Advances in treatment of hypercholesterolemia

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Objectives

- Pharmacist Objectives:
  - Recall the Adult Treatment Panel (ATP) IV guidelines
  - Review the lipid-lowering medications
  - Develop a patient specific treatment algorithm
- Pharmacy Technician Objectives:
  - Recognize the Adult Treatment Panel (ATP) IV guidelines
  - Acknowledge the health risks of hypercholesterolemia
  - Appreciate the lipid-lowering medications

Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Hypercholesterolemia in the United States [1,2]

- 73.5 million adults (31.7%) have high LDL
- 31 million adults have a total cholesterol greater than 240 mg/dL
- Most prevalent among white, non-hispanic females
- 48.1% of adults with high LDL cholesterol are receiving lipid-lowering therapy
  - 29.5% with high LDL are optimized

Causes of Lipoprotein Abnormalities[3]

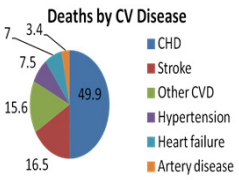
- Primary
  - Homozygous familial hypercholesterolemia (HoFH)
  - Heterozygous familial hypercholesterolemia (HeFH)
- Secondary
  - Hypercholesterolemia
    - Hypothyroidism, obstructive liver disease, nephrotic syndromes, medications (thiazides, progestins, steroids)
  - Hypertriglyceridemia
    - Obesity, diabetes mellitus, sepsis, pregnancy, lipodystrophy, acute hepatitis, alcohol, medications (β-blockers, azoles)
  - Low HDL
    - Malnutrition, obesity, medications (progestins, anabolic steroids)

Lipid Panel [3]

- Standard lipid panel includes:
  - Total cholesterol (TC)
    - TC= LDL + HDL + (TG/5)
    - Optimal range: less than 200 mg/dL
  - Low-density lipoprotein (LDL) cholesterol
    - Optimal range: less than 130 mg/dL
  - High-density lipoprotein (HDL) cholesterol
    - Optimal range: greater then 40 mg/dL
  - Triglycerides (TGs)
    - Optimal range: less than 200 mg/dL

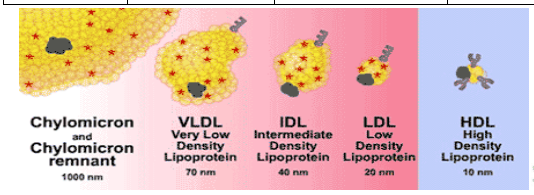
Risks of Hypercholesterolemia[3]

- Acute myocardial infarction
- Heart failure
- Coronary arteriosclerosis
- Thromboembolic stroke
- Peripheral vascular disease
- Pancreatitis



Lipoproteins[3]

Lipoprotein	Triglyceride (%)	Phosphoslipid (%)	Protein (%)
Chylomicron	80-95	3-9	1-2
VLDL	55-80	10-20	6-10
LDL	5-15	18-24	18-22
HDL	5-10	20-30	45-55



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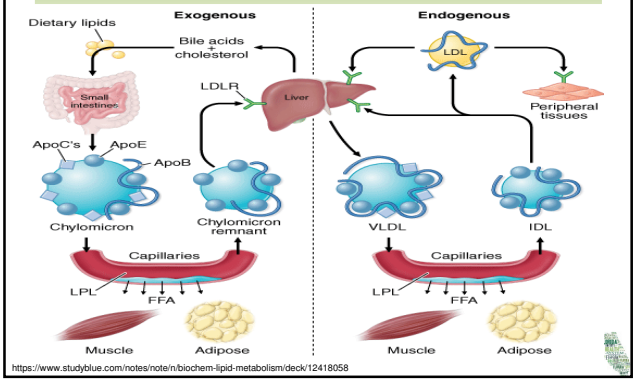
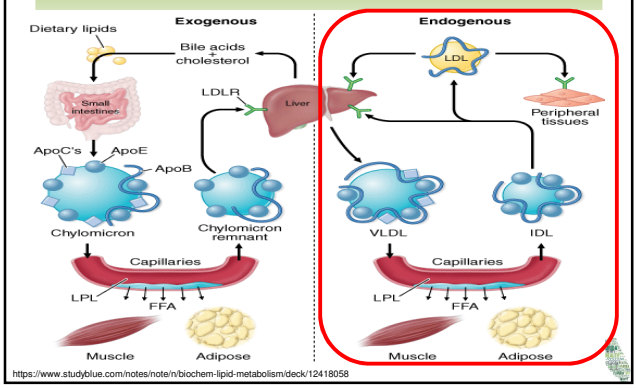
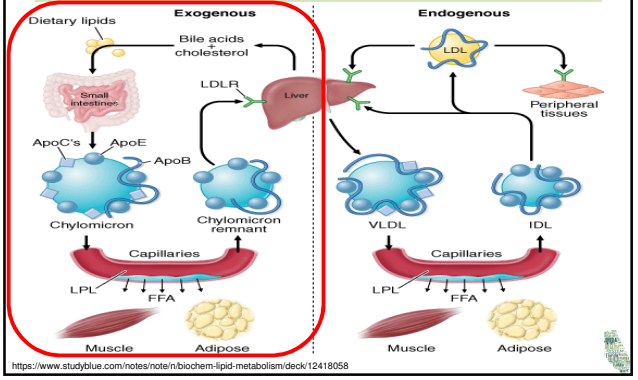
Cholesterol Synthesis [3]



Cholesterol Synthesis[3]



Cholesterol Synthesis[3]



Atherosclerotic Cardiovascular Disease (ASCVD) [3,4,5]

- ASCVD includes coronary heart disease (CHD), stroke, and peripheral artery disease
- Primary prevention:
  - Prevent the onset of ASCVD
- Secondary prevention:
  - Requires identification of ASCVD at early stage and initiation of management

Evolution of the ACC/AHA Cholesterol Guidelines

ATP-I: Focus on primary prevention
LDL target < 130 mg/dL

ATP-II: Focus on secondary prevention
LDL target < 100 mg/dL ; HDL introduced as CVD risk

ATP-III: Primary and secondary prevention
Life-modification program (TLC); Framingham Risk Score

