDL-particle diameter (small, dense LDL-particles)
   - Postprandial accumulation of TG-rich lipoproteins
4. Hemodynamic changes
   - Sympathetic nervous system activity
   - Renal sodium retention
   - Blood pressure (~50% of patients with hypertension are insulin resistant)
5. Prothrombotic factors
   - Plasminogen activator inhibitor 1
   - Fibrinogen
6. Markers of inflammation
   - C-reactive protein, white blood cell count, etc.
7. Endothelial dysfunction
   - Mononuclear cell adhesion
   - Plasma concentration of cellular adhesion molecules
   - Plasma concentration of asymmetric dimethylarginine
   - Endothelial-dependent vasodilatation

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Table 15. Major Imaging Trials

Trial	Agent	Primary endpoint parameter	Patients, No.		F/U, y	Mean baseline lipid values, mg/dL			Mean achieved lipid values, mg/dL			Mean experimental % change, primary endpoint		Mean control % change, primary endpoint	
			M	F		LDL-C	HDL-C	TG	LDL-C	HDL-C	TG	Overall	Most diseased sub-segment	Overall	Most diseased sub-segment
STATINS															
MARS	Lovastatin, 80 mg (experimental) vs PBO (control)	Percent diameter stenosis measured by QCA	247	23	2.2	157[a]	43	159	86[a]	46	120	1.6	–4.1[b]	2.2	–0.9[b]

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HATS (imaging arm)	Simvastatin + niacin (experimental) vs PBO (control)[c,d]	Percent diameter stenosis measured by QCA	139	21	3.2	125	31	212	75	40	126	0.4	–5.8[a]	3.9	0.1[b]
REVERSAL	Atorvastatin, 80 mg (experimental) vs pravastatin, 40 mg (control)	Atheroma volume measured by coronary IVUS	362	140	1.5	150	42	197	79 on atorvastatin, 80 mg; 110 on pravastatin, 40 mg	43 on atorvastatin, 80 mg; 45 on pravastatin, 40 mg	148 on atorvastatin, 80 mg; 166 on pravastatin, 40 mg	4.1	–4.2[a]	5.4	–1.7[e]
ASTEROID	Rosuvastatin, 40 mg no control group	Atheroma volume measured by coronary IVUS	245	104	2	130	43	152	61	49	121	–0.98	–8.5	NA	NA
Schmermund	Atorvastatin, 80 mg (experimental) vs atorvastatin, 10 mg (control)	Coronary artery calcification measured by EBCT	149	217	1	155[f,g]	50[f,g]	208[f,g]	87 on atorvastatin, 80 mg; 109 on atorvastatin, 10 mg	53 on atorvastatin, 80 mg; 54 on atorvastatin, 10 mg	137 on atorvastatin, 80 mg; 151 on atorvastatin, 10 mg	27	NA	25	NA
ENHANCE	Simvastatin, 80 mg + ezetimibe, 10 mg (experimental) vs simvastatin, 80 mg + placebo (control)	Carotid-artery intima-media thickness measured by carotid ultrasound	370	350	2	319 (simvastatin/ ezetimibe); 317.8 (simvastatin)	46.7 (simvastatin/ ezetimibe); 47.4 (simvastatin)	157 (simvastatin/ ezetimibe); 160 (simvastatin)[h]	141.3 (simvastatin/ ezetimibe); 192.7 (simvastatin)	50.9 (simvastatin/ ezetimibe); 50.7 (simvastatin)	108 (simvastatin/ ezetimibe); 120 (simvastatin)[h]	0.0111[i]	NA	0.0058[i]	NA
METEOR	Rosuvastatin, 40 mg (experimental) vs PBO (control)	Carotid-artery intima-media thickness measured by carotid ultrasound	588	396	2	155 (rosuvastatin); 154 (PBO)	50 (rosuvastatin); 49 (PBO)	126 (rosuvastatin); 134 (PBO)	78	53	98	–0.0014[i]	NA	0.0131[i]	NA
Niacin, Colestipol and/or Combination															
ARBITER-3	Extended-release niacin added to statin therapy	Mean carotid-artery intima-media change measured by ultrasound following up to 24 months of niacin use	120	10	1 or 2	90.5	39.2	180.4	79.2 (1 year niacin use); 78.4 (2 years niacin use)	48.5 (1 year niacin use); 48.6 (2 years niacin use)	120.5 (both 1 and 2 years niacin use)	–0.027 (12 months); –0.041 (24 months)	NA	NA	NA
CLAS	Niacin + colestipol	Change in Global Coronary Change Score based on combined coronary, femoral, and carotid angiograms	162	0	2	171.0	44.6	151.0	97.0	60.8	110	0.3[j]	NA	0.8[j]	NA
FATS	Colestipol 30 g; + niacin 4 g; Colestipol 30 g + lovastatin 40 mg	Percentage change in disease severity (proximal coronary artery lesion stenosis), measured by arteriography	146	0	2.5	189.9 (niacin + colestipol); 196.1 (lovastatin + colestipol)	39.0 (niacin + colestipol); 35.1 (lovastatin + colestipol)	193.8 (niacin + colestipol); 200.9 (lovastatin + colestipol)	128.9 (niacin + colestipol); 106.9 (lovastatin + colestipol)	54.8 (niacin + colestipol); 40.9 (lovastatin + colestipol)	137.2 (niacin + colestipol); 183.2 (lovastatin + colestipol)	–1.1% (niacin + colestipol); –0.3% (lovastatin + colestip	–6.4% (niacin + colestipol); –2.6% (lovastatin + colestipol)	2.0%	1.1%
PCSK9 inhibitors															
GLAGOV	Evolocumab, 420 mg (experimental) vs PBO (control)	Nominal change in % atheroma volume, measured by intravascular ultrasound	699	269	6.5	92.6 (evolocumab); 92.4 (PBO)	46.7 (evolocumab); 45.4 (PBO)	117 (evolocumab); 124.5 (PBO)	36.6 (evolocumab)	51.0 (evolocumab)	105.1 (evolocumab)	-0.95	NA	+0.05	NA

