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LIPIDS (E. MICHOS, SECTION EDITOR)

A Look Beyond Statins and Ezetimibe: a Review of Other Lipid-Lowering Treatments for Cardiovascular Disease Prevention in High-Risk Patients

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Abstract

Purpose of Review There has been significant progress made during the last few decades in the management of atherosclerotic cardiovascular disease (ASCVD). Despite this, residual risk remains an unmet need for secondary prevention and high-risk primary prevention patients. First onset and recurrent cardiovascular events remain a major issue despite recommendations for a healthy lifestyle and current optimal medical therapy, which includes the use of maximally tolerated statin therapy plus or minus add-on ezetimibe therapy.

Recent Findings These findings have led to the development of new treatments that modulate lipid targets in order to improve prognosis of these patients at highest ASCVD risk. These include inhibitors of proprotein convertase subtilisin/kexin type 9 (evolocumab and alirocumab), an inhibitor of adenosine triphosphate citrate lyase (bempedoic acid), and a high-dose omega-3 formulation (icosapent ethyl), which have been evaluated in large phase III randomized clinical trials and/or currently undergoing continued study. The clinical efficacy of these drugs and their application in cardiovascular prevention are discussed in this review article. Of note, there are other novel lipid-lowering therapeutics with potential cardiovascular benefit, not discussed in this review, that include inhibitors of lipoprotein (a), apolipoprotein CIII, and angiopoietin-like 3. These drugs may also play a future role in reducing residual lipid-mediated ASCVD risk, if efficacy and safety confirmed in cardiovascular outcome trials.

Summary In this review, we provide an overview of the current knowledge regarding treatment with several new lipid strategies for high-risk patients, along with suggestions on their use in ASCVD prevention management.

Keywords Residual risk · Lipid-lowering treatments · Bempedoic acid · Eicosapentaenoic acid · PCSK9 inhibitors · Inclisiran

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Introduction

Significant progress has been made during the last few decades in the reduction of deaths from cardiovascular diseases (CVD) [1]. However, despite recommendations for a healthy lifestyle and the use of appropriate medical therapy (i.e., maximally tolerated statin alone or in combination with ezetimibe), residual risk still remains an unmet need for the secondary prevention of recurrent atherosclerotic CVD (ASCVD) events [2] and the primary prevention of de novo events in high-risk patients. Causes of this residual risk are multifactorial [3], but include insufficient lowering of plasma low-density lipoprotein cholesterol (LDL-C) concentration and persistently elevated triglyceride-rich lipoproteins (TRLs) [4].

Statins still remain the first-line agents for primary and secondary prevention of ASCVD; their safety and clinical efficacy is well established [5••, 6•, 7•]. However, reported statin-associated muscle symptoms (SAMS) in some patients

might limit their use [7•]. In addition, even when tolerating some or maximal statin therapy, further LDL-C lowering beyond that provided by statin therapy alone may be needed. The 2018 American College of Cardiology (ACC)/American Heart Association (AHA)/Multi-Society guidelines have endorsed that, among high-risk patients, an LDL-C threshold of ≥ 70 mg/dL despite maximally tolerated statin therapy may prompt the addition of a proven non-statin therapy for further LDL-C lowering [5••]. Additionally, an LDL-C threshold ≥ 100 mg/dL despite maximally tolerated statin therapy may prompt the addition of a non-statin for patients with severe primary hypercholesterolemia [5••]. Ezetimibe was endorsed as the preferred initial add-on therapy given its lower cost and its demonstrated clinical efficacy in the IMPROVE-IT trial [8•]. However, persistent inadequate LDL-C control and residual ASCVD risk have stimulated the search of new lipid modulating therapies to further reduce cardiovascular events in these high-risk patients.

New approaches that target atherogenic lipoproteins include some of the following (Figure 1): (1) inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) to decrease circulating LDL-C; (2) inhibition of adenosine triphosphate (ATP) citrate lyase to reduce hepatic cholesterol synthesis; and (3) use of high-dose omega-3 fatty acids which reduce triglyceride levels and have other risk-lowering mechanisms. This review describes the scientific basis and rationale for developing these lipid therapeutics and provides a brief summary of results from large randomized control trials.