Revised ATP-III: LDL target < 70 mg/dL for high risk patients

ATP-IV: Tailored treatment approach

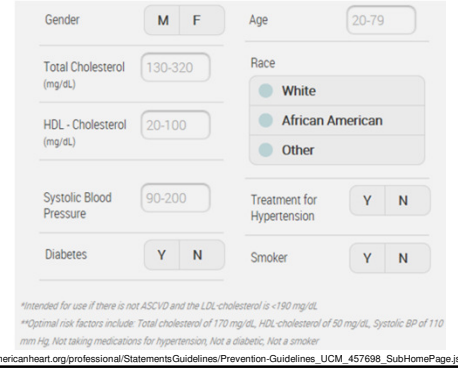
Global Risk Assessment for Primary Prevention[4]

- Pooled Cohort Equation
  - Replaces Framingham Risk Score
  - Enables health care providers and patients to estimate 10-year and lifetime risks for ASCVD
- Required information to estimate ASCVD risk includes age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status

2013 ACC/AHA Cholesterol Guidelines: ATP IV[4]

- Updates in the guidelines
  - A new perspective on LDL/ HDL treatment goals
    - Giving up the goal to treat paradigm
    - No RCTs support achieving a certain target LDL improve ASCVD outcomes
    - Use of LDL targets may lead to:
      - Suboptimal dose of statins
      - Overtreatment with non-statin drugs that have not shown a ASCVD risk reduction
  - Focus on ASCVD risk reduction
    - 4 statin benefit groups

Pooled Cohort Equation[4]



https://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp

Treatment Approach

Lipid Lowering Therapy

- Current Therapies
  - Fibric Acid Derivatives (Fibrates)
  - Nicotinic Acid (Niacin)
  - Omega-3 Fatty Acids (FAs)
  - Bile Acid Sequestrants (BAS)
  - Cholesterol Absorption Inhibitor (CAI)
  - **HMG-CoA Reductase Inhibitors (Statins)**
  - PCSK9 Monoclonal Antibody (mAB)
- Future Therapy
  - Cholesteryl Ester Transfer Protein (CETP) Inhibitors

PCSK9: proprotein convertase subtilisin kexin type 9

Lifestyle Modifications[4,5]

- Diet:
  - Saturated and *trans* fat restriction
  - Dietary salt restriction
  - Achieve with the USDA dietary pattern, DASH, or ADA diet
- Exercise (aerobic and resistance training)
  - Moderate intensity: 150 minutes/week
  - Vigorous intensity: 75 minutes/week

Lipid Lowering Therapy[3,4]

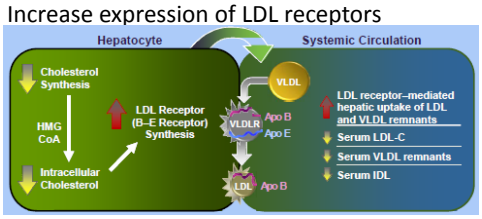
Drug Class	Mechanism	Adverse Events	Comments
Fibrates Gemfibrozil Fenofibrate Fenofibric acid	Inhibit lipolysis, decreases hepatic fatty acid uptake and inhibit hepatic secretion of VLDL;	Dyspepsia, upper GI distress, cholesterol gallstones, myopathy	Major effects are to decrease triglycerides and increase HDL Variable effect on LDL
BAS Colesevelam Cholestyramine Colestipol	Bind bile acids in the intestine that is eliminated in feces which results in lowering of cholesterol	Upper and lower GI distress, constipation	Typically used as adjunctive therapies

Lipid Lowering Therapy[3,4]

Drug Class	Mechanism	Adverse Events	Comments
Nicotinic Acid (CR, SR)	Inhibits mobilization of free fatty acids from peripheral adipose tissue to the liver and reduces VLDL synthesis	Flushing, hyperglycemia, hyperuricemia, GI distress, hepatotoxicity	•Can reduce triglyceride levels (less than fibrates) •May worsen glucose tolerance, caution in diabetics •Combination with statins may have harmful effects
Omega-3 FAs	Unknown Possible modulation VLDL and chylomicron metabolism	Bleeding complications	•Increase HDL and decrease triglycerides •Important as a supplement in patients with CHD

Statin: Mechanism[3]

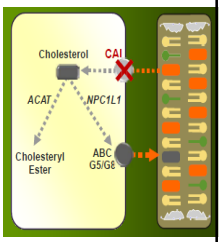
- Drug of choice for high LDL or CHD/CHD risk
- Inhibit HMG-CoA reductase
- Reduce hepatic cholesterol content
- Increase expression of LDL receptors



http://www.lipidsonline.org/slides/slide01.cfm?q=cholesterol+synthesis&dpg=8

Cholesterol Absorption Inhibitor [3,6-8]

- Ezetimibe (ZETIA®), 10 mg tablet
- Outcomes Data:
  - IMPROVE-IT
    - Ezetimibe 10 mg + simvastatin 40 mg PO daily vs simvastatin 40 mg PO daily
    - LDL reduction: 53.7 mg/dL vs 69.5 mg/dL (P < 0.001)
    - Event rate at 7 years: 32.7% vs 34.7% (P = 0.016)
    - Total events: 4,562 vs. 4,983 (P = 0.007)



Event: cardiovascular [CV] death, myocardial infarction, stroke, unstable angina leading to hospitalization, coronary revascularization > 30 days post-randomization

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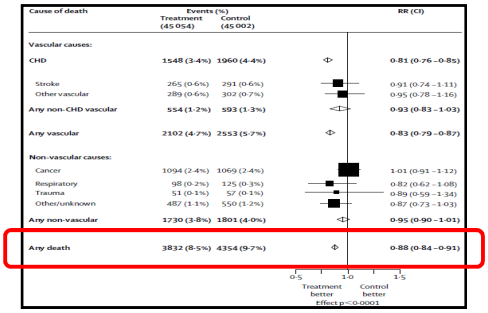
Statin: Clinical Efficacy[9]



In a meta-analysis of 14 primary and secondary prevention trials with statins, all-cause death was reduced by 12%.