Abbreviations: ARBITER, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; CLAS, Cholesterol Lowering Atherosclerosis Study; EBCT, electron-beam computed tomography; ENHANCE, Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression; F, female; F/U, follow-up; FATS, Familial Atherosclerosis Treatment Study; GLAGOV: Global Assessment of Plaque Regression with a PCSK9 Antibody; HATS, HDL-Atherosclerosis Treatment Study; HDL-C, high-density lipoprotein cholesterol; IVUS, intravascular

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ultrasonography; LDL-C, low-density lipoprotein cholesterol; M, male; MARS, Monitored Atherosclerosis Regression Study; METEOR, Measuring Effects on Intima Media Thickness: An Evaluation of Rosuvastatin; PBO, placebo; REVERSAL, Reversing Atherosclerosis with Aggressive Lipid Lowering; TC, total cholesterol; TG, triglycerides; QCA, quantitative coronary angiography.

[a] LDL-C levels measured by preparative ultracentrifugation.

[b] Lesions with stenosis ≥50% at baseline.

[c] The HATS trial also randomly assigned patients to antioxidant vitamins or simvastatin + niacin + antioxidant vitamins. Results provided do not include antioxidant groups; however, results in the vitamin-only group and the drug + vitamin group did not vary significantly from the placebo and drug groups, respectively.

[d] Dosages varied. Means were 13 mg daily of simvastatin and 2.4 g daily of niacin.

[e] Nominal change (end of treatment minus baseline).

[f] Calculated based on reported figures.

[g] At screening. After a 4-week run-in period on atorvastatin, 10 mg daily, for all patients, LDL-C, HDL-C, and TG levels were 107 mg/dL, 52 mg/dL, and 149 mg/dL, respectively.

[h] Median.

[i] Results reported as millimeter change, not percentage change.

[j] Global Change Category: -3 to 0=no change; 1=mild worsening; 2-3=moderate worsening

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Table 16
Summary of Major Randomized Controlled Drug Trials for Primary Prevention of Coronary Artery Disease

Trial	Treatment	Patients, No.		F/U y	Baseline value[a],mg/dL			Reduction, %					Increase, %
		Male	Female		LDL-C	TG	HDL-C	LDL-C	TG	PTCA	MI	Cor Death	HDL-C
Statins													
WOSCOPS	Pravastatin, 40 mg vs PBO	6595	0	4.9 y	192	164	44	26	12	37[b]	31	28	5
AFCAPS/TexCAPS	Lovastatin, 20-40 mg vs PBO	5608	997	5.2 y	150	158[c]	38	25[d]	15[d]	33[e]	40	[f]	6.0[d]
ALLHAT-LLT	Pravastatin, 40 mg vs PBO	5304	5051	4.8 y	146	152	48	28	4[g]	NA	9[h,i]	[i]	3.3
ASCOT-LLA	Atorvastatin, 10 mg vs PBO	8363	1942	3.3 y	132	149	50	29	14	NA	36[i]	36[i]	0.0
CARDS	Atorvastatin, 10 mg vs PBO	1929	909	4.0 y	117	147[c]	54	40	19	31[e]	33[j]	33[j]	1.0
JUPITER	Rosuvastatin, 20 mg vs PBO	11001	6801	1.9 y[c,k]	108	118	49	NA[k]	NA[k]	NA[k]	54[k]	47[k,l]	NA[k]
Fibrates													
WHO	Clofibrate	3806	0	5.3 y	188	NA	NA	9 (TC)	NA	NA	19	19	NA
HHS	Gemfibrozil	4081	0	5.0 y	201	182	47	11	35	NA	34	37	8.5
FIELD	Fenofibrate	6138	3657	5.0 y	119	154	43	6	22	21[e]	24	+19	1.2
Bile acid													
LRC	Cholestyramine[m]	3806	NA	7.4 y	205	155	44	15[g]	+17[g]	NA	19	24	5.4[g]

Abbreviations: AFCAPS/TexCAPS, Airforce/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; CARDS, Collaborative Atorvastatin Diabetes Study; Cor, coronary; F/U, follow-up; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; HDL-C, high-density lipoprotein cholesterol; HHS, Helsinki Heart Study; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; LRC-CPPT, Lipid Research Clinics Coronary Primary Prevention Trial; MI, myocardial infarction; NA, not applicable; NC, no change; PBO, placebo; PTCA, percutaneous transluminal coronary angioplasty; TC, total cholesterol; TG, triglycerides; WHO, World Health Organization; WOSCOPS; West of Scotland Coronary Prevention Study; y, year.

