

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS | AMERICAN COLLEGE OF ENDOCRINOLOGY

Novel New Therapeutics for Atherosclerotic Cardiovascular Disease

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Introduction

- What have recent studies shown regarding residual CV risk in patients on statins?
- What new agents are available to address residual risk?
- What are the mechanisms of action of these therapeutics, and what patient populations do they benefit?
- What are current AACE recommendations for the use of novel new therapeutic agents for ASCVD?

AACE=American Association of Clinical Endocrinologists; ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular.

Novel New Therapeutics for ASCVD

- Proprotein convertase subtilisin / kexin type 9 (PCSK9) inhibitors
- Microsomal triglyceride transfer protein (MTP) inhibitor
- Antisense apolipoprotein B oligonucleotide inhibitor
- Cholesteryl ester transfer protein (CETP) inhibitor
- Omega-3 fatty acids

ASCVD=atherosclerotic cardiovascular disease.



Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Introduction to PCSK9 Inhibitors

- What are PCSK9 inhibitors and how do they work?
- Which patients are candidates for PCSK9 inhibitor therapy?
- What major clinical trials have shaped what we know about PCSK9 inhibitor therapy?
- Do PCSK9 inhibitors reduce ASCVD events?
- What are current AACE recommendations related to PCSK9 inhibitor use?

AACE=American Association of Clinical Endocrinologists; ASCVD=atherosclerotic cardiovascular disease; PCSK9=pro-protein converase subtilisin/kexin 9.

PCSK9 Inhibitors: FDA-Approved Agents

- Two PCSK9 inhibitors are currently on the market: evolocumab and alirocumab
- Current FDA indications for these agents are:
 - Evolocumab
 - To reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD
 - As an adjunct to diet, alone or in combination with other lipid-lowering therapies (eg, statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C
 - As an adjunct to diet and other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional LDL-C lowering
 - Alirocumab:
 - As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD who require additional LDL-C lowering

ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; FDA=US Food and Drug Administration; HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; MI=myocardial infarction; LDL-C=low-density lipoprotein cholesterol; PCSK9=pro-protein converase subtilisin/kexin 9.

1. Praluent (alirocumab) [PI] 2018. 2. Repatha (evolocumab) [PI]; 2017.

PCSK9 Inhibitors: Patient Populations

Patients with an unmet need for additional LDL-C lowering

FH Population	High/Very High CV Risk Population	Statin-Intolerant Population
<ul style="list-style-type: none">• Genetic disorder• High risk of early CHD• HeFH prevalence 1:200 to 1:250• Untreated LDL-C of 200-400 mg/dL	<ul style="list-style-type: none">• Previous MI/stroke/CVD or multiple CV risk factors including T2D• Difficult to achieve LDL-C goals, despite current therapies	<ul style="list-style-type: none">• 10%-15% on high-intensity statins show intolerance• Many discontinue due to muscle pain and/or weakness
79% with HeFH not at goal (<100 mg/dL)	<ul style="list-style-type: none">• 20% with CHD not at goal (<100 mg/dL)• 59% at very high CV risk not at goal (<70 mg/dL)	Nearly all patients who need considerable LDL-C reductions will not reach goal without further treatment

CHD=coronary heart disease; CV=cardiovascular; FH=familial hypercholesterolemia; HeFH=heterozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; PCSK9=pro-protein converase subtilisin/kexin 9; T2D=type 2 diabetes.

1. Nordestgaard BG, et al. *Eur Heart J.* 2013;34:3478–2490. 2. Sjouke B, et al. *Eur Heart J.* (in press). 3. ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J.* 2011;32(14):1769–1781. 4. Pijlman AH, et al. *Atherosclerosis* 2010;209:189–194. 5. Virani SS, et al. *Am Heart J.* 2011;161:1140–1146. 6. Arca M, et al. *Diabetes Metab Syndr Obes.* 2011;4:155–166.

Familial Hypercholesterolemia

- FH is an autosomal dominant genetic condition resulting from mutations of the LDL-C receptor, apo B, or PCSK9¹
- Depending on the genetic mutation, patients can be identified as having heterozygous or homozygous FH¹
- HeFH is more common, occurring in approximately 1 in 250-500 individuals worldwide;² typical lipid abnormalities are as follows:¹
 - TC 350–550 mg/dL
 - LDL-C 200–400 mg/dL
- HoFH is seemingly rare, occurring in approximately 1 in every 1 million individuals; typical lipid abnormalities are as follows:¹
 - TC 650–1000 mg/dL
 - LDL-C >600 mg/dL

Apo B=apolipoprotein B; FH=familial hypercholesterolemia; HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; PCSK9=pro-protein converase subtilisin/kexin 9; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol.