Statin Safety[4]

- Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
  - Multiple or serious comorbidities, including impaired renal or hepatic function
  - History of previous statin intolerance or muscle disorders
  - Unexplained ALT elevations ≥3 times ULN
  - Patient characteristics or concomitant use of drugs affecting statin metabolism
  - Age >75 years
- Obtain baseline CK and LFTs

4 Statin Benefit Groups[4]

Benefit Group	Statin Therapy
Clinical ASCVD	
Diabetes mellitus (age 40-75) LDL 70-189	
LDL ≥ 190	
≥ 7.5% 10 year risk (age 40-75)	

Statin Therapy[4]

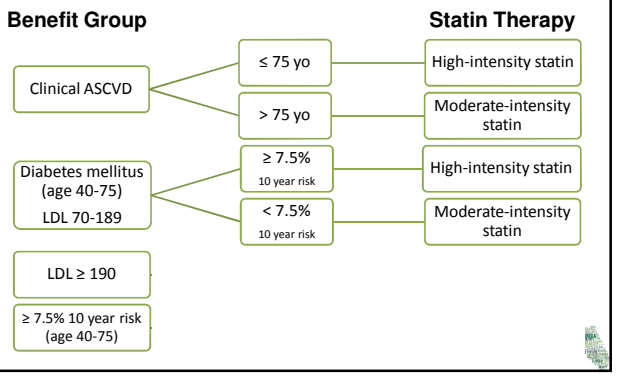
High-Intensity Statins	Moderate-Intensity Statins	Low-Intensity Statins
Lowers LDL by approx. ≥50%	Lowers LDL by approx. 30-50 %	Lowers LDL by approx. <30%
Atorvastatin (40*)- 80 mg **Rosuvastatin 20** (*40*) **mg**	**Atorvastatin 10** (*20*) **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20-40 mg**** **Pravastatin 40** (*80*) **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg daily* **Fluvastatin 40 mg BID** *Pitavastatin 2-4 mg*	Simvastatin 10 mg **Pravastatin 10-20 mg** **Lovastatin 20 mg** Fluvastatin 20-40 mg BID Pitavastatin 1 mg

Bold indicates evaluated by RCTs
Italics indicates doses approved by FDA but not tested
*= Evidence from 1 RCT
**= Initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy

4 Statin Benefit Groups[4]

Benefit Group		Statin Therapy
Clinical ASCVD	≤ 75 yo	High-intensity statin
	> 75 yo	Moderate-intensity statin
Diabetes mellitus (age 40-75) LDL 70-189		
LDL ≥ 190		
≥ 7.5% 10 year risk (age 40-75)		

4 Statin Benefit Groups[4]



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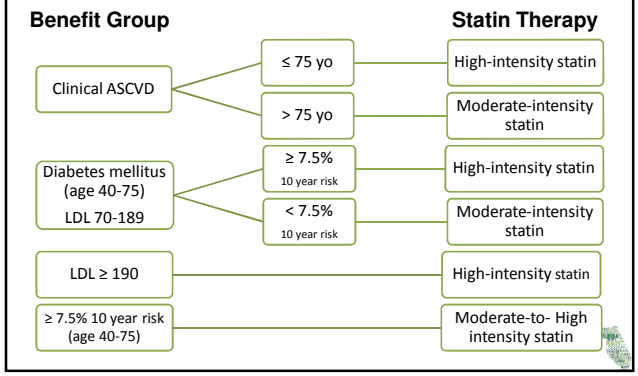

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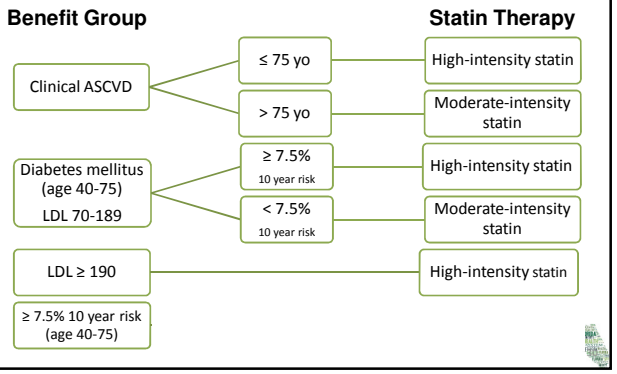
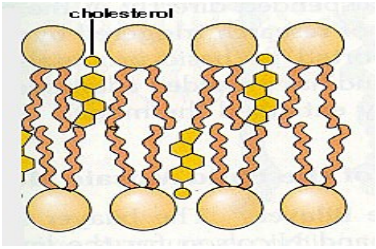


Biomarkers and Noninvasive Tests[4]

- Primary ASCVD prevention for individuals ***not*** in a statin benefit group and to initiation of statin therapy is unclear
- Additional Factors to Consider
  - Elevated lifetime risk of ASCVD
  - LDL ≥160 mg/dL*
  - hs-CRP>2 mg/L
  - Ankle-brachial index <0.9
  - Family history of premature ASCVD
  - CAC score ≥300 Agatston units

hs-CRP: high-sensitivity C-reactive protein
CAC: coronary artery calcium
*= or other evidence of genetic dyslipidemias

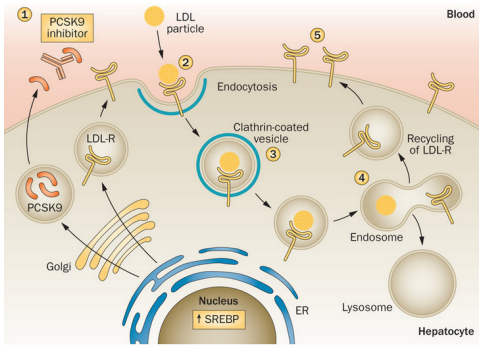
Advances and New Treatment Options



PCSK9 Monoclonal Antibodies[11,12]

	Alirocumab (Praluent™)	Evolocumab (Repatha™)
Approval Date	July 2015	August 2015
Approved Indications	• Clinical atherosclerotic disease • HeFM	• Clinical atherosclerotic disease • HeFM • HoFM
Dosing	75 mg – 150 mg SQ every 2 weeks	140 mg SQ every 2 weeks or 420 mg SQ every 4 weeks (HoFM)
Pharmacokinetics	Tmax: 3 to 7 days Bioavailability: 85% Elimination: binding to target, proteolytic pathway T1/2: 17-20 days	Tmax: 3 to 4 days Bioavailability: 72% Elimination: binding to target, proteolytic pathway T1/2: 11 to 17 days