[a] Mean values, expressed in mg/dL.
[b] Percutaneous transluminal coronary angioplasty or coronary artery bypass graft.
[c] Median.
[d] At 1 year.
[e] All revascularizations.
[f] Too few events to perform survival analysis.
[g] Calculated based on reported figures.
[h] At 6 years.
[i] Endpoint is combined nonfatal myocardial infarction plus fatal coronary heart disease.
[j] Acute coronary events, not including unstable angina.
[k] The JUPITER trial was halted in March 2008 because of unequivocal evidence indicating reductions in cardiovascular morbidity and mortality in patients receiving rosuvastatin compared with placebo. Maximum follow-up period was 5 years.
[l] Myocardial infarction, stroke, or confirmed cardiovascular death.
[m] The bile acid sequestrant colestipol has a mechanism of action and effect similar to that of cholestyramine.
[n] Pooled across multiple dosages of ezetimibe/simvastatin. At highest dosage, reductions in LDL-C and TG were 60.2% and 30.7%, respectively. The increase in HDL-C was 9.8%.

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Table 17

Summary of Major Randomized Controlled Drug Trials for Secondary Prevention of Atherosclerotic Cardiovascular Disease

Trial	Treatment	Patients (no.)		F/U (yr)	Baseline[a] (mg/dL)			Reduction (%)					Increase (%)
		Male	Female		LDL-C	TG	HDL-C	LDL-C	TG	PTCA	MI	Cor Death	HDL-C
Statins													
4S	Simvastatin, 20-40 mg	3617	827	5.4	188	131	46	35	10	37	37	42	8
CARE	Pravastatin, 40 mg	3583	576	5.0	135	91	39	28	14	27	27	24	5
LIPID	Pravastatin, 40 mg	7498	1516	6.1	146[b]	145[b]	36[b]	25	11	19	29	24	5
AVERT	Atorvastatin, 80 mg	288	53	1.5	152	172	40[c]	46	11	[d]	[d]	[d]	8
HPS	Simvastatin, 40 mg	15454	5082	5	132	184	41	32[e]	n/a	22[e,f]	37	17[e]	n/a
GREACE	Atorvastatin, 10-80 mg	624	176	3	180	184	39	46	31	51[g]	59	47	7
A to Z	Simvastatin, 40/80 mg vs PBO/simvastatin, 20 mg	3396	1100	2	112	149	39	41[e]	22[e]	7[f]	4	20	12[e]
IDEAL	Atorvastatin, 80 mg vs simvastatin, 20 mg	7187	1701	4.8	121	149	46	23[h]	26[h]	23[f]	17	1	1.3 (simvastatin over atorvastatin)
TNT	Atorvastatin, 80 mg vs atorvastatin, 10 mg	8099	1902	4.9[b]	98	151	47	18[c,e]	8[c,e]	4	22	20	0
Fibrates													
BECAIT	Bezafibrate	92[i]	n/a	5.0	180[b,j]	214[b,j]	34[b,j]	1.9	31.4	[k]	[k]	[k]	9.2
BIP	Bezafibrate	2825	265	6.2	148	145	35	6.5	20.6	0	12.8[l]	0[l]	17.9
VA-HIT	Gemfibrozil	2531	n/a	5.1	112	160	32	0	31	21[m]	23	22	6
Niacin													
CDP	Niacin	8341	0	15	n/a	n/a	n/a	n/a	n/a	n/a	n/a	11[n]	n/a
Combination													
HATS	Simvastatin + Niacin	139	121	3.2	125	213	31	42	36	90[o]	90[o]	90[o]	26
ARBITER2	Niacin + background statin	152	15	1	89[e]	163[e]	40[e]	2.3[e]	13[e]	[p]	[p]	[p]	21[e]
IMPROVE-IT	Simvastatin, 40 mg + ezetimibe, 10 mg vs simvastatin, 40 mg + PBO	13729	4415	6	93.8	137.6	42.2	24	[q]	1.4[r]	1.7	1.8	[s]
HPS2 THRIVE	Extended-release niacin, 2 g + laropiprant, 40 mg	21229	4444	3.6	63	126.7	43.9	13.8	Mean -33 mg/dL change	10[t]	0.3[u]	+0.1[u]	14.3
AIM-HIGH	Simvastatin + niacin, 1500-2000 mg vs simvastatin + PBO[v]	2910	504	3	74.2	167.5	34.5	13.6[b]	30.8[b]	0.2[w]	+0.7	0.3	25[b]