1. Wong E, et al. *P&T*. 2014;39(2):199–122.

2. Bouharie VE, et al. *Cardiol Clin*. 2015;33(2):169–179.

PCSK9 Inhibitors: Dosing, Metabolic Effects, and Other Considerations

Lipid-Lowering Drug Therapies, Starting Doses, and Dosage Ranges

Agent	Usual recommended starting daily dose	Dosage range	Method of administration
PCSK9 inhibitors			
Alirocumab	75 mg every 2 weeks or 300 mg every 4 weeks	75–150 mg every 2 weeks or 300 mg every 4 weeks	SQ
Evolocumab	140 mg every 2 weeks or 420 mg once monthly	Same as starting dose	SQ

Metabolic Effects:

- ↓LDL-C 48%–71%, ↓ non-HDL-C 49%–58%, ↓TC 36%–42%, ↓Apo B 42%–55% by inhibiting PCSK9 binding with LDL-Rs, increasing the number of LDL-Rs available to clear LDL, and lower LDL-C levels

Main Considerations:

- Require subcutaneous self-injection; refrigeration generally needed
- Overall levels of adverse reactions and discontinuation very low

- Adverse reactions with significantly different rates between drug and placebo were: local injection site reactions and influenza
- The most common adverse reactions had similar rates for drug vs placebo and were not likely caused by the PCSK9 inhibitor. These were:
 - Alirocumab: nasopharyngitis, influenza, urinary tract infections, diarrhea, bronchitis, and myalgia
 - Evolocumab: nasopharyngitis, back pain, and upper respiratory tract infection

Apo B=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; LDL-R=low-density lipoprotein receptor; PCSK9=proprotein convertase subtilisin/kexin type 9; SQ=subcutaneous injection; TC=total cholesterol.

1. Jellinger P, et al. *Endocr Pract.* 2017;23(4):479–497. 2. Praluent (alirocumab) [PI] 2018. 3. Repatha (evolocumab) [PI]; 2017.

Clinical Trials of PCSK9 Inhibitors: FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)

Target Population:

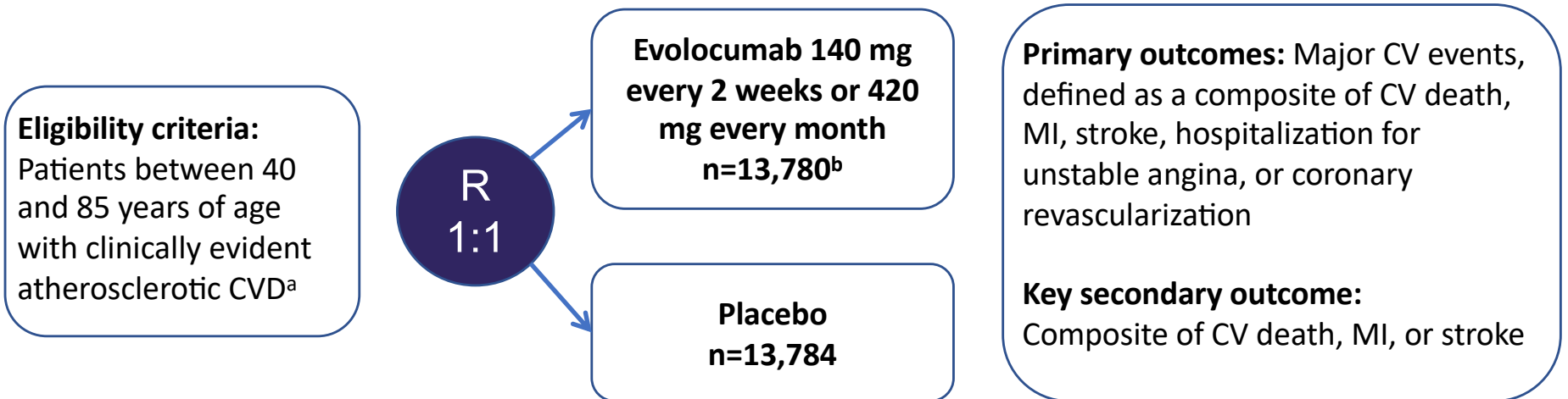
1. History of clinically evident CVD as evidenced by any of the following:
 - Prior MI
 - Prior non-hemorrhagic stroke (TIA does not qualify as stroke)
 - Symptomatic PAD, as evidenced by intermittent claudication with ABI <0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease
2. ≥ 1 major risk factor or ≥ 2 minor risk factors

ABI=ankle-brachial index; CVD=cardiovascular disease; MI=myocardial infarction; PAD=peripheral arterial disease; PCSK9=proprotein convertase subtilisin/kexin type 9; TIA=transient ischemic attack.