PCSK9 Regulation[10]



http://www.nature.com/nrcardio/journal/v12/n10/full/nrcardio.2015.92.html?message-global=remove

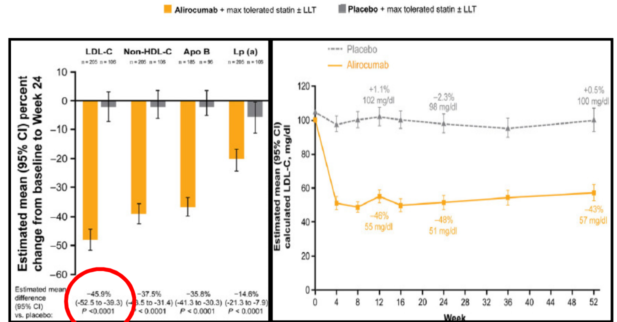
PCSK9 Monoclonal Antibodies[11,12]

	Alirocumab (Praluent™)	Evolocumab (Repatha™)
Warnings/ Precautions	Hypersensitivity reactions	Hypersensitivity reactions
Adverse Events	• Injection site reaction (7.2%) • Nasopharyngitis (11.3%) • Influenza (5.7%) • Allergic reaction (8.6%)	• Injection site reaction (5.7%) • Influenza (7.5-9.1%) • Nasopharyngitis (6.1- 10.5%) • Upper respiratory infection (9.1%) • Rash (1%), urticaria (0.4%)
How Supplied	75 mg/ml and 150 mg/ml single dose prefilled pen/syringe	140 mg/ml single dose prefilled pen/syringe
Phase III trial programs	ODYSSEY (14 trials)	PROFICIO (22 trials)

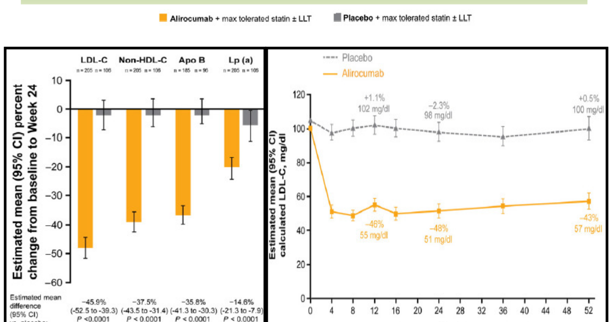
ODYSSEY COMBO I [13]

- Population:
  - Documented CVD and LDL-C ≥ 70 mg/dL **OR** high risk for CVD and LDL-C ≥ 100 mg/dL
  - All patients uncontrolled on standard therapy
- Primary Endpoint:
  - Reduction of LDL-C at the end of 24 weeks
- Treatment Arms: (+ max tolerated statin)
  - Alirocumab 75 mg SQ every 2 weeks (n= 205)
    - May be increased to 150 mg SQ every 2 weeks if LDL at week 8 was > 70 mg/dL
  - Placebo SQ every 2 weeks (n= 207)

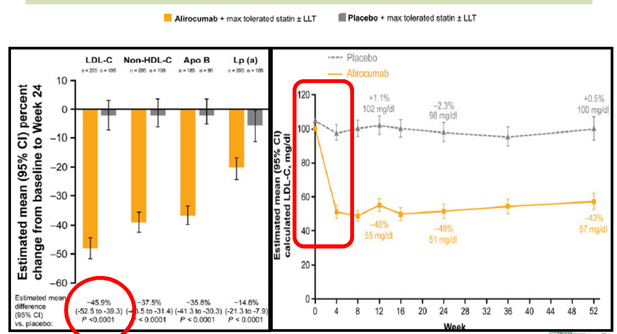
ODYSSEY COMBO I: Results [13]



ODYSSEY COMBO I: Results [13]



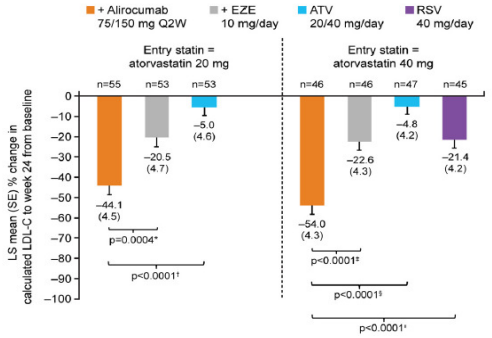
ODYSSEY COMBO I: Results [13]



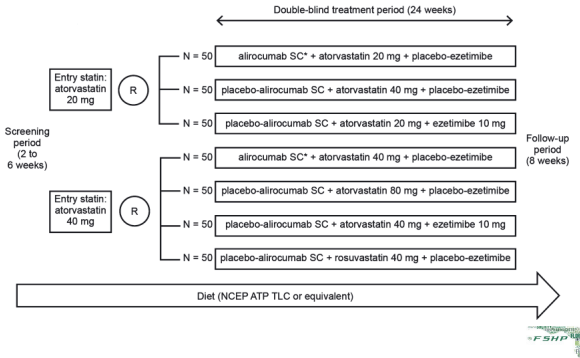
ODYSSEY OPTIONS I [14]

- Population:
  - Documented CVD and LDL-C ≥ 70 mg/dL **OR** high risk for CVD and LDL-C ≥ 100 mg/dL
  - All patients uncontrolled on standard therapy
- Primary Endpoint:
  - LDL-C reduction from baseline to 24 weeks

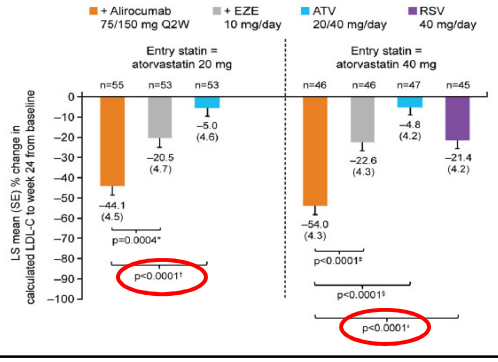
ODYSSEY OPTIONS I: Results[14]