Abbreviations: AIM-HIGH, Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; ARBITER2, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2; AVERT, Atorvastatin Versus Revascularization Treatment Study; BECAIT, Bezafibrate Coronary Atherosclerosis Intervention Trial; BIP, Bezafibrate Infarction Prevention Study; CABG, coronary artery bypass graft; CDP, Coronary Drug Project; CARE, Cholesterol and Recurrent Events Trial; Cor, Coronary; F/U, follow-up; GREACE, GREek Atorvastatin and Coronary-Heart-Disease Evaluation; HATS, HDL-Atherosclerosis Treatment Study; HDL-C, high-density lipoprotein cholesterol; HPS, Heart Protection Study; HPS2 THRIVE, Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events; IMPROVE-IT, IMProved Reduction of Outcomes, Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-Term Intervention With Pravastatin in Ischemic Disease; MI, myocardial infarction; n/a, not applicable; PBO, placebo; PTCA, percutaneous transluminal coronary angioplasty; 4S, Scandinavian Simvastatin Survival Study; TC, total cholesterol; TG, triglycerides; TNT, Treating to New Targets; VA-HIT, Veteran Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

[a] Mean values (unless otherwise noted).

[b] Median.

[c] Estimated.

[d] Ischemic events reduced 36% vs. comparator patients, who underwent angioplasty (not statistically significant).

[e] Calculated based on reported figures.

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[f] All revascularizations.
[g] PTCA/CABG.
[h] At 1 year.
[i] Total number of patients, male and female.
[j] Bezafibrate group baseline only.
[k] 6.4% coronary event rate (reinfarction, CABG, PCTA) in the bezafibrate group compared with a 24.4% event rate in the placebo group.
[l] A post-hoc analysis found that among patients with highest baseline TG (≥ 200 mg/dL), primary endpoint (nonfatal MI and sudden death) was reduced by 39.5%.
[m] Carotid endarterectomy reduced 65%.
[n] Overall mortality reduction, measured after drug discontinuation
[o] Reduction compared with placebo in composite endpoint (cardiovascular death, nonfatal MI, or revascularization).
[p] Clinical cardiovascular events occurred in 3.8% of statin + niacin patients compared with 9.6% of statin + placebo patients.
[q] -14.04 difference in least squares means at 1 year for simvastatin + ezetimibe vs. simvastatin only, *P*<0.001.
[r] Any revascularization ≥30 days post-randomization.
[s] 0.67 difference in least squares means at 1 year for simvastatin + ezetimibe vs. simvastatin only, *P*<0.001.
[t] Arterial revascularization (rate ration, 0.90; 95% CI, 0.82 to 0.99; *P*=0.03).
[u] Absolute difference between event rates.
[v] Placebo included 50 mg niacin to mask the identity of blinded treatment to patients and study personnel.
[w] Symptom-driven coronary or cerebral revascularizations.

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Table 18

Primary and Secondary Statin Atherosclerotic Cardiovascular Disease Prevention Trials

Trial	Agent	Inclusion criteria (mg/dL)			Mean baseline values (mg/dL)	Mean achieved values (mg/dL)	Relative risk reduction	Experimental event rate %[a,g]	Control event rate %	Absolute risk reduction %	NNT
		TG	HDL-C	LDL-C	LDL-C	LDL-C					
Primary Prevention											
WOSCOPS 0% Female	Pravastatin, 40 mg vs PBO	---	---	155-232	192	159	30%	5.5% at 5.0 yrs	7.9%	2.4%	42
AFCAPS 15% Female	Lovastatin, 20-40 mg vs PBO	≤400	<45 M <47 F	130-190	150	115	40%	4.0% at 5.2 yrs	6.8%	1.2%	83
ASCOT-LLA 19% Female	Atorvastatin, 10 mg vs PBO	<400	---	TC <250	134	90	37%	1.9% at 3.3 yrs	3.0%	1.1%	91
CARDS 32% Female	Atorvastatin, 10 mg vs PBO	<600	---	≤160	118	82	35%	3.0% at 4.0 yrs	4.6%	1.6%	63
JUPITER[b] 38% Female	Rosuvastatin, 20 mg vs PBO	<500	---	<130[c]	108[d]	55[d]	44%	1.6% at 1.9 yrs[b,e]	2.8% at 1.9 yrs[b,e]	---	95[f]
Secondary Prevention											
4S 19% Female	Simvastatin, 20-40 mg vs PBO	≤225	---	TC = 215-315	190	124	35%	8.2% at 5.4 yrs	11.5%	9.2%	11
CARE 14% Female	Pravastatin, 40 mg vs PBO	<350	---	115-74	139	98	23%	10.2% at 5.0 yrs	13.2%	3.0%	33
LIPID 17% Female	Pravastatin, 40 mg vs PBO	<445	---	TC = 155-271	150	112	23%	12.3% at 6.1 yrs	15.9%	3.6%	28
HPS 25% Female	Simvastatin, 40 mg vs PBO	---	---	TC ≥135	129	90	26%	8.7% at 5.0 yrs	11.8%	3.1%	32
TNT 19% Female	Atorvastatin, 80 mg vs atorvastatin, 10 mg	≤600	---	<130	98	77 on atorvastatin, 80 mg; 101 on atorvastatin, 10 mg	21% in favor of atorvastatin, 80 mg	6.9% at 4.9 yrs	8.7%	1.8%	56
PROVE IT – TIMI 22% Female	Atorvastatin, 80 mg vs pravastatin, 40 mg	---	---	TC ≤240 or TC ≤200 on therapy	106 (median)	62 on atorvastatin, 80 mg; 95 on pravastatin, 40 mg	17% in favor of atorvastatin	8.3% at 2 yrs	10.0% at 2 yrs	1.7%	59
A to Z 25% Female	Simvastatin, 40/80 mg vs PBO/ simvastatin, 20 mg	---	---	TC ≤250[g]	112	66 on simvastatin, 40/80 mg; 81 on PBO/ simvastatin,	11% in favor of simvastatin, 40/80 mg	14.4% at 2 yrs	16.7% at 2 yrs	---	77[h]

