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SECONDARY PREVENTION AND INTERVENTION (D. STEINBERG, SECTION EDITOR)

Emerging Lipid-Lowering Therapies in Secondary Prevention

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Abstract

Purpose of Review The primary purpose of this article was to review the next-generation lipid-lowering therapies that are under current development and clinical testing. We reviewed the mechanism of action of these drugs and how they act on different pathways of lipid metabolism. Additionally, we aimed to present data from clinical trials evaluating clinical outcomes, efficacy, and safety of these novel agents. Lastly, we sought to provide recommendations for clinical practice and to comment on the cost-benefit analyses of such drugs.

Recent Findings We evaluated the following lipid-lowering agents as they pertain to secondary prevention of atherosclerotic cardiovascular disease (ASCVD): ezetimibe, proprotein convertase subtilisin/kexin (PCSK) type 9 inhibitors, cholesteryl ester transfer protein inhibitors, and eicosapentaenoic acid ethyl ester. The two novel therapies currently approved by the US Food and Drug Administration and endorsed by the latest ACC/AHA cholesterol guidelines include ezetimibe and PCSK9 inhibitors. Although other drug classes have shown promising preliminary results, clinical trials evaluating cardiovascular outcomes are ongoing.

Summary Patients with known ASCVD are at risk for recurrent ischemic events. Lipid-lowering therapies are an integral part of secondary prevention measures in such patients. There has been an upsurge in development of newer generation lipid-lowering therapies which have shown excellent results in preclinical studies. When added to statin therapy in high-risk patients or patients with suboptimal lipid profile despite statin therapy, these agents may significantly lower recurrent adverse cardiovascular events. Thorough cost-effectiveness simulations need to be performed prior to introduction of these agents in routine clinical practice.

Keywords PCSK9 inhibitors · Atherosclerotic cardiovascular disease · Low-density lipoprotein · Major adverse cardiac events · Ezetimibe · Secondary prevention

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Introduction

Patients with established cardiovascular disease remain at high risk for future cardiovascular events resulting in increased morbidity and mortality. Secondary prevention strategies to curtail recurrent cardiovascular events include lifestyle modifications, compliance with antiplatelet or antithrombotic agents, and lipid-lowering therapy. Statins have remained the cornerstone of lipid-lowering therapy for greater than 25 years [1] and have been an integral part of national cholesterol guidelines [2]. Despite positive clinical evidence surrounding statin therapy [3, 4], patient adherence remains suboptimal secondary to prescriber patterns and statin intolerance [5–7]. A subset of statin-treated patients fails to achieve adequate reduction in low-density lipoprotein cholesterol (LDL-C) or remains at increased residual risk for recurrent cardiovascular events. The need for alternate lipid-lowering agents or additional non-statin drugs for such high-risk patients has paved the way for the development of newer lipid-

lowering pharmaceutical agents over the last decade (Table 1). In the following manuscript, we will review the emerging lipid-lowering drugs and the clinical evidence behind their use in secondary prevention of cardiovascular events.

Ezetimibe

Mechanism of Action and Clinical Evidence

In search of newer lipid-lowering agents, Altmann and colleagues discovered the Niemann-Pick C1-like 1 (NPC1L1) protein in 2004. This is a human sterol transport protein that is expressed on enterocytes and on the hepatobiliary interface. NPC1L1 protein plays a crucial role in absorption of cholesterol by working in conjunction with the adaptor protein2 (AP2) to internalize cholesterol into the enterocyte [20]. Ezetimibe was developed to target NPC1L1 and hence reduce the absorption of cholesterol from the gastrointestinal tract [21, 22]. An earlier trial, ENHANCE, evaluating changes in the carotid-artery intima-media thickness (CIMT) with the use of ezetimibe failed to show significant differences in CIMT despite sizeable reductions in LDL-C and C-reactive protein (CRP) [23]. The debate generated after the results from ENHANCE was put to rest after Cannon and colleagues published positive clinical outcomes data from their randomized controlled trial, IMPROVE-IT [8]. This was a randomized, double-blind, placebo-controlled, secondary prevention trial in patients hospitalized for acute coronary syndrome (ACS). This trial randomized over 18,000 subjects to either a simvastatin monotherapy (40 mg/d) arm or a simvastatin (40 mg/d)-ezetimibe (10 mg/d) dual-therapy arm. The primary endpoint included a composite of cardiovascular death, nonfatal myocardial infarction, coronary revascularization, nonfatal stroke, or hospitalization for unstable angina within 30 days. At the 6-year follow-up, the patients in the dual-therapy arm had greater reduction in LDL-C (53.7 mg/dL vs. 69.5 mg/dL) compared with those in the monotherapy arm. Additionally, compared with patients treated with simvastatin alone, patients treated with both simvastatin and ezetimibe experienced a lower event rate for the primary endpoint (32.7% vs. 34.7%; ARR 2%; HR 0.94; 95% CI 0.89–0.99; $p = 0.016$). No major safety signals were seen. The results from this landmark trial resulted in widespread acceptance of ezetimibe as an additional lipid-lowering drug in patients with established atherosclerotic cardiovascular disease (ASCVD) who are not at their target LDL-C. The current and recently updated cholesterol guidelines give a class IIa LOE B recommendation to the use of ezetimibe in patients with clinical ASCVD who are on maximally tolerated statin therapy, judged to be at very high risk for recurrent cardiovascular events and have a LDL-C level ≥ 70 mg/dL [24••].

Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Mechanism of Action

The development of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has been a major advancement in the realm of lipid-lowering therapies. Low-density lipoprotein receptors (LDLRs) are present on the surface of hepatocytes to which PCSK9 binds. This binding results in lysosomal degradation of LDLRs which reduces LDL uptake from the periphery and thereby results in increased LDL concentrations in the plasma [25]. Given its pivotal role in LDL-C homeostasis, PCSK9 has become an appealing target for lipid-lowering pharmacotherapies. Alirocumab, evolocumab, and bococizumab are the three PCSK9 inhibitors or monoclonal antibodies that have been studied. These monoclonal antibodies bind to the PCSK9 protein molecule which in turn inhibits PCSK9 from binding to LDLRs and prevents degradation of LDLRs. This not only results in the preservation of LDLR but also increases LDLR density on the surface of hepatocytes, thereby promoting LDL uptake and recycling [26].

Current PCSK9 Inhibitors

Alirocumab and evolocumab are the two PCSK9 inhibitors that have received FDA approval for treatment of patients with clinical ASCVD in need for greater reductions in LDL-C or those with heterozygous familial hypercholesterolemia [27]. In addition, evolocumab is approved for treatment of patients with homozygous familial hypercholesterolemia. Both of these lipid-lowering human monoclonal antibodies are approved to be administered subcutaneously every 2 weeks or every month. The approved starting dose for alirocumab is 75 mg every 2 weeks, 150 mg every 2 weeks, or 300 mg every month, while evolocumab is approved for 140 mg every 2 weeks or 420 mg once monthly [28]. Bococizumab was investigated in the Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE) 1 and SPIRE 2 trials [29]; however, it was later discontinued by its manufacturer due to concerns over higher levels of immunogenicity and a higher rate of injection site reactions.

Impact on Clinical Cardiovascular Outcomes

Both evolocumab and alirocumab had shown positive results in their respective phase II trials [30, 31]. Based on these trials, although these monoclonal antibodies were successful in reducing LDL-C levels, whether this would translate into improvement in cardiovascular outcomes remained unclear. Similarly, the Global Assessment of Plaque Regression with a PCSK9 Antibody (GLAGOV) trial showed positive results in terms of plaque reduction in favor of evolocumab but did

Table 1 Novel lipid-lowering therapies with their respective clinical trials and clinical outcomes