ODYSSEY OPTIONS I: Treatment Arms[14]



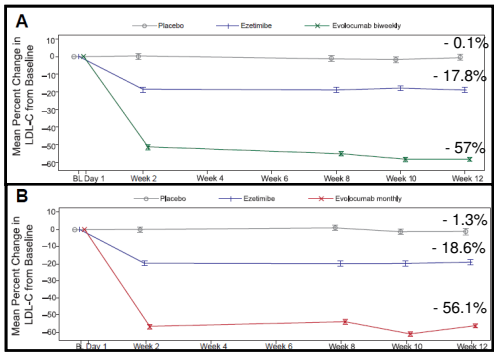
ODYSSEY OPTIONS I: Results[14]



ODYSSEY ALTERNATIVE[15]

- Population:
  - Moderate (LDL-C > 70 mg/dL) to high (LDL-C > 100 mg/dL) CV risk
  - Previous intolerance to ≥ 2 statins
- Primary Endpoint:
  - LDL-C reduction from baseline to 24 weeks for alirocumab vs ezetimibe
- Treatment Arms:
  - Alirocumab 75 mg SC every 2 weeks (n= 126)
  - Ezetimibe 10 mg PO daily (n= 122)
  - Atorvastatin 20 mg PO daily (n= 62)
- Results:
  - LDL-C reduction of 45.0% for alirocumab and 14.6% for ezetimibe, with a difference between groups of 30.4% (P < .0001)
  - Incidence of skeletal muscle adverse event: 32.5% (ALI), 41.1% (EZE), 46% (ATR)

Mendel-2: Results[16]



p < 0.001

p < 0.001

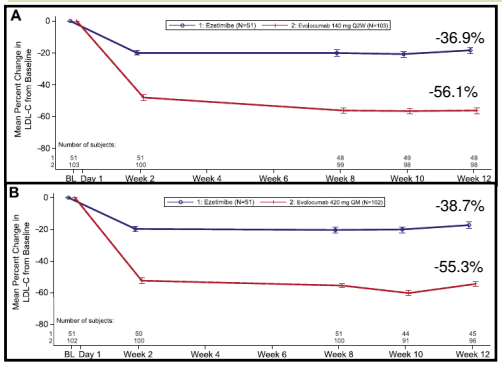
Mendel-2 [16]

- Largest monotherapy trial with PCSK9 inhibitors
- Population:
  - Adults with fasting LDL-C ≥ 100 and <190 mg/dl and Framingham risk scores ≤ 10%
- Primary Endpoint:
  - LDL-C reduction from baseline to 12 weeks
- Treatment Arms:
  - Placebo (n = 151)
  - Ezetimibe 10 mg PO daily (n = 149)
  - Evolocumab 140 mg SQ every 2 weeks (n = 153)
  - Evolocumab 420 mg SQ every 4 weeks (n = 153)

GAUSS-2 [17]

- Population:
  - Adults (18 to 80 yo) with uncontrolled LDL-C on no or low-dose statins
  - Previous intolerance to ≥ 2 statins
- Primary Endpoint:
  - LDL-C reduction from baseline mean of weeks 10 and 12
- Treatment Arms:
  - Evolocumab 140 mg SQ every 2 weeks (n = 103)
  - Evolocumab 420 mg SQ every 4 weeks (n = 102)
  - Ezetimibe 10 mg PO daily (n = 102)

GAUSS-2: Results[17]



p <0.001

p <0.001

Considerations for Use[10-12]

- Injections and acceptability by patients
- Immunogenicity
  - Anti-drug antibodies
  - Neutralizing antibodies
- Cost impact
  - Alirocumab → 75 mg/mL or 150 mg/mL : $672.00 per dose
  - Evolocumab →140 mg/mL : $650.77 per dose
- Hypolipidemia

> $16,000 per year

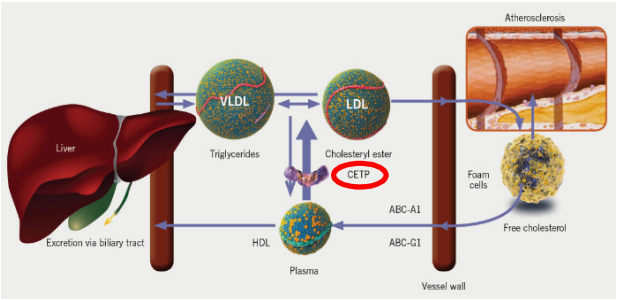
Place in therapy[10-17]

- Indicated as:
  - Adjunctive therapy with maximally tolerated statin
  - LDL as primary endpoint vs clinical outcomes/mortality benefit
  - Ongoing trials examining clinical endpoints should provide additional information on longer-term efficacy and side effects
- Possible future indications:
  - Monotherapy for patients

In the pipeline

- PCSK9 inhibitors
  - Bococizumab (RN316/PF-04950615; Pfizer)
    - Currently in Phase III trials
  - LGT209 (Novartis)
  - LY3015014 (Eli Lilly)
  - RG7652 (Roche/Genentech)
    - Discontinued in 2014 due to funding
- CETP inhibitors
  - Torcetrapib
    - Discontinued due to increased mortality
  - Evacetrapib
    - Abandoned due to lack of efficacy
  - Dalcetrapib, Anacetrapib
    - Phase III trials
  - TA-8995
    - Awaiting clinical trials

Cholesteryl Ester Transfer Protein (CETP)



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Overview of Agents and Developing a Treatment Plan

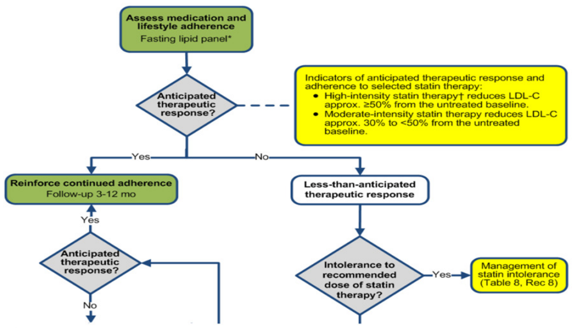
DEFINE[18]