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						20 mg					
IDEAL 19% Female	Atorvastatin, 40-80 mg vs simvastatin, 20-40 mg	≤600	---	---	121.5	80 on atorvastatin, 40-80 mg; 100 on simvastatin, 20-40 mg	12% in favor of atorvastatin	9.9% at 4.8 yrs	11.2% at 4.8 yrs	1.2%	77
AIM-HIGH %15 female	Simvastatin + niacin, 1500-2000 mg vs simvastatin + PBO[i]	150-400 mg/dL	<40 mg/dL for men; <50 mg/dL for women	<180 mg/dL	74	65	-1%[j]	16.4	16.2	-0.2[j]	-5[j]
IMPROVE-IT 24% female	Simvastatin, 40 mg + ezetimibe, 10 mg vs simvastatin, 40 mg + PBO	≤350	---	≥50 and ≤125 or ≥50 and ≤100 on therapy	93.8	53.2	5.8%[j]	32.7	34.7	2.0%	50[j]
HPS2-THRIVE 17.3% female	In combination with simvastatin or simvastatin + ezetimibe, extended-release niacin, 2 g + laropiprant, 40 mg vs PBO	None[k]	None[k]	None[k]	63	Mean -10 mg/dL change	3.7%[j]	13.2	13.7	0.5%[j]	200[j]

Abbreviations: AIM-HIGH, Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; AFCAPS, Airforce Coronary Atherosclerosis Prevention Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events Trial; HDL-C, high-density lipoprotein cholesterol; HPS, Heart Protection Study; HPS2 THRIVE, Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events; IDEAL, Incremental Decrease in Endpoints Through Aggressive Lipid lowering; IMPROVE-IT, IMProved Reduction of Outcomes, Vytorin Efficacy International Trial; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-Term Intervention With Pravastatin in Ischemic Disease; NNT, number needed to treat to prevent 1 event during study; PBO, placebo; PROVE IT – TIMI, Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction; 4S, Scandinavian Simvastatin Survival Study; TC, total cholesterol; TG, triglycerides; TNT, Treating to New Targets; WOSCOPS; West of Scotland Coronary Prevention Study; yrs, years.

[a] Events: Acute myocardial infarction and coronary heart disease death, percentage with events at study end.

[b] The JUPITER trial was halted in March, 2008. Median follow-up was 1.9 years; maximal follow-up was 5 years.

[c] Inclusion criteria included hsCRP protein concentration ≥2.0 mg/L.

[d] Median.

[e] Calculated based on 142 and 251 events in rosuvastatin and placebo groups, respectively.

[f] Number needed to treat for 2 years. Number needed to treat for 4 years is 31; 4-year risks projected over average 5-year treatment periods results in number needed to treat of 25.

[g] Additional inclusion criteria were either non-ST-elevation acute coronary syndrome or ST-elevation myocardial infarction.

[h] Cardiovascular death only.

[i] Placebo included 50 mg niacin to mask the identity of blinded treatment to patients and study personnel.

[j] Calculated based on reported figures.

[k] Participant's doctor was provided with total cholesterol result, measured during LDL-C-lowering run-in phase. Whether an individual could participate in randomization was then decided by their own doctor.

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Table 19
Lipid-Lowering Drug Therapies, Usual Starting Dosages and Dosage Ranges