Sabatine MS, et al. *NEJM*. 2017;376:1713–1722,FOURIER Supplementary appendix

PCSK9 Inhibitors: FOURIER

FOURIER Evolocumab Study Design and Objectives



- **Study design:** Randomized, double-blind, placebo-controlled, multinational clinical trial conducted at 1242 sites in 49 countries
- **Primary objective:** To test the clinical efficacy and safety of evolocumab when added to high-intensity or moderate-intensity statin therapy in patients with clinically evident atherosclerotic CVD

^a Defined as a history of myocardial infarction, nonhemorrhagic stroke, or symptomatic peripheral artery disease, as well as additional characteristics that placed them at higher cardiovascular risk.

^b Patients were randomly assigned in a 1:1 ratio to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month, according to patient preference).

CV=cardiovascular; CVD=cardiovascular disease; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; MI=myocardial infarction; PCSK9=proprotein convertase subtilisin/kexin type 9.

Sabatine MS, et al. *Am Heart J.* 2016;173:94–101.

PCSK9-Inhibitor Cardiovascular Outcomes Trials

	Alirocumab	Evolocumab	Bococizumab	
Trial	ODYSSEY Outcomes	FOURIER	SPIRE-1	SPIRE-2
Sample size	~19,000	~27,500	~16,800	~10,600
Patients	History of ACS (1-12 months)	History of MI, stroke, or PAD	At high risk for CV event	
Statin	Evidence-based treatment	Atorvastatin \geq 20 mg/day or equivalent	Evidence-based treatment	
LDL-C	\geq 70 mg/dL	\geq 70 mg/dL	\geq 70 mg/dL	\geq 100 mg/dL
PCSK9 inhibitor dosing	Every 2 weeks	140 mg/2 weeks or 420 mg/4 weeks	Every 2 weeks	
Endpoint	CHD death, MI, ischemic stroke, or unstable angina hospitalization	Primary outcome: Composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. Key secondary outcome: Composite of CV death, MI, or stroke.	Primary outcome: Composite of CV death, MI, nonfatal stroke, or hospitalization for urgent revascularization	
Publication	<i>Pending</i>	May 2017	April 2017	

***SPIRE-1 and SPIRE-2 were stopped prematurely in November 2016 after the lipid-lowering trial failed to show benefit, leading the sponsor to discontinue the drug's development.**

ACS=acute coronary syndrome; CV=cardiovascular; CHD=congenital heart disease; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C= low-density lipoprotein cholesterol; MI=myocardial infarction; PAD=peripheral artery disease; PCSK9=proprotein convertase subtilisin/kexin type 9; SPIRE=Studies of PCSK9 Inhibition and the Reduction of Vascular Events.

1. Schwartz GG, et al. American College of Cardiology – 67th Scientific Sessions. March 10, 2018. 2. Sabatine MS, et al. *NEJM*. 2017;376(18):1713–1722. 3. Ridker PM, et al. *N Engl J Med*. 2017;376:1527–1539.

PCSK9 Inhibitors: ODYSSEY (Alirocumab) Outcomes Trial

- ODYSSEY data were presented at the American College of Cardiology Annual Scientific Session in Orlando, Florida, March 10, 2018, and are not yet published
- ODYSSEY Outcomes trial was an international, multicenter, randomized, double-blind, placebo-controlled study investigating the use of alirocumab vs placebo in patients receiving statins and with inadequate lipid control
 - Inadequate lipid control, defined as LDL-C \geq 70 mg/dL, non-HDL-C \geq 100 mg/dL, or apo B \geq 80 mg/dL
- The trial randomized 18,924 patients to receive either alirocumab or placebo
- All patients had a recent ACS event within 1 year of randomization
- Median follow-up, 34 months
- Primary endpoint: Time to first occurrence of CHD, MI, stroke or unstable angina requiring hospitalization
- **Overall 15% reduction in MACE and all-cause death**
 - In subgroup with LDL $>$ 100 mg/dL, MACE was reduced by 24% and all-cause death by 29%

ACS=acute coronary syndrome; apo B=apolipoprotein B; CHD=congenital heart disease; HDL-C=high-density lipoprotein cholesterol; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; MACE=major adverse cardiac events; MI=myocardial infarction; PCSK9=proprotein convertase subtilisin/kexin type 9.

Schwartz GG, et al. American College of Cardiology – 67th Scientific Sessions. March 10, 2018; Schwartz GG, et al. Am Heart J. 2014;168(5):682-689.