Additionally, there are other pharmacotherapeutics that have been studied or currently undergoing evaluation, which also address lipid residual risk. These include:

(1) Blockage of lipoprotein (a) (Lp(a)) synthesis with antisense oligonucleotide (ASO) therapy;
(2) Inhibition of apoC-III with ASOs to reduce TRLs and to enhance high-density lipoprotein (HDL) function;
(3) Inhibition of angiopoietin-like 3 (ANGPTL3) by ASO or monoclonal antibody therapy;
(4) Inhibition of microsomal triglyceride transfer protein;
(5) Inhibition of cholesteryl ester transfer protein (CETP) to reduce atherogenic lipoproteins concentration and increase the level and function of the potentially anti-atherogenic HDL fraction; and
(6) Therapies that specifically target HDLs include infusions of reconstituted HDLs, HDL delipidation, and infusions of apoA-I mimetic peptides that mimic some HDLs functions.

Due to space limitations of this review, these therapies will not be discussed here, but some of these (e.g., inhibition of Lp(a), apoC-III, and ANGPTL3) may also become important in ASCVD prevention and management in the future if their clinical efficacy and safety are confirmed in large cardiovascular outcome trials (CVOTs).

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme encoded by the *PCSK9* gene in humans on chromosome 1 [9]. This protein plays a major regulatory role in cholesterol homeostasis, mainly by reducing the levels of LDL receptors (LDL-R) on the plasma membrane [9]. When LDL binds to LDL-R, it induces internalization of LDL-R/LDL complex within an endosome. The acidity of the endosomal environment induces LDL-R to adopt a hairpin conformation. The conformational change causes LDL-R to release its LDL ligand, and the receptor is recycled back to the plasma membrane. However, when PCSK9 binds to the LDL-R (through the EGF-A domain), PCSK9 prevents the conformational change of the receptor-ligand complex which results in redirection of the LDL-R from the endosome to the liposome instead where it is degraded [10]. Drugs that inhibit the PCSK9 enzyme thus prevent the degradation of LDL-R, which leads to upregulation of hepatic LDL-R and enhanced LDL clearance from circulation. Evolocumab and alirocumab are two fully human anti-PCSK9 antibodies, which can induce significant and prolonged decreases of LDL-C (by approximately 50 to 70%) and other atherogenic particles such as Lp(a), even on top of background statin therapy [9, 11••, 12••, 13]. The clinical efficacy and safety of these agents have been demonstrated in two large phase III randomized CVOTs (FOURIER and ODYSSEY OUTCOMES), which were conducted among secondary prevention patients.

The FOURIER trial enrolled a large spectrum of high-risk stable secondary prevention patients including not only coronary artery disease (CAD) patients but also patients with peripheral arterial disease (PAD) or prior stroke [11••]. A total of 27,564 patients with LDL-C levels of 70 mg/dL or higher despite maximally tolerated statin therapy were randomly assigned to receive double-blinded subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or placebo. The primary outcome was 5-point major adverse cardiovascular events (MACE) including cardiovascular (CV) death, myocardial infarction (MI), stroke, hospitalization for unstable angina, or coronary revascularization. Over a median follow-up of just 26 months, evolocumab, compared to placebo, significantly reduced the risk of this primary composite endpoint by an absolute risk reduction (ARR) of 1.5% and a relative risk reduction (RRR) of 15%: 1344 (9.8%) vs.1563 patients (11.3%); hazard ratio (HR) 0.85; 95% confidence interval (CI) 0.79–0.92; $p < 0.001$. Evolocumab also reduced the key secondary endpoint (MI, stroke, or CV death): 816 (5.9%) vs.1013 (7.4%); HR 0.80 (95% CI 0.73–0.88); $p < 0.001$ [11••].