Agent	Usual recommended starting daily dosage	Dosage range
Statins		
Lovastatin	20 mg	10-80 mg
Pravastatin	40 mg	10-80 mg
Simvastatin	20-40 mg	5-80 mg[a]
Fluvastatin	40 mg	20-80 mg
Atorvastatin	10-20 mg	10-80 mg
Rosuvastatin	10 mg	5-40 mg
Pitavastatin	2 mg	2-4 mg
Cholesterol absorption inhibitors		
Ezetimibe	10 mg	10 mg
PCSK9 Inhibitors		
Alirocumab	75 mg every 2 weeks	75-150 mg every 2 weeks
Evolocumab	140 mg every 2 weeks or 420 mg once monthly	Not applicable
Fibrates		
Fenofibrate	48-145 mg	48-145 mg
Gemfibrozil	1200 mg	1200 mg
Fenofibric acid	45-135 mg	45-135 mg
Niacin		
Immediate-release	250 mg	250-3000 mg
Extended-release	500 mg	500-2000 mg
Bile acid sequestrants		
Cholestyramine	8-16 g	4-24 g
Colestipol	2 g	2-16 g
Colesevelam	3.8 g	3.8-4.5 g
Combination therapies (single-pill)		
Ezetimibe/simvastatin	10/20 mg	10/10 to 10/80 mg
Extended-release niacin/simvastatin	500/20 mg	500/20-1000/20 mg
Microsomal Transfer Protein (MTP) inhibitor		
Lomitapide	5 mg, with subsequent titration	5 mg-60 mg
Anti-sense apolipoprotein B oligonucleotide		
Mipomersen (SubQ injection)	200 mg once weekly	200 mg once weekly
Omega-3 Fatty Acids		
Omega-3-acid ethyl esters (Lovaza)	4 g per day	4 g per day
Icosapent ethyl (Vascepa®)	4 g per day	4 g per day

[a] Simvastatin, 80 mg, not approved for therapy unless individual has been on treatment for more than 1 year without myopathy.

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Table 20
Comparison of Statin Effects on Lipids After 6 Weeks of Treatment in Men and Women With Low-Density Lipoprotein Cholesterol ≥160 mg/dL and ≤250 mg/dL[a,b] (N = 2431)

Statin	Dosage range, mg daily	TC	LDL-C	HDL-C	TG
Lovastatin	20-80	↓ 21 to ↓ 36	↓ 29 to ↓ 48	↑ 4.6 to ↑ 8.0	↓ 12 to ↓ 13
Pravastatin	10-40	↓15 to ↓ 22	↓ 20 to ↓30	↑ 3.2 to ↑ 5.6	↑ 8 to ↓ 13
Simvastatin	10-80[d]	↓ 20 to ↓ 33	↓ 28 to ↓ 46	↑ 5.2 to ↑ 6.8	↓ 12 to ↓ 18
Fluvastatin	20-40	↓ 13 to ↓ 19	↓ 17 to ↓ 23	↑ 0.9 to ↓ 3.0	↓ 5 to ↓ 13
Atorvastatin	10-80	↓ 27 to ↓ 39	↓ 37 to ↓ 51	↑ 2.1 to ↑ 5.7[c]	↓ 20 to ↓ 28
Rosuvastatin	10-40	↓ 33 to ↓ 40	↓ 45 to ↓ 55	↑ 7.7 to ↑ 9.6	↓ 20 to ↓ 26

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

[a] The lipid-lowering effects of the various statins in these studies are representative of those seen in other controlled trials, with one exception. In the CARE (Cholesterol and Recurrent Events), WOSCOPS (West of Scotland Coronary Prevention Study), and LIPID (Long-Term Intervention With Pravastatin in Ischemic Disease) trials, pravastatin had a slightly greater TG-lowering effect.

[b] Figures for lovastatin and fluvastatin are from the 8-week CURVES trial (Comparative Dose Efficacy of Atorvastatin, Simvastatin, Pravastatin, Lovastatin, and Fluvastatin), a comparison of the effects on lipids of lovastatin, fluvastatin, atorvastatin, simvastatin, and pravastatin in men and women with LDL-C levels from 192 to 244 mg/dL (N = 534).

[c] HDL-C increase was with the lowest atorvastatin dosage, and benefit decreased as dosage increased.

[d] Not to be used at dosages of 80 mg unless individual has been on treatment for more than 12 months.

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Figure 2. Meta-analysis of proportional effects on major vascular events per mmol/L LDL-C reduction in 169,138 participants in 26 randomized trials of statins over a median period of 5 years (Cholesterol Treatment Trialists' Collaborators, 2010). Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; RR, relative risk. Reprinted from *The Lancet*, Vol 376, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, 1670-1681, Copyright (2010), with permission from Elsevier.