Drug class	Pharmacological agent	Effect on lipid profile	Clinical trial(s)	Results
NPC1L1 inhibitors	Ezetimibe	LDL-C reduction	IMPROVE-IT [8]	Patients receiving statin and ezetimibe as compared with those receiving statin monotherapy had greater reduction in LDL-C along with a lower event rate for cardiovascular death, nonfatal myocardial infarction, coronary revascularization within 30 days, nonfatal stroke, or unstable angina.
PCSK9 inhibitors	Alirocumab	LDL-C reduction	ODYSSEY OUTCOMES [9•]	On background of high-intensity statin therapy, the addition of alirocumab (as compared with placebo) resulted in significantly lower rates nonfatal myocardial infarctions, fatal or nonfatal ischemic strokes, or unstable angina.
	Evolocumab		FOURIER [10•]	Compared to placebo, addition of evolocumab to high-intensity statin therapy resulted in significantly reduced risk of the primary endpoint which was inclusive of cardiovascular death, myocardial infarction, and stroke.
	Inclisiran		ORION-1 [11]	Addition of inclisiran on background of statin therapy in patients with clinical ASCVD resulted in significant and prolonged reductions in all atherogenic lipoproteins.
CETP inhibitors	Torcetrapib	HDL-C increment; LDL-C reduction	ILLUMINATE [12]	Use of torcetrapib was associated with significant increase in HDL-C and reduction in LDL-C; however, it also resulted in increased rates of high blood pressure, higher aldosterone, and endothelin-1 levels.
	Dalcetrapib		dal-OUTCOMES [13]	No significant differences in MACE were detected between patients treated with study drugs versus placebo.
	Evacetrapib		ACCELERATE [14]	No significant differences in MACE were detected between patients treated with study drugs versus placebo.
	Anacetrapib		DEFINE [15]	Anacetrapib was associated with a significant increase in HDL-C and decrease in LDL-C.
			REVEAL [16]	On background of high-intensity statin therapy, addition of anacetrapib in patients with clinical ASCVD resulted in lower rates of the primary endpoint consisting of the first major coronary event, coronary death, myocardial infarction, or coronary revascularization.
EPA	Icosapent ethyl	Increased TG clearance without increase in LDL-C	MARINE [17]	Use of EPA resulted in significant reductions in TG without an increase in LDL-C.
			ANCHOR [18]	Use of EPA resulted in significant reductions in TG without an increase in LDL-C.
			REDUCE-IT [19••]	In patients with established ASCVD, who were on statin therapy, and had fasting TG between 135 and 499 mg/dL, the use of EPA (versus placebo) was associated with significant reduction in cardiovascular death, nonfatal myocardial infarction, and nonfatal strokes.

ASCVD atherosclerotic cardiovascular disease, *CETP* cholesteryl ester transfer protein, *EPA* eicosapentaenoic acid, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *NPC1L1* Niemann-Pick C1-like 1 protein, *PCSK9* proprotein convertase subtilisin/kexin type 9 inhibitors, *TG* triglycerides

not evaluate clinical endpoints [32]. Although post hoc analyses of these trials indicated that the use of these drugs on background of statin therapy was associated with a reduction in cardiovascular events, dedicated trials evaluating clinical outcomes were warranted.

Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) was the first trial focused on evaluating the effect of evolocumab on clinical outcomes in patients with cardiovascular disease [10•]. This was a randomized, double-blind, placebo-controlled trial consisting of almost 28,000 patients with known cardiovascular disease and LDL-C levels of 70 mg/dL or higher or non-HDL cholesterol levels of 100 mg/dL or higher, who were already on statin therapy. The primary endpoint of this trial was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. Patients were followed for a mean duration of 2.2 years. The investigators found that,

compared with placebo, evolocumab resulted in significantly reduced risk of primary endpoint (9.8% vs. 11.3%; ARR = 0.5%; HR 0.85; 95% CI 0.79–0.92; $p < 0.001$). These results persisted in subgroup analyses of various key subgroups including patients in the lowest quartile of baseline LDL-C levels. Several subgroup analyses from FOURIER have been conducted identifying patients who are at higher risk for recurrent ischemic events and hence are more likely to have a larger absolute risk reduction with the use of evolocumab. A subgroup analysis from FOURIER showed that patients with peripheral artery disease (PAD) experienced a greater absolute risk reduction in both primary (ARR; 3.5% with PAD, 1.6% without PAD) and secondary (ARR; 3.5% with PAD, 1.4% without PAD) ischemic endpoints [33]. Similarly, another analysis showed that patients with high-risk features (recent MI within the last 2 years, ≥ 2 prior MIs, and those with residual multivessel CAD) had significantly higher relative risk reductions and absolute risk reductions as compared with low-risk groups. At the 3-year follow-up, the respective absolute risk reduction in these high-risk patients were 3.4%, 3.7%, and 3.6% as compared with 0.8%, 1.3%, and 1.2% in the low-risk population [34].