The benefits of reduced ischemic events increased over time with a higher benefit observed the second year of treatment with evolocumab. No significant risk reduction was observed for CV mortality nor total mortality, but this could be

partly by the relative short-term follow-up in this trial. Subsequent sub-analysis from FOURIER have indicated that patients at higher absolute baseline risk derived the greatest absolute and relative risk reductions with evolocumab therapy such as those with PAD [14], recent or multiple prior MIs or residual severe multi-vessel CAD [15], or with elevated Lp(a) [13].

The ODYSSEY OUTCOMES trial focused on PCSK9 inhibition among secondary prevention patients who had recent acute coronary syndromes (ACS) within 1–12 months from enrollment (medium time between index ACS and randomization, 2.6 months) [12••]. A total of 18,924 post-ACS patients were enrolled, with a mean age of 58 years, who had sub-optimally controlled lipids despite maximally tolerated statins (as defined by LDL-C ≥ 70 mg/dL, non-HDL-C ≥ 100 mg/dL, or apoB ≥80 mg/dL). Participants were randomized to receive either twice-monthly injections of alirocumab (75 or 150 mg) or placebo. Different from the FOURIER design, in ODYSSEY Outcomes, there was a dose-titration for PCSK9 inhibition. Patients randomized to receive alirocumab had a double-blinded dose adjustment in order to reach the target LDL-C levels of 25–50 mg/dL. If LDL-C levels dropped consistently below 15 mg/dL, patient was switched to placebo (7.7% in the alirocumab group). The mean follow-up was for 34 months, with 44% of patients having a longer follow-up ≥3 years.

Overall, the alirocumab group had a 1.6% ARR (9.5% vs 11.1%) and 15% RRR (HR 0.85 (95% CI 0.78–0.93), $p = 0.0003$) for the primary composite endpoint (coronary heart disease (CHD) death, non-fatal MI, ischemic stroke, or hospitalization for unstable angina) compared with the placebo group. All components of the primary endpoint were significantly reduced except CV death. The absolute event rate of all-cause death was significantly reduced in the alirocumab group compared to the control group (3.5% vs 4.1%, with a RRR of 15% (HR 0.85 (95% CI 0.30–0.98; nominal p value = 0.026))) but was not considered statistically significant due to predefined hierarchical testing. The number needed to treat (NNT) with alirocumab for the mean duration of 36 months was 64 for MACE and 163 for all-cause mortality. These NNT were much lower in the subgroup with an LDL-C above 100 mg/dL reaching 29 for MACE and 60 for all-cause mortality, with most of the benefit for alirocumab observed in this subgroup.

These studies, with both of these PCSK9 inhibitors, reported an excellent safety profile with no adverse signal alert, neither for induced-diabetes (as has been reported for high-doses statin therapy [16]), cognitive dysfunction [17], nor for hemorrhagic stroke or muscular outcome. Patient in the PCSK9 inhibitor groups did report, as expected, more minimal injection site reactions. While the ARR and RRR were largely similar for the primary outcomes in FOURIER and ODYSSEY OUTCOMES, when considering differences in regard to the outcome of all-cause death, it is notable to mention that the drugs were tested in different secondary prevention setting (stable atherosclerotic patients vs. early post-ACS patients), with different dosing strategies, and different length of follow-up (shorter in FOURIER) [11••, 12••]. When considering PCSK9 inhibition, the chemical nature of the drugs likely matters. The SPIRE program was halted prematurely, due to a lack of clinical efficacy of another PCSK9 monoclonal antibody, bococizumab, which might have due to insufficient reduction in plasmatic LDL-C levels partly by the induction of antibodies against the drug, which was not fully human [18••].

In view of the available evidence from these trials, the patients who appear to benefit the most from these new treatments are higher risk secondary prevention patients with residual LDL-C above 70 mg/dL (with increased benefit for those with even higher residual LDL-C such as ≥ 100 mg/dL) despite maximal tolerated high-dose statin and ezetimibe, patients with recent ACS, and patients with recurrent ischemic events or poly-vascular disease (especially PAD [14]). The US guidelines have recently defined the current place of PCSK9 inhibitors, underlying the need of long-term follow-up with these molecules to confirm the safety and efficacy [5••]. The weight of the evidence from these trials have further strengthened the LDL hypothesis that indeed further lowering of LDL-C is a powerful preventive action for the management of high-risk patient. From a methodological perspective, it will now be difficult to conduct trials without a PCSK9 inhibitor as comparator.