PCSK9 Inhibitors: AACE Recommendations

- The use of PCSK9 inhibitors in combination with statins is recommended to lower LDL-C in individuals with FH.
- Clinical trial data indicate that the use of PCSK9 inhibitors can significantly lower LDL-C vs placebo (up to 61% in individuals with HeFH and 39% in individuals with HoFH).
- PCSK9 inhibitors should be considered in individuals with clinical CVD who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy.
- PCSK9 inhibitors should not be used as monotherapy except in statin-intolerant individuals.
- The additional ASCVD benefit when LDL-C is lowered to <55 mg/dL in very high-risk individuals (using statin therapy in combination with ezetimibe or a PCSK9 inhibitor) forms the basis of the AACE recommendation for a new risk category, extreme risk.

AACE=American Association of Clinical Endocrinologists; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; FH=familial hypercholesterolemia; HDL-C=high-density lipoprotein cholesterol; HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9.

Jellinger P, et al. *Endocr Practice*. 2017;23(4):479–497.

PCSK9-Inhibitors: Summary

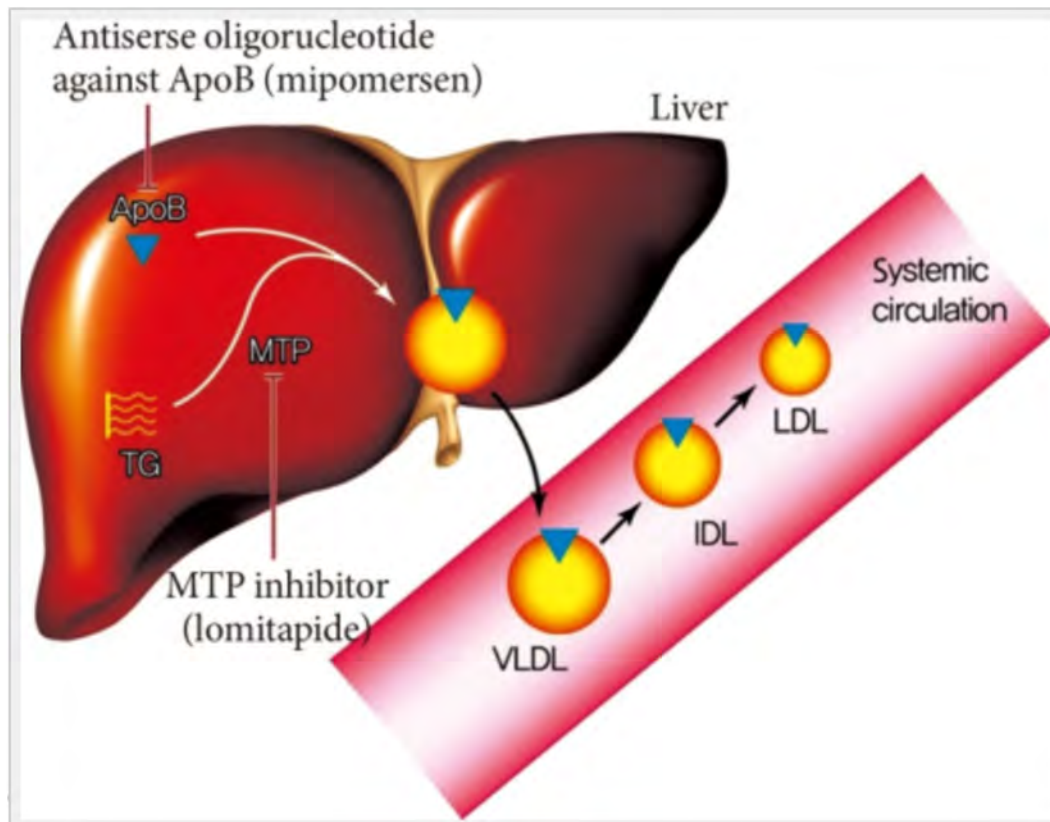
- PCSK9 is a pro-protein produced in hepatocytes; it binds to LDL-R and is internalized within the endosome.
- PCSK9 inhibitors lower LDL-C levels by preventing LDL-R degradation and effectively increasing LDL receptors on the cell surface.
- Target populations that may benefit from PCSK9 inhibitors include patients with FH, patients with clinical CVD unable to reach LDL-C/non-HDL-C goals, and patients with statin intolerance.
- CVOTs have demonstrated that PCSK9 inhibitors significantly reduce major adverse CV events.
- AACE recommends the use of PCSK9 inhibitors as combination therapy with statins in identified target populations.

AACE=American Association of Clinical Endocrinologists; CV=cardiovascular; CVD=cardiovascular disease; CVOT=cardiovascular outcome trial; FH=familial hypercholesterolemia; HDL-C=high-density lipoprotein cholesterol; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; LDL-R=low-density lipoprotein receptor; PCSK9=proprotein convertase subtilisin/kexin type 9.



Microsomal Triglyceride Transfer Protein Inhibitor

Lomitapide: MTP Inhibitor



Apo B=apolipoprotein B; IDL=intermediate-density lipoprotein; LDL=low-density lipoprotein; MTP=microsomal triglyceride transfer protein; TG=triglycerides; VLDL=very low-density lipoprotein.