As for adverse events with evolocumab, the results from FOURIER showed that adverse events between the two groups were similar except for injection site reactions which were more common with evolocumab. The very low LDL-C levels achieved by PCSK9 inhibitors raised concerns over neurocognitive side effects that were suggested by smaller studies [30, 31]. However, critics pointed out that the incidence of neurocognitive side effects in these trials was < 1% with a broad confidence interval. These concerns were put to rest by the Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) trial [35], a prospective trial consisting of roughly 1200 patients who were part of a randomized, placebo-controlled trial of evolocumab plus statin therapy vs. statin therapy alone. Patients were followed for a median of 19 months with the primary endpoint being the score on the spatial working memory strategy index of executive function. This was measured at baseline, at 24 weeks, and then at the conclusion of the trial. The results of this trial dismissed any concerns regarding neurocognitive side effects from PCSK9 inhibitors by showing that the change in the spatial working memory strategy index (compared with baseline) in patients with evolocumab (-0.21 ± 2.62) was noninferior to that of patients in the placebo (-0.29 ± 2.81) arm ($p < 0.001$ for noninferiority; $p = 0.85$ for superiority). Moreover, a recent pooled safety analysis of evolocumab consisting of over 6000 patients showed similar rates of adverse events and a favorable benefit-risk profile for the use of evolocumab [36].

Improvement in clinical outcomes in patients with ASCVD via use of alirocumab was evaluated by the Effects of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome (ODYSSEY) trial [37]. This was a large ($n = 18,924$), multicenter, randomized, double-blind, placebo-controlled trial investigating whether addition of alirocumab on background of high-intensity statin therapy lowers risk of recurrent ischemic cardiovascular events, in patients who had recently experienced an acute coronary syndrome (ACS). The long-term outcomes from the ODYSSEY OUTCOMES trial [9•] were in favor of the use of alirocumab for secondary prevention of ASCVD. During the median follow-up duration of 2.8 years, the composite primary endpoint (inclusive of nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or hospitalization for unstable angina) occurred in significantly less patients in the alirocumab group compared with patients receiving placebo (9.5% vs. 11.1%; ARR = 1.6%; HR 0.85; 95% CI 0.78–0.93; $p < 0.001$). A significant mortality benefit was also detected among patients in the alirocumab group compared with those receiving placebo (3.5% in the alirocumab group vs. 4.1% in the placebo group; HR 0.85; 95% CI 0.73–0.98). The significant differences in the event rate of the primary endpoint between the two cohorts were even more profound in patients with higher baseline LDL-C levels. Patients who had a baseline LDL-C level ≥ 100 mg/dL, compared with those with lower baseline levels, experienced a much greater absolute risk reduction with alirocumab in terms of the primary endpoint.

A head-to-head comparison trial between these two monoclonal antibodies and associated clinical outcomes is currently lacking. However, efficacy analysis of alirocumab vs. evolocumab showed that treatment with 140 mg/d of evolocumab vs. 150 mg/d of alirocumab showed no significant differences in LDL-C reduction (64% reduction vs. 63% reduction, $p < 0.0001$) [38]. A recent meta-analysis consisting of 11 randomized control trials surmounting to > 38,000 ASCVD patients treated with alirocumab and evolocumab (on baseline maximally tolerated statin therapy) demonstrated significant reductions in myocardial infarction, stroke, and coronary revascularization [39]. Such data, including results from ODYSSEY OUTCOMES and FOURIER, suggest that these monoclonal antibodies directed at PCSK9 are suitable as secondary prevention agents in patients with ASCVD currently on statin therapy. The 2018 ACC/AHA blood cholesterol guidelines give the addition of PCSK9 inhibitors a class IIa LOE A recommendation in patients with clinical ASCVD, who are deemed to be very high risk for future events and who are already on maximally tolerated LDL-C-lowering therapy (including maximally tolerated statin therapy and ezetimibe), and with LDL-C ≥ 70 mg/dL or non-HDL-C level of ≥ 100 mg/dL [24••].

Other PCSK9 Inhibitors

Another injectable PCSK9 inhibitor on the horizon is a long-acting RNA interference (RNAi) agent called inclisiran

(Alnylam Pharmaceuticals, Inc., Cambridge, MA). This RNAi agent targets the synthesis of PCSK9 in the hepatocytes. Given that the synthesis of PCSK9 is turned off at the translational level by this agent, this drug has a lipid-lowering effect which lasts much longer (~ 140 days) than the aforementioned monoclonal antibodies [40]. In its phase II trial, the ORION-1 trial [11], inclisiran (compared with placebo) significantly lowered PCSK9 and LDL-C levels in patients at high cardiovascular risk and who had elevated LDL-C levels. A recent trial consisting of over 500 patients, most with clinical ASCVD, evaluated the addition of inclisiran and its effect on reduction in atherogenic lipoproteins [41]. Almost three-fourths of the patients in this trial were already on statin therapy, and the mean LDL-C was 128 mg/dL. The results of this trial showed that inclisiran resulted in significant and prolonged reductions in all atherogenic lipoproteins. The data regarding safety are still emerging from phase III trials of this drug, and the ORION-4 trial expects to enroll roughly 15,000 patients with ASCVD to evaluate the impact of inclisiran on clinical cardiovascular outcomes [42].