- Population:
  - Adults with CHD or CHD Risk-Equivalent Disease and receiving a statin, with well controlled LDL-C
- Primary Endpoint:
  - LDL-C reduction from baseline at 76 weeks
- Treatment Arms: (+ standard therapy)
  - Anacetrapib 100 mg PO daily (n = 811)
  - Placebo (n = 812)
- Results:
  - Anacetrapib lowered LDL by 39.8% ($p < 0.001$) and increased HDL by 138.1% ($p < 0.001$)

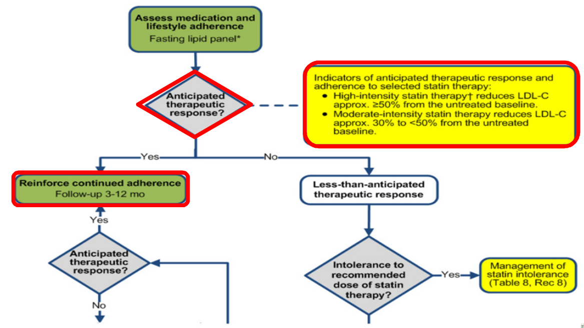
Treatment Summary[1-21]

Drug	LDL Reduction (%)	TC Reduction (%)	HDL Effects (%)
Statins	18- 55	14- 26	+ 2-15
CAI	18	8	+ 1
Fibrates	5- 20	20- 50	+ 10- 35
Bile Acid Sequestrants	15- 30	No effect	+ 3- 5
Nicotinic Acid	5- 25	20- 50	+ 15- 35
Omega-3 FAs	Increase/ No change	20- 50	Increase/ No change
PCSK9 Antibody	28- 65	Not reported	Not reported
CETP inhibitor	7- 45	Not reported	+ 30- 180

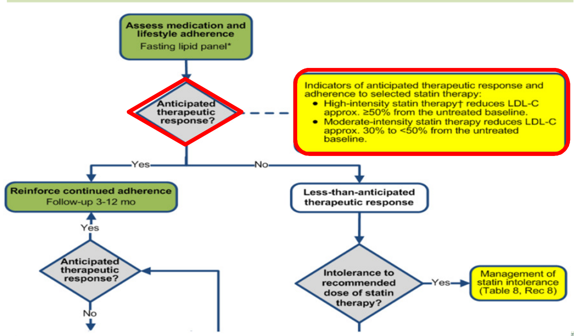
Treatment Algorithm[4]



Treatment Algorithm[4]



Treatment Algorithm[4]



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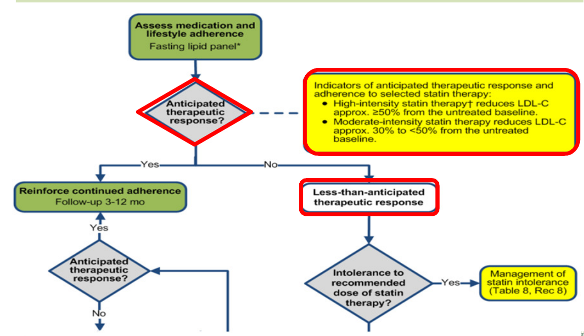

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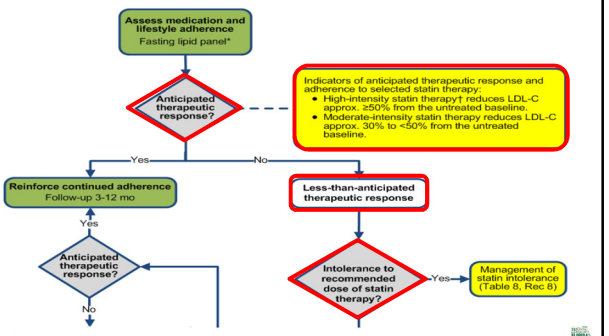

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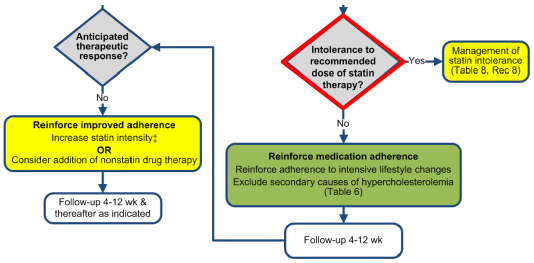

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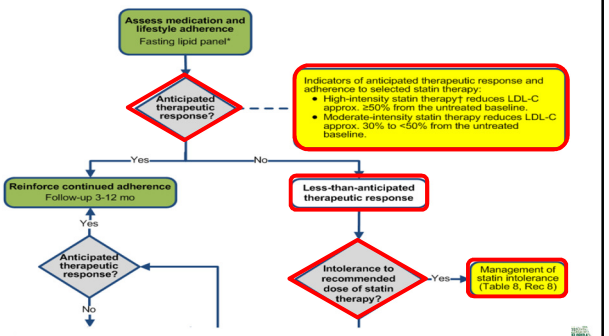

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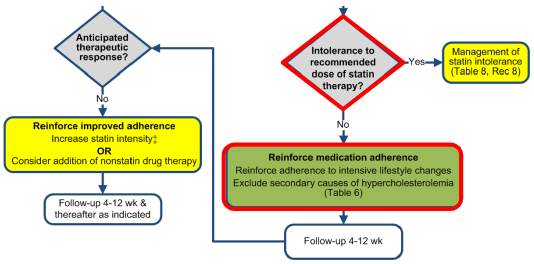

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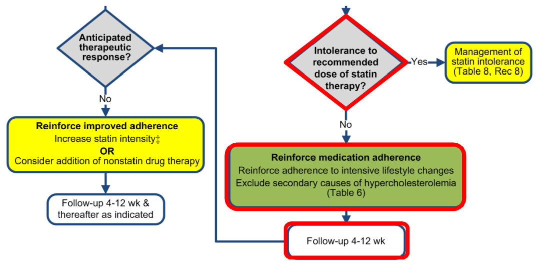