1. https://openi.nlm.nih.gov/detailedresult.php?img=PMC4411552_dmj-39-87-g003&req=4. 2. Ahn CH, et al. *Diabetes Metab J*. 2015;39(2):87–94.

MTP is predominantly expressed in hepatocytes and enterocytes (required to synthesize apo B-containing lipoproteins). MTP transfers TG, phospholipids, and cholesteryl esters to apo B and has a critical role in VLDL and chylomicron synthesis in the liver and intestine. MTP inhibition results in decreased hepatic VLDL synthesis and secretion and may help to reverse increased hepatic VLDL production and secretion due to insulin resistance.

MTP inhibition in enterocytes can reduce plasma TG levels by reducing dietary fat absorption through the chylomicrons.

An orally active small molecule inhibitor of MTP, lomitapide has been approved for the treatment of homozygous familial hypercholesterolemia.¹

Lomitapide Dosing and Metabolic Effects

Agent	Usual recommended starting daily dosage	Dosage range	Method of administration
Lomitapide	5 mg, with subsequent titration	5-60 mg	Oral

Metabolic Effects:

- ↓ Up to LDL-C 40%, TC 36%, apo B 39%, TG 45%, and non-HDL-C 40% (depending on dose) in individuals with HoFH by binding and inhibiting MTP, which inhibits synthesis of chylomicrons and VLDL

Main Considerations:

- Can cause increases in transaminases (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 transaminases, 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 hepatotoxicity; because of hepatotoxicity risk, only available through REMS program

ALT=aspartate amino transferase; apo B=apolipoprotein B; AST=amino alanine transferase; FDA=Food and Drug Administration; HDL-C=high-density lipoprotein cholesterol; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; MTP=microsomal transfer protein; REMS=risk evaluation and mitigation strategy; TC=total cholesterol; TG=triglycerides; VLDL=very low-density lipoprotein.

1. Jellinger P, et al. *Endocr Practice*. 2017;23(4):479–497.
2. Juxtapid (lomitapide) [PI]; 2012.



Antisense Apolipoprotein B Oligonucleotide Inhibitor

Mipomersen Dosing and Metabolic Effects

Agent	Usual recommended starting daily dosage	Dosage range	Method of administration
Antisense apolipoprotein B oligonucleotide			
Mipomersen (SQ injection)	200 mg once weekly	200 mg once weekly	SQ

Metabolic Effects

- ↓ LDL-C 21%, TC 19%, apo B 24%, and non-HDL-C 22% in individuals 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)
- and total bilirubin before initiation and of ALT and AST during treatment is recommended
- Causes increases in hepatic fat (steatosis) with or without concomitant elevated transaminases, which may be a risk for progressive liver diseases
- Caution should be exercised when used with other drugs with potential hepatotoxicity; because of hepatotoxicity risk, only available through REMS program

Main Considerations

- Can cause increases in transaminases (ALT, AST); monitoring of ALT, AST, alkaline phosphatase,

ALT=aspartate amino transferase; apo B=apolipoprotein B; AST=amino alanine transferase; HDL-C=high-density lipoprotein cholesterol; HoFH=homozygous familial hypercholesterolemia; IDL=intermediate-density lipoprotein; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; mRNA=messenger ribonucleic acid; REMS=risk evaluation and mitigation strategy; SQ=subcutaneous; TC=total cholesterol; VLDL=very low-density lipoprotein.

1. Jellinger P, et al. *Endocr Practice*. 2017;23(4):479–497. 2. Kynamro (mipomersen sodium) Injection [PI]; 2016.

Lomitapide and Mipomersen Summary

- These 2 first-in-class LDL-C-lowering drugs were approved in December 2012 (lomitapide) and January 2013 (mipomersen)
- Both drugs reduce LDL-C by reducing hepatic VLDL production, making them independent of the LDL-R and thus effective in HoFH
- Both were approved only for the most serious form of inherited hypercholesterolemia (HoFH), because they cause increased hepatic fat
- Although these drugs have not been compared head-to-head, in patients with HoFH, lomitapide ≥ 20 mg daily appears to have somewhat greater mean efficacy in LDL-C reduction vs mipomersen at a fixed weekly dose of 200 mg SC
- For patients with HoFH, lomitapide and mipomersen may reduce the risk of ASCVD and premature mortality

ASCVD=atherosclerotic cardiovascular disease; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LDL-R=low-density lipoprotein receptor; SC=subcutaneous; VLDL=very low-density lipoprotein.

Rader DJ, et al. *Circulation*. 2014;129:1022–1032.