Cholesteryl Ester Transfer Protein Inhibitors

Mechanism of Action

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that assists in exchanging cholesteryl ester from high-density lipoproteins (HDL) for triglycerides (TG) in apolipoprotein B (ApoB)–containing lipoproteins. These lipoproteins include LDL, chylomicrons, and very low–density lipoprotein (VLDL) [43]. CETP inhibitors thereby increase plasma HDL-C levels and reduce levels of atherogenic ApoB-containing lipoproteins [44]. The development of the CETP inhibitors stemmed from the large body of evidence which suggests an inverse relationship between major adverse cardiovascular events (MACE) and plasma HDL-C levels [45].

Clinical Evidence

Torcetrapib was the first CETP inhibitor tested in patients already on statin therapy. The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) was a randomized control trial consisting of over 15,000 patients [12]. This trial showed that although torcetrapib significantly increased HDL-C levels and decreased LDL-C levels, the use of this drug was associated with increased blood pressure and higher aldosterone and endothelin-1 levels. The phase III trial of this drug soon revealed increased incidence of MACE, and hence its development was halted by the manufacturer [46]. Similarly, dalcetrapib and evacetrapib were investigated in their respective phase III trials, the dal-OUTCOMES [13] and ACCELERATE [14] trials. The investigators showed that although the lipid parameters were favorably modified by the use of these drugs, there were no differences in MACE among patients treated with placebo vs. those treated with these CETP inhibitors. Given the lack of benefit, dalcetrapib and evacetrapib were both pulled from production.

The Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) trial [15] showed a significant increase in HDL-C and decrease in LDL-C level with the use of anacetrapib. This drug was finally tested in its phase III trial, the Randomized Evaluation of the Effects of Anacetrapib Through Lipid-Modification (REVEAL) [16], a randomized, double-blind, placebo-controlled trial consisting of over 30,000 patients with known atherosclerotic vascular disease who were on high-intensity statin therapy. At the beginning of this trial, the mean LDL-C was 61 mg/dL, non-HDL-C was 92 mg/dL, and HDL-C was 40 mg/dL. The primary outcomes of this study included the first major coronary event and a composite of coronary death, myocardial infarction, or coronary revascularization. At the conclusion of this trial and after a median 4.1-year follow-up, the primary outcome occurred in fewer patients who were in the anacetrapib group compared with the placebo arm (10.8% vs. 11.8%; RR 0.91; 95% CI 0.85–0.97; $p = 0.004$). There were no significant differences in adverse events between groups. It is noteworthy that the follow-up in REVEAL was significantly longer than the follow-up in dal-OUTCOMES or in ACCELERATE. Additionally, the number of patients enrolled in REVEAL was much higher than that of the other two trials. These two factors may have contributed to the lack of clinical benefit seen with dalcetrapib and evacetrapib. Researchers have highlighted that the positive results from REVEAL were due to reduction in LDL-C and non-HDL-C levels rather than the simultaneous increase in HDL-C levels. This was also demonstrated in recent Mendelian randomization studies that showed that the reduction in HDL-C levels had no bearing on cardiovascular adverse events [47] while lowering of LDL-C and TG levels proved to be protective against cardiovascular disease [48, 49]. Despite positive results from REVEAL, researchers have wondered whether the positive clinical outcomes associated with anacetrapib were due to its effect on increasing HDL-C or lowering LDL-C levels. Unfortunately, the manufacturer of anacetrapib decided not to proceed toward approval from a regulatory agency, due to concerns over the clinical profile of the drug not meeting the regulatory filings.

Although there are two CETP inhibitors currently under development, CKD 519 and dalcetrapib (dal-GenE-study), given prior failures with this class of medication, there is less hope for CETP inhibitors to serve as secondary prevention lipid-lowering therapy in the near future.