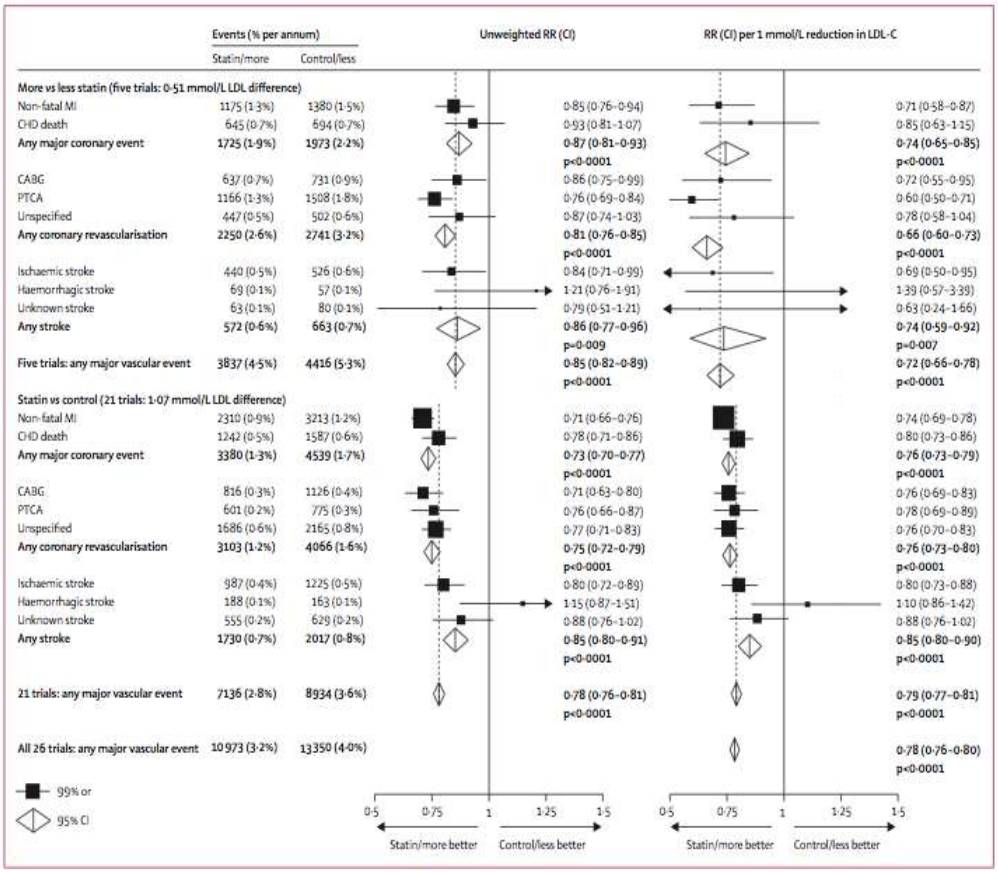

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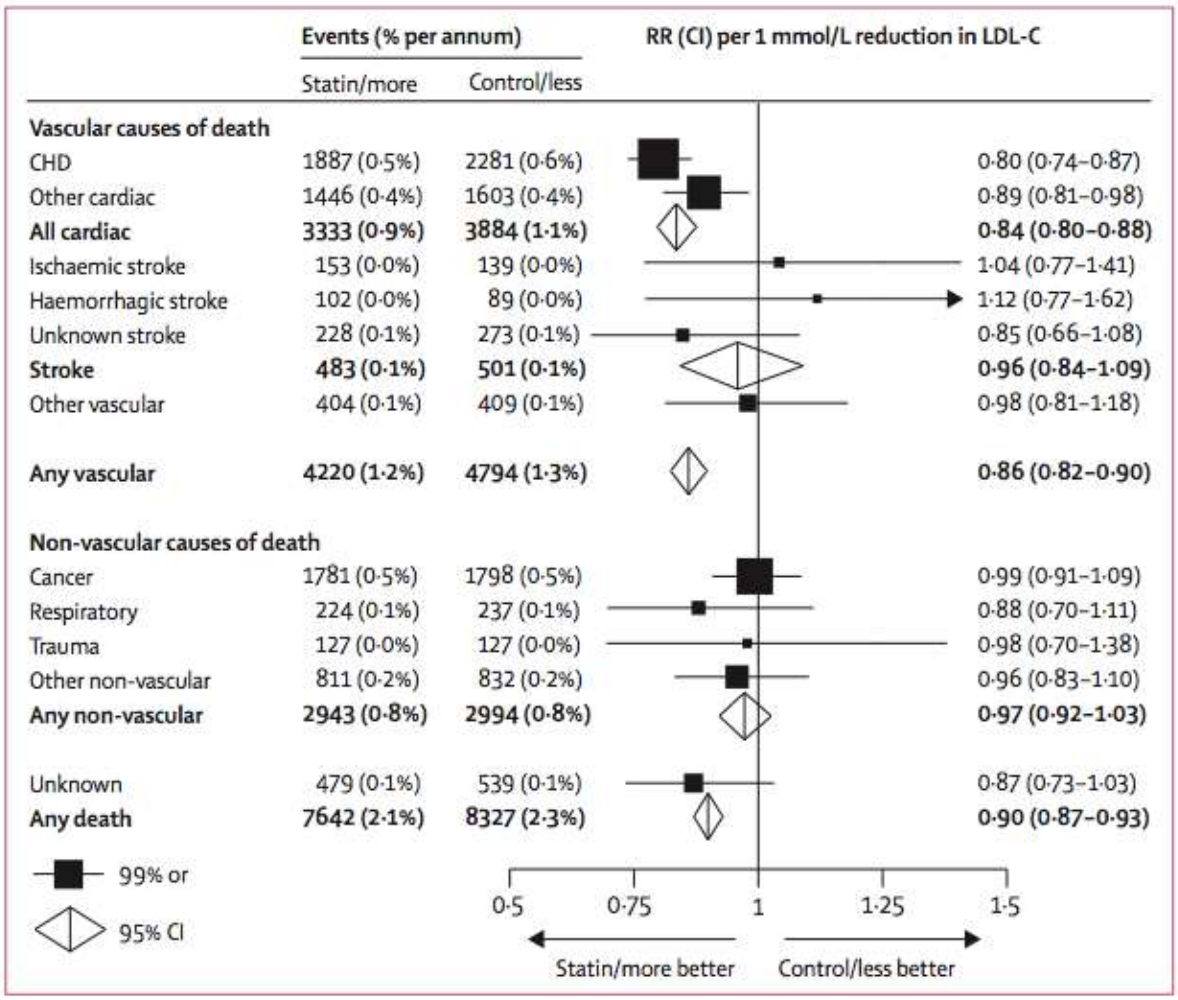
Figure 3. Meta-analysis of proportional effects on cause-specific mortality per mmol/L LDL-C cholesterol reduction in 169,138 participants in 26 randomized trials of statins over a median period of 5 years, by baseline prognostic factors (Cholesterol Treatment Trialists' Collaborators, 2010). Abbreviations: CHD, coronary heart disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; RR, relative risk. Reprinted from *The Lancet*, Vol 376, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, 1670-1681, Copyright (2010), with permission from Elsevier.