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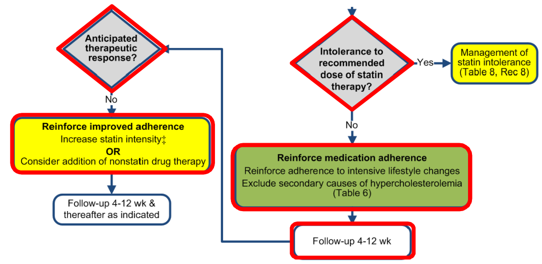

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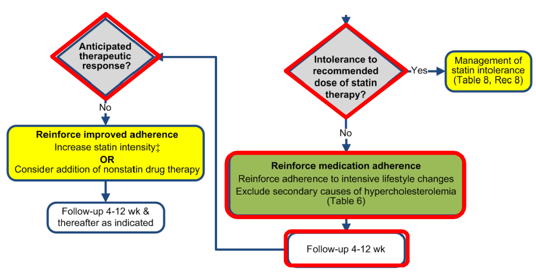

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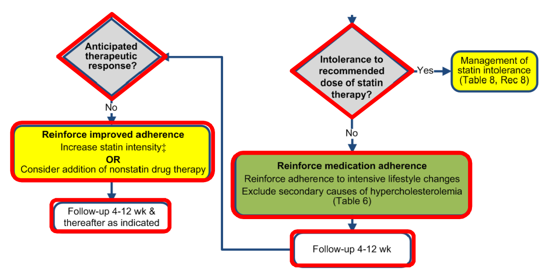

Summary

- Lifestyle modifications are the cornerstone of ATP IV
- Do not focus on LDL-C or non–HDL-C levels as treatment goals
- Statins are the recommended first line pharmacotherapy—reduce ASCVD risk
- Adjunctive therapies may be added in the case of statin intolerance or failure
- PCSK9 inhibitors are a promising new therapy
- CETP inhibitors shows potential as a new medication for dyslipidemias

Assessment Questions

- The newest cholesterol guidelines base cardiovascular risk solely on LDL.
  - True/**False**

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Advances in treatment of hypercholesterolemia

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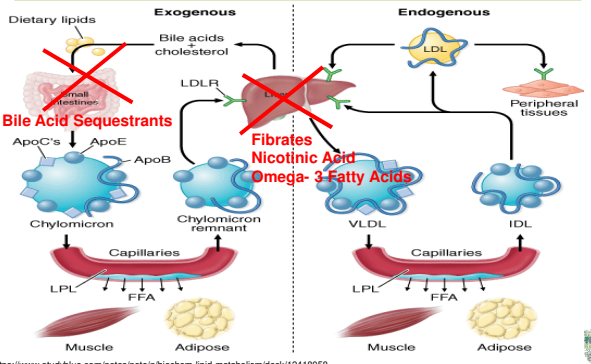
Medication Site of Action



https://www.studyblue.com/notes/note/n/biochem-lipid-metabolism/deck/12418058

Laplace-2 [20]

- Population:
  - Adults (18- 80 yo) with:
    - No previous statin with fasting LDL-C ≥ 150 mg/dL
    - Previous non-intensive statin with fasting LDL-C ≥ 100 mg/dL
    - Previous intensive statin with fasting LDL-C ≥ 80 mg/dL
- Primary Endpoint:
  - LDL-C reduction from baseline to 12 weeks and mean of weeks 10 and 12

Laplace-2: Results [20]

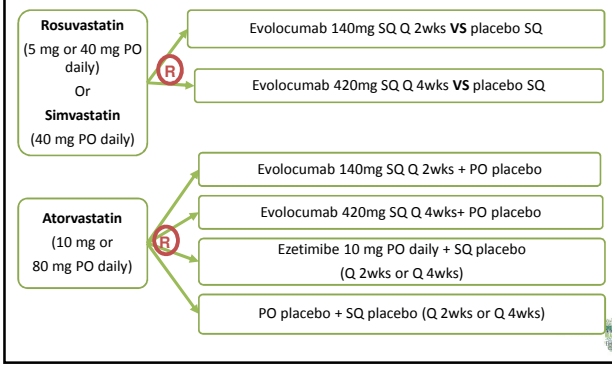
	Mean (95% CI)[a]											
	High-Intensity Statin						Moderate-Intensity Statin					
	Atorvastatin (80 mg)				Rosuvastatin (40 mg)		Atorvastatin (10 mg)				Simvastatin (40 mg)	Rosuvastatin (5 mg)
	vs Placebo		vs Ezetimibe		vs Placebo		vs Placebo		vs Ezetimibe		vs Placebo	vs Placebo
LDL-C	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Every 2 wk	Monthly	Every 2 wk	Monthly
% change at wk 12	−76.3 (−86.9 to −65.7)	−70.5 (−79.8 to −61.2)	−47.2 (−57.5 to −36.9)	−38.9 (−48.2 to −29.6)	−68.3 (−77.0 to −59.6)	−55.0 (−65.3 to −44.7)	−71.4 (−77.6 to −65.3)	−59.2 (−65.9 to −52.4)	−39.6 (−45.8 to −33.4)	−41.1 (−47.8 to −34.4)	−70.6 (−76.7 to −64.4)	−60.4 (−69.1 to −51.7)	−68.2 (−74.7 to −61.7)	−64.5 (−70.8 to −58.1)
% change at mean of wk 10 and 12	−74.9 (−84.5 to −65.4)	−74.8 (−83.0 to −66.6)	−44.9 (−54.3 to −35.6)	−43.8 (−52.1 to −35.6)	−65.7 (−73.2 to −58.1)	−62.9 (−71.4 to −54.5)	−70.0 (−75.4 to −64.5)	−62.8 (−69.1 to −56.6)	−37.5 (−43.0 to −32.0)	−43.5 (−49.7 to −37.3)	−69.4 (−74.9 to −64.0)	−68.5 (−76.7 to −60.2)	−66.9 (−72.7 to −61.1)	−66.6 (−72.6 to −60.6)
Change at wk 12, mg/dL	−71.7 (−84.4 to −59.0)	−61.8 (−71.6 to −52.0)	−49.0 (−61.5 to −36.6)	−35.3 (−45.2 to −25.5)	−57.2 (−65.1 to −49.4)	−44.6 (−55.9 to −33.4)	−85.5 (−95.2 to −75.9)	−75.8 (−86.8 to −64.9)	−46.8 (−56.6 to −37.1)	−51.7 (−62.6 to −40.9)	−79.0 (−87.5 to −70.4)	−71.9 (−83.8 to −60.0)	−77.1 (−86.2 to −67.9)	−75.8 (−86.3 to −65.3)
Change at mean of wk 10 and 12, mg/dL	−69.9 (−81.9 to −57.8)	−65.6 (−74.5 to −56.7)	−45.8 (−57.7 to −33.9)	−38.8 (−47.8 to −29.9)	−55.8 (−63.1 to −48.4)	−50.6 (−60.6 to −40.6)	−83.6 (−92.6 to −74.6)	−79.7 (−90.2 to −69.2)	−44.4 (−53.4 to −35.3)	−55.0 (−65.4 to −44.6)	−78.1 (−86.2 to −70.0)	−80.1 (−91.7 to −68.6)	−75.4 (−83.9 to −67.0)	−77.9 (−88.0 to −67.8)