Eicosapentaenoic Acid Ethyl Ester

Mechanism of Action

Icosapent ethyl is an ethyl ester of eicosapentaenoic acid (EPA) that reduces the synthesis and secretion of VLDL triglycerides from the liver. This results in TG clearance by VLDL particles. The exact molecular mechanism of this drug remains unknown; however, it is hypothesized that this EPA has several mechanisms by which it increases the clearance of TG. These mechanisms include increased activity of plasma lipoprotein lipase activity, decreased hepatic lipogenesis, inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, and increase in beta oxidation [50].

Clinical Evidence

In contrast with previously developed TG-lowering therapies such as fibrates and fish oils, which can increase LDL-C, EPA promised to lower TG without the rise in LDL-C. This efficacy of this drug was first evaluated by the MARINE [17] and ANCHOR [18] trials, both of which demonstrated that EPA was well tolerated and significantly reduced TG levels without increasing LDL-C. Although these were randomized, placebo-controlled trials, they did not evaluate clinical endpoints.

The Japan EPA Lipid Intervention Study (JELIS) randomized over 18,000 patients with hyperlipidemia to receive either low-intensity statin therapy plus 1.8 g per day of EPA or statin therapy alone (control) [51]. The baseline median TG levels were 1.74 mmol/L (~ 154 mg/dL) in the control group and 1.73 mmol/L (~ 153 mg/dL) in the group receiving the EPA treatment. At a mean follow-up of 4.6 years, patients in the statin plus EPA arm had a significantly lower incidence of the primary endpoint, which was any major coronary event, sudden cardiac death, or fatal or nonfatal myocardial infarction (2.8% vs. 3.5%, $p = 0.011$). With its 19% relative risk reduction, EPA became a promising agent in patients with hyperlipidemia. More recently, clinical data from the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) were published [19••].

Compared with JELIS, which was a primary prevention trial with patients without cardiovascular disease, a majority (70.7%) of patients enrolled in REDUCE-IT had established ASCVD [19••]. Additionally, as opposed to REDUCE-IT which was a multinational, multicentered, randomized, double-blind, placebo-controlled trial, JELIS was an open-label trial and did not have an active placebo. REDUCE-IT included patients with either clinical cardiovascular disease or diabetes, who were on statin therapy, and had a fasting TG level between 135 and 499 mg/dL. Patients were randomized to either receive 4 g/day EPA or placebo (mineral oil). The primary endpoint of this trial included a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, and the key secondary endpoints included cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The results of this trial were largely in favor of EPA; at a median follow-up of 4.9 years, the incidence of primary endpoint was significantly higher in patients who received EPA compared with those in the placebo arm (17.2% vs. 22.0%; ARR = 4.8%; HR 0.75; 95% CI 0.68–0.83; $p < 0.001$). The number needed to treat was 21 patients, to avoid one primary endpoint event over the median follow-up period of 4.9 years. The rates of secondary endpoints were also in favor of EPA with significant reductions in cardiovascular death (HR 0.80; 95% CI 0.66–0.98; $p = 0.03$; ARR = 0.9%), fatal or nonfatal MI (HR 0.69; 95% CI 0.58–0.81; $p < 0.001$; ARR = 2.6%), fatal or nonfatal stroke (HR 0.72; 95% CI 0.55–0.93; $p = 0.01$; ARR = 0.9%), urgent or emergent revascularization (HR 0.65; 95% CI 0.55–0.78; $p < 0.001$; ARR = 2.5%), and hospitalization for unstable angina (HR 0.68; 95% CI 0.53–0.87; $p = 0.002$; ARR = 1.2%). Compared with placebo, patients in the EPA arm experienced slightly higher rates of hospitalization for atrial fibrillation or flutter (3.1% vs. 2.1%, $p = 0.004$) and had a non-significant higher propensity of serious bleeding (2.7% vs. 2.1%, $p = 0.06$). Overall, the absolute risk was deemed to be much lower than the absolute benefit of this drug. The STRENGTH trial (NCT02104817) is another large randomized trial that is currently underway and is evaluating effects of omega-3-carboxylic acid in similar groups of patients who are already on statin therapy. This trial is expected to conclude in October 2019 and, along with the results of REDUCE-IT, may bring forward practice-changing evidence for the use of fish oil substances for secondary prevention of cardiovascular disease.