Cholesteryl Ester Transfer Protein Inhibitor

CETP Inhibitor (Anacetrapib): Target Population

- Evidence from randomized trials of statin therapy shows that each LDL-C reduction of 38.7 mg/dL (1 mmol/L) reduces the risk of coronary events (including coronary death, MI, and revascularization procedures) and ischemic stroke by 22%
- Further LDL-C reductions produce additional CV risk reductions
- Nevertheless, risk remains high among people with ASCVD
- Although higher HDL-C levels are associated with a lower risk of vascular events, previous trials have not shown that raising HDL-C levels reduces risk

ASCVD=atherosclerotic cardiovascular disease; CETP=cholesteryl ester transfer protein; CV=cardiovascular; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction.

1. CTT Collaboration. *Lancet*. 2010;376:1670–1681. 2. HPS3/TIMI55–REVEAL Collaborative Group. *NEJM*. 2017;377(13):1217–1227.

CETP Inhibitors Research Summary

- **ILLUMINATE** terminated early because of excess risk of cardiac events and death with torcetrapib; this was attributed to off-target drug effects
- **Dal-OUTCOMES** and **ACCELERATE** both stopped after ~2 years of treatment due to an apparent lack of efficacy
- **REVEAL** showed no significant safety issues or adverse events with anacetrapib:
 - No significant effect on rates of CVD (3.4% with anacetrapib vs 3.7% with placebo, $P=0.17$), death from all non-CV causes (4.0% vs 3.9%, $P=0.77$), or death from all causes combined (7.4% vs 7.6%, $P=0.46$)
 - No significant effects on incidence of fatal or nonfatal cancer, either overall (6.4% vs 6.3%, $P=0.71$) or at any prespecified site
 - No significant excess in any major category of serious or non-serious adverse event

ACCELERATE=Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients with a High Risk for Vascular Outcomes; ACS=acute coronary syndromes; CETP=cholesteryl ester transfer protein; CV=cardiovascular; CVD=cardiovascular disease; ILLUMINATE=Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events Outcomes; LDL-C=low-density lipoprotein cholesterol; REVEAL=Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification.

HPS3/TIMI55–REVEAL Collaborative Group. *NEJM*. 2017;377(13):1217–1227.

CETP Inhibitors Summary

- CETP inhibitors represent a potentially useful addition to existing treatments for high-risk patients who are intolerant to or not adequately managed with statins
- CETP inhibitors seem to be more effective as monotherapy than combination therapy with statins
 - CETP inhibitor impact on reducing apo B levels and increasing cholesterol efflux capacity is substantially greater when used alone vs added to statins (~1.5- to 2-fold)
- CETP inhibitors should be further evaluated for use as monotherapy (eg, in statin-intolerant individuals)
- In earlier trials, the degree of LDL-C lowering by CETP inhibitors was overestimated, which likely reflected changes in apo B particle composition; non-HDL-C should be used to assess the effects of CETP inhibition
- Unlike previous trials of CETP inhibitors, REVEAL reduced coronary events with no significant adverse events or safety concerns

Apo B=apolipoprotein B; CETP=cholesteryl ester transfer protein; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; REVEAL=Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification.

Tall AR, et al. *Circ Res*. 2018;122:106–112.



Omega-3 Fatty Acids

Potential Benefits and Mechanism of Action of Omega-3 Fatty Acids

Anti-arrhythmic¹

- ↓ Sudden death (GISSI-P study)
- ↓ Atrial fibrillation
- Protection against ventricular arrhythmias
- Improved heart rate variability

Anti-atherogenic¹

- ↓ Non-HDL-C
- ↓ TG and ↓VLDL-C
- ↓ Chylomicrons
- ↓ VLDL and chylomicron remnants
- ↑ HDL-C levels
- ↑ LDL and HDL particle size
- Plaque stabilization

Antithrombotic¹

- ↓ Platelet aggregation
- ↑ Blood rheologic flow

Anti-inflammatory and endothelial protective effects¹

- ↓ Endothelial adhesion molecules
- ↓ Leukocyte adhesion receptor expression
- ↓ Proinflammatory eicosanoids
- ↓ Proinflammatory leukotrienes
- Vasodilation

↓Systolic and diastolic blood pressure¹

Omega-3 fatty acids are incorporated into the cellular membranes of all tissues. They cannot be endogenously synthesized; thus, the extent of incorporation is dependent on dietary intake. Omega-3-enriched membranes modulate cellular signaling events, membrane protein function, and pro-inflammatory genetic expression;^{2,3} their mechanism of action is not fully understood, but is distinct from other treatment options.³

EPA=eicosapentaenoic acid; GISSI-P=GISSI-Prevenzione trial; HDL=high-density lipoprotein; HDL-C=high-density lipoprotein cholesterol; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; TG=triglycerides; VLDL=very low-density lipoprotein; VLDL-C=very low-density lipoprotein cholesterol.