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert LDL-C values to mmol/L, multiply by 0.0259.

[a] Adjusted $P < .05$ for all treatment differences.

Laplace-2: Treatment Arms [20]



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	vs Placebo		vs Ezetimibe		vs Placebo		vs Placebo		vs Ezetimibe		vs Placebo	vs Placebo
LDL-C	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Monthly	Every 2 wk	Every 2 wk	Monthly	Every 2 wk	Monthly
% change at wk 12	−76.3 (−86.9 to −65.7)	−70.5 (−79.8 to −61.2)	−47.2 (−57.5 to −36.9)	−38.9 (−48.2 to −29.6)	−68.3 (−77.0 to −59.6)	−55.0 (−65.3 to −44.7)	−71.4 (−77.6 to −65.3)	−59.2 (−65.9 to −52.4)	−39.6 (−45.8 to −33.4)	−41.1 (−47.8 to −34.4)	−70.6 (−76.7 to −64.4)	−60.4 (−69.1 to −51.7)	−68.2 (−74.7 to −61.7)	−64.5 (−70.8 to −58.1)
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[a] Adjusted $P < .05$ for all treatment differences.

ODYSSEY COMBO II [21]

- Population:
  - Documented CVD and LDL-C ≥ 70 mg/dL **OR** high risk for CVD and LDL-C ≥ 100 mg/dL
  - All patients uncontrolled on standard therapy
- Primary Endpoint:
  - Reduction of LDL-C at the end of 24 weeks
- Treatment Arms: (+ standard care)
  - Alirocumab 75 mg SQ every 2 weeks (n = 467)
    - May be increased to 150 mg SQ every 2 weeks if LDL at week 8 was > 70 mg/dL
  - Ezetimibe 10 mg PO daily (n = 240)

ODYSSEY COMBO II: Results[21]

All patients on maximally tolerated statin therapy[a]	Alirocumab[b]	Ezetimibe[c]	Alirocumab vs. ezetimibe		
			LS mean difference ± SE (%)	95% CI	P-value
Primary endpoint: LDL-C					
ITT	n = 467	n = 240			
LS mean ± SE change from baseline (%)	−50.6 ± 1.4	−20.7 ± 1.9	−29.8 ± 2.3	−34.4 to −25.3	<0.0001
On-treatment	n = 464	n = 235			
Baseline LDL-C, mean ± SD (mmol/L)	2.8 ± 0.9	2.7 ± 0.9	–	–	–
Range	0.6–7.9	1.0–6.3			
LS mean ± SE change from baseline (%)	−52.4 ± 1.3	−21.8 ± 1.8	−30.6 ± 2.2	−34.9 to −26.2	<0.0001

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least squares; Q2W, every 2 weeks; SC, subcutaneous; SE, standard error.
[a]One patient was not on maximally tolerated statin therapy.
[b]Alirocumab 75 mg SC Q2W with a dose increase to 150 mg Q2W at Week 12 if Week 8 LDL-C was ≥1.8 mmol/L (≥70 mg/dL).
[c]10 mg/day oral ezetimibe.

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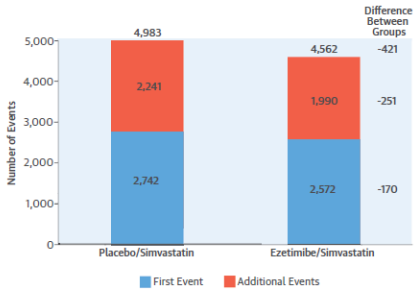
IMPROVE-IT: Results



Dalcetrapib Clinical Data[23]

Trial Title	dal- OUTCOMES
Population	Clinically stable adult patients, ≥45 years of age Recently hospitalized for ACS Receiving evidence-based medical and dietary management of dyslipidemia
Endpoint	Time to first occurrence of any component of the composite cardiovascular event (cardiovascular mortality and morbidity)
Methods	Randomized, double-blind, parallel assignment, phase III treatment study Patients received either Dalcetrapib 600mg QD or placebo
Results	N= 15,871 HDL increased by 31-40% (Dalcetrapib) vs 4-11% (placebo) Did not reduce the risk of recurrent cardiovascular events

Evacetrapib Clinical Data

Trial Title	ACCELERATE (Assessment of the Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at High-Risk for Vascular Outcomes)
Population	Diagnosis of high risk vascular disease Must be treated with a statin for at least 30 days prior to screening HDL-C ≤80 mg/dL, TG ≤400 mg/dL LDL-C no more than 10 mg/dL above the target chosen by the investigator (100 mg/dL or 70 mg/dL) OR (if LDL-C is greater than target) must be on maximally tolerated statin
Endpoint	Time to first occurence of the composite endpoint of CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina
Methods	Randomized, double-blind, parallel allocation, safety/efficacy phase III trial Patients receive either Evacetrapib 130mg PO daily or placebo for up to 4 yrs
Results	Discontinuation of drug development due to lack of evidence