While the benefit/risk ratio favors both alirocumab and evolocumab in this described high-risk population, it is important to note that the RCTs lack sufficient power to detect rare adverse drug reactions and the follow-up for both trials was relatively short. Only post-marketing studies and risk management appraisal by drug agency will be able to identify mid- and long-term risk. Additionally, the cost of this new class of lipid-lowering therapy is still above what many payers are readily willing to reimburse (list price initially of more than US $14,000 and now reduced to ~ $6000). However, since the price cut, a 2019 cost effectiveness analysis did find that evolocumab meets acceptable cost effectiveness thresholds in patients at very high ASCVD risk [19]. Burdensome paperwork and pre-authorization remains a barrier for many eligible patients to receive this beneficial therapy.

Inclisiran

Given the success of monoclonal antibody inhibition of PCSK9, other types of PCSK9 inhibitors are being intensively developed. Inclisiran is a small interfering RNA (siRNA) targeting PCSK9 hepatic production. Inclisiran binds to intra cellular PCSK9 mRNA inducing its degradation and

preventing its translation to PCSK9 acting protein. An early phase clinical trial (Orion 1) demonstrated that a single subcutaneous injection of inclisiran resulted in a sustained and significant 6-month reduction of PCSK9 and LDL-C concentration [20••]. An ongoing phase III RCT is currently investigating the clinical efficacy of inclisiran in high-risk secondary prevention patients on MACE incidence (Orion 4, NCT NCT03705234).

Bempedoic Acid

Bempedoic acid (BA) (ETC-1002) is new agent that reduces cholesterol synthesis through inhibition of adenosine triphosphate (ATP) citrate lyase, an enzyme upstream from 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the target of statins. This reduced cholesterol synthesis results in LDL-R upregulation and increased clearance of LDL from the bloodstream. Bempedoic acid is converted to its active moiety primarily in the liver by ACSVL1, which is not present in skeletal muscle. Therefore, BA has not been associated with muscle symptoms, as has been attributed to statin therapy, and may be particularly useful in patients with SAMS [21].

In animal models, BA also influences fatty acid synthesis, but in humans, its role is limited primarily to lowering LDL-C. In early clinical trials, BA was well tolerated and without major side effects. Alone or in various combinations with statin and/or ezetimibe, the LDL-C lowering attributed to BA is approximately 17–30% [21, 22•, 23••]. In addition, BA lowers levels of non-HDL-C, high sensitivity C-reactive protein (hsCRP), and apolipoprotein B (apoB). BA appears to enhance LDL-C lowering beyond that achieved with statin monotherapy [21, 22•]. The effectiveness of LDL-C lowering of BA appears to be enhanced when combined with ezetimibe therapy [24•].

A global, pivotal, phase III clinical development program is ongoing to evaluate the safety, tolerability, and LDL-C-lowering efficacy of BA among patients with documented ASCVD or patients who are at high-risk with dyslipidemia, who remain with elevated LDL-C levels despite maximally tolerated statin dosage. The Cholesterol Lowering via Bempedoic Acid, an ACL-inhibiting Regimen (CLEAR) program includes 5 studies including about 4000 patients; 4 trials are evaluating BA in monotherapy and one with BA plus ezetimibe fixed-dose combination. Clear Serenity evaluated BA vs. placebo in 345 patients with statin intolerance [21]. Clear Tranquility evaluated BA plus ezetimibe in 269 patients with statin intolerance and LDL-C ≥ 100 mg/dL [22•]. These smaller studies showed that BA was safe and effective at LDL-C lowering. There have been 2 large pivotal studies recently reported that have evaluated the clinical efficacy of BA: CLEAR Harmony [23••] and CLEAR Wisdom [25] (comprising 3009 patients with ASCVD on maximally tolerated statin