1. Bays HE. Chapter 21. *The John Hopkins Textbook of Dyslipidemia*, by Peter O Kwiterovich, 2010; 245–257. 2. Surette ME. *CMAJ*. 2008;178(2):177-180; 3. Endo J, Arita M. *J Cardiol*. 2016;67:22-27.

Omega-3 Fatty Acids: Current AACE Recommendations

Several studies suggest that TG reduction is associated with a significant decrease in nonfatal MI, with a trend toward reduced ASCVD events

- OTC omega-3 supplements are not FDA-regulated:
 - May not have the quantity of omega-3 listed on the label
 - May contain other ingredients or contaminants
 - May cause mild side effects such as fish burps and upset stomach
- Use prescription omega-3 oil 2 to 4 g daily 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

AACE=American Association of Clinical Endocrinologists; ASCVD=atherosclerotic cardiovascular disease; FDA=US Food and Drug Administration; MI=myocardial infarction; OTC=over-the-counter; TG=triglycerides.

Jellinger P, et al. *Endocr Practice*. 2017;23(4):479–497; WebMD. Omega-3 fish oil supplements and prescriptions. <https://www.webmd.com/diet/omega-3s-in-fish-oil-and-supplements-whats-your-best-strategy#1>.

Icosapent Ethyl: Omega-3 Fatty Acid

- Icosapent ethyl, also known as eicosapentaenoic acid (EPA), is a highly purified ethyl ester of EPA, reported to improve atherogenic dyslipidemia characterized by reductions in TG, TG-rich lipoproteins, and factors involved in their metabolism, without raising LDL-C¹
- Based on trials with TG-lowering as the primary endpoint, this prescription therapy is approved by the US FDA for use as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia (≥ 500 mg/dL)¹

Agent	Usual recommended starting daily dosage	Dose range	Method of administration
Icosapent ethyl (Vascepa)	4 g per day	4 g per day (2 doses)	Oral

EPA=eicosapentaenoic acid; FDA=Food and Drug Administration; LDL-C=low-density lipoprotein cholesterol; TG=triglycerides.

Bhatt DL, et al. *Clin Cardiol.* 2017;40:138–148.

Icosapent Ethyl: REDUCE-IT Trial Background

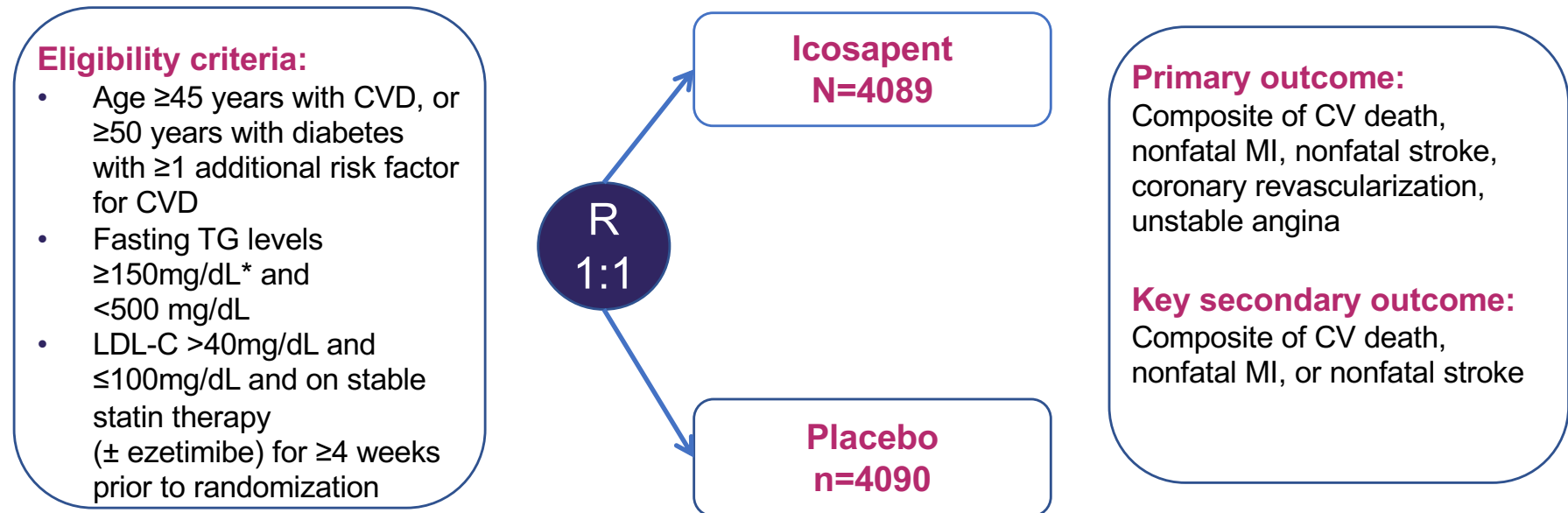
- Clinical and epidemiologic studies show that TG elevation is an independent risk factor for increased CV events and may represent a contributory factor for residual CV risk¹
- Prior CV outcome studies that administered therapies with TG-lowering effects (niacin or fenofibrate) plus statin therapy did not reach their primary endpoints¹
- REDUCE-IT is a Phase 3 international, multicenter, prospective, randomized, double-blind, placebo-controlled, parallel-group trial of stable statin therapy plus icosapent ethyl 4 grams/day (2 grams twice daily with food) vs stable statin therapy plus placebo²
- The main objective is to evaluate whether treatment with icosapent ethyl reduces ischemic events in patients at elevated CV risk and concurrently treated with statins²
- Icosapent ethyl is being studied in REDUCE-IT as an add-on to statin therapy to further reduce CV risk, not as a replacement for statin therapy²

CV=cardiovascular; REDUCE-IT=Reduction of Cardiovascular Events Outcomes trial; TG=triglycerides.

1. Bhatt DL, et al. *Clin Cardiol.* 2017;40:138–148. 2. Karatasakis A, et al. *J Am Heart Assoc.* 2017;6:e006910.

REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial)

REDUCE-IT Study Design and Objectives



- **Study design:** Phase 3B, multi-center, randomized, double-blind, placebo-controlled trial with long-term follow-up at 470 centers, worldwide
- **Primary objective:** To assess whether treatment with icosapent ethyl reduces ischemic events in statin-treated patients with high TG at elevated CV risk

*Due to the variability of TGs, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying TG ≥ 135 mg/dL. CV, cardiovascular; CVD, cardiovascular disease, LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglycerides. Bhatt DL, et al. *Clin Cardiol.* 2017;40(3)138-148. (Epub prior to print).

Icosapent Ethyl Summary

- Clinical and epidemiologic studies show that TG elevation is an independent risk factor for increased CV events and may represent a contributory factor for residual CV risk beyond statin therapy
- Icosapent ethyl, an omega-3 fatty acid, is recommended as adjuvant therapy to diet and statins in patients with severe hypertriglyceridemia
- Evidence indicates that daily consumption of 2 g to 4 g of fish oil can reduce TG by $\geq 25\%$ while producing only slight increases in LDL-C levels
- The REDUCE-IT trial evaluated high-dose EPA to determine whether treatment with icosapent ethyl reduced ischemic events in patients at elevated CV risk concurrently treated with statins
- Based on REDUCE-IT data, icosapent ethyl may substantially improve CV outcomes in patients with persistently high TG levels

CV=cardiovascular; EPA=eicosapentaenoic acid; LDL-C=low-density lipoprotein cholesterol; REDUCE-IT=Reduction of Cardiovascular Events Outcomes; TG=triglycerides.

Summary and Conclusions

- **PCSK9 inhibitors** reduce LDL-C by preventing LDL-R degradation and increasing LDL-R receptors on the cell surface. AACE recommends PCSK9 inhibitors as combination therapy with statins in identified target populations and as monotherapy in patients with statin intolerance.
- **Lomitapide and mipomersen** effectively lower LDL-C by reducing hepatic VLDL production, making them independent of LDL-R and effective in HoFH.
- **CETP inhibitors** reduce LDL-C levels by decreased transfer of HDL-C ester into triglyceride-rich lipoproteins converted into LDL, decreased transfer of HDL CE into LDL, and increased uptake of LDL-P by the hepatic LDL receptor. The CETP inhibitor anacetrapib has been shown to reduce coronary events.
- **Omega-3 fatty acids** have multiple potential molecular efficacy mechanisms. They are available as both prescribed and OTC treatment. AACE recommends prescription omega-3 oil 2 to 4 g daily to treat severe hypertriglyceridemia (TG >500 mg/dL). Icosapent ethyl, evaluated in the recent REDUCE-IT trial, was shown to significantly reduce the risk of a MACE endpoint.

AACE=American Association of Clinical Endocrinologists; CETP=cholesteryl ester transfer protein; CV=cardiovascular; HDL-C=high-density lipoprotein cholesterol; HDL CE=high-density lipoprotein cholesteryl ester; HoFH=homozygous familial hypercholesterolemia; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; LDL-P=low-density lipoprotein particles; LDL-R=low-density lipoprotein receptor; MACE=major adverse cardiovascular events; OTC=over-the-counter; PCSK9=pro-protein converase subtilisin/kexin 9; REDUCE-IT=Reduction of Cardiovascular Events Outcomes trial; VLDL=very low-density lipoprotein.