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DISCLOSURES

Chair

Dr. Paul S. Jellinger reports that he has received speaker honoraria from BI-Lilly, AstraZeneca, Novo Nordisk, Merck, and Amgen.

Task Force Members

Dr. Donald A. Smith reports that he has received research grant support from Sanofi Regeneron and Amgen.

Dr. Yehuda Handelsman reports that he is a consultant for Amarin, Amgen, AstraZeneca, Boehringer Ingelheim (BI), Janssen, Eli Lilly, Eisai, Intarcia, Merck, Novo Nordisk, Sanofi, and Regeneron. He is a speaker for Amarin, Amgen, AstraZeneca, BI-Lilly, Janssen, Novo Nordisk, Sanofi, and Regeneron. Dr. Handelsman has received research grant support from Amgen, AstraZeneca, BI, Esperion, Grifols, Hamni, GSK, Lexicon, Merck, Novo Nordisk, and Sanofi.

Dr. David S. H. Bell reports that he is a consultant and speaker for AstraZeneca, Takeda, Janssen, and Novo Nordisk.

Dr. Zachary T. Bloomgarden reports that he is a consultant for AstraZeneca, Johnson & Johnson, Merck, Intarcia, and Novartis. He is also a speaker for Merck, AstraZeneca, and Johnson & Johnson. He is a shareholder in Allergan, Pfizer, Zimmer Biomet, and Novartis.

Dr. Eliot Brinton reports that he is a consultant for Alexion, Amarin, Aralez, Arisaph, AstraZeneca, Kowa, Merck, Regeneron, Sanofi-Aventis, and PTS Diagnostics. He is also a speaker for Alexion, Amarin, Amgen, Boehringer Ingelheim, Janssen, Kastle, Kowa, Merck, Novo Nordisk, Sanofi-Aventis, Takeda, and Regeneron.

Dr. Michael H. Davidson reports that he is a consultant for Amgen, Regeneron, Sanofi, Merck, and AstraZeneca. He has also received speaker honoraria and has served on the speaker's bureau for Amgen, Regeneron, and Sanofi.

Dr. Sergio Fazio reports that he is a consultant for Amgen, Sanofi, Amarin, Aegerion, and Kowa.

Dr. Vivian A. Fonseca reports that he is a consultant for Takeda, Novo Nordisk, Sanofi, Eli Lilly, Pamlabs, AstraZeneca, Abbott, Boehringer Ingelheim, Janssen, and Intarcia. He is also a speaker for Takeda, AstraZeneca, and Sanofi. Dr. Fonseca has received research grants from Novo Nordisk, Asahi, Eli Lilly, Abbott, Endo Barrier, Bayer, and Gilead.

Dr. Alan J. Garber reports that he is a consultant for Novo Nordisk and Intarcia.

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Dr. George Grunberger reports that he has received speaker honoraria from Eli Lilly, BI-Lilly, Novo Nordisk, Sanofi, Janssen, and AstraZeneca. He has received research funding from AstraZeneca, Eli Lilly, Lexicon, and Medtronic.

Dr. Chris Guerin reports that he is a consultant for Janssen and a speaker for Novo Nordisk.

Dr. Jeffrey Mechanick reports that he is a consultant for Abbott Nutrition International.

Dr. Rachel Pessah-Pollack reports that she is a consultant and speaker for Boehringer Ingelheim/Eli Lilly.

Dr. Paul D. Rosenblit reports that he is a consultant for AstraZeneca and a speaker for AstraZeneca (Bristol Myers Squibb), Boehringer Ingelheim, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, and Takeda. He has also received research grant support from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Ionis, Eli Lilly, Lexicon, Merck, Novo Nordisk, Orexigen, Pfizer, Sanofi.

Dr. Kathleen Wyne reports that she is a consultant for Novo Nordisk and Abbvie. She has also received speaker honoraria from Roche and Bayer and research grant support from Sanofi and Eli Lilly.

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