Clinical Management and Cost-Benefit Analysis

Patients with established cardiovascular disease are at high risk for recurrent ASCVD events. Lowering LDL-C when ≥ 70 mg/dL or non-HDL-C when ≥ 100 mg/dL is recommended [24••]. To assist in achieving these goals for secondary prevention of ASCVD, providers currently have ezetimibe and PCSK9 inhibitors at their disposal in addition to high-intensity statin therapy. Both ezetimibe and PCSK9 inhibitors should be reserved as add-on therapies for patients who are at very high risk for recurrent ASCVD events and in whom LDL-C remains ≥ 70 mg/dL despite maximally tolerated statin therapy. The recommended strategy per 2018 cholesterol guidelines [24••] is that clinicians should use maximally tolerated statin therapy plus ezetimibe prior to initiation of PCSK9 inhibitors in very high–risk ASCVD patients. This very high–risk group consists of patients who have suffered multiple major ASCVD events or one major ASCVD event along with having multiple high-risk conditions such as current smoking, hypertension, diabetes, age ≥ 65 years, chronic kidney

disease, history of prior coronary artery bypass surgery or percutaneous coronary intervention, persistently elevated LDL-C ≥ 100 mg/dL, history of congestive heart failure, or heterozygous familial hypercholesterolemia [24••]. Although the trials evaluating the efficacy of PCSK9 inhibitors did not require patients to have been treated with ezetimibe prior to initiation of PCSK9 inhibitors, the use of ezetimibe was allowed in both FOURIER and ODYSSEY OUTCOMES [10•, 37]. Ezetimibe is a widely available and affordable generic drug with an excellent safety profile which makes it a preferred option prior to the use of PCSK9 inhibitors. A simulation study showed that among the veteran population, over 154,000 patients would be eligible for evolocumab based on the FOURIER inclusion and exclusion criteria [52]. Treating these eligible patients would cost $2.08 billion per year. However, based on their simulation, the authors showed that the size of this group of evolocumab-eligible patients can be reduced by up-titration to high-intensity statin therapy and via addition of ezetimibe. Up-titration to high-intensity statin in this group of patients is expected to reduce LDL-C levels < 70 mg/dL in an additional 18.7% of evolocumab-eligible patients, while addition of ezetimibe would achieve this LDL-C target goal in additional 50.7% of evolocumab-eligible patients. Lastly, a combination of high-intensity statin therapy and ezetimibe is expected to decrease evolocumab-eligible patients by almost 60%. This would translate to approximately $1.13 billion in annual cost savings [52]. Similarly, another recently published simulation study showed that LDL-C goal of < 70 mg/dL can be achieved in 67.3% of patients with ASCVD with optimization of statin monotherapy while another 18.7% of patients can achieve this goal with addition of ezetimibe to statin therapy [53]. With proper titration of statin therapy and addition of ezetimibe, only 14% of patients would require addition of PCSK9 inhibitors to achieve LDL-C < 70 mg/dL. Hence, the current guidelines recommend optimization of statin therapy, followed by addition of ezetimibe, prior to consideration of PCSK9 inhibitors in very high–risk individuals with ASCVD and LDL-C > 70 mg/dL. Lastly, several cost-effectiveness analyses have been performed since the introduction of PCSK9 inhibitors [54, 55•, 56]. However, with the 2018 list prices, most models currently project the PCSK9 inhibitors to be of "low value," that is, costing an additional ≥ $150,000 per quality-adjusted life year for secondary prevention of ASCVD events, although this may change based on a recent announcement of price reduction by one sponsor.

Conclusion

Over the last half decade, numerous lipid-lowering pharmacological agents have been introduced, developed, and tested in both human genetic and clinical outcomes trials. While these novel therapies may be extremely effective at blocking their respective targeted pathway in the lipid metabolism, thereby creating a favorable lipid profile, several requirements must be met in order for a therapy to become the next standard of care for secondary prevention of ASCVD, including proven safety, efficacy, affordability, and accessibility. Additionally, in which secondary prevention patient subgroups should these agents be used remains a question of continued debate. Robust clinical outcomes and safety data along with cost effectiveness simulations are needed for these novel agents prior to being recommended for routine clinical use.

Compliance with Ethical Standards

Conflict of Interest Dr. Dhruv Mahtta and Dr. Anthony A. Bavry declare that they have no conflict of interest. Dr. Salim S. Virani: research support: VA Health Services Research and Development, American Heart Association, American Diabetes Association, and research fund from Drs. Abida and Nuruddin Jooma. Dr. Virani also serves on the steering committee for the Patient and Provider Assessment of Lipid Management (PALM) registry at the Duke Clinical Research Institute (DCRI) (no financial remuneration).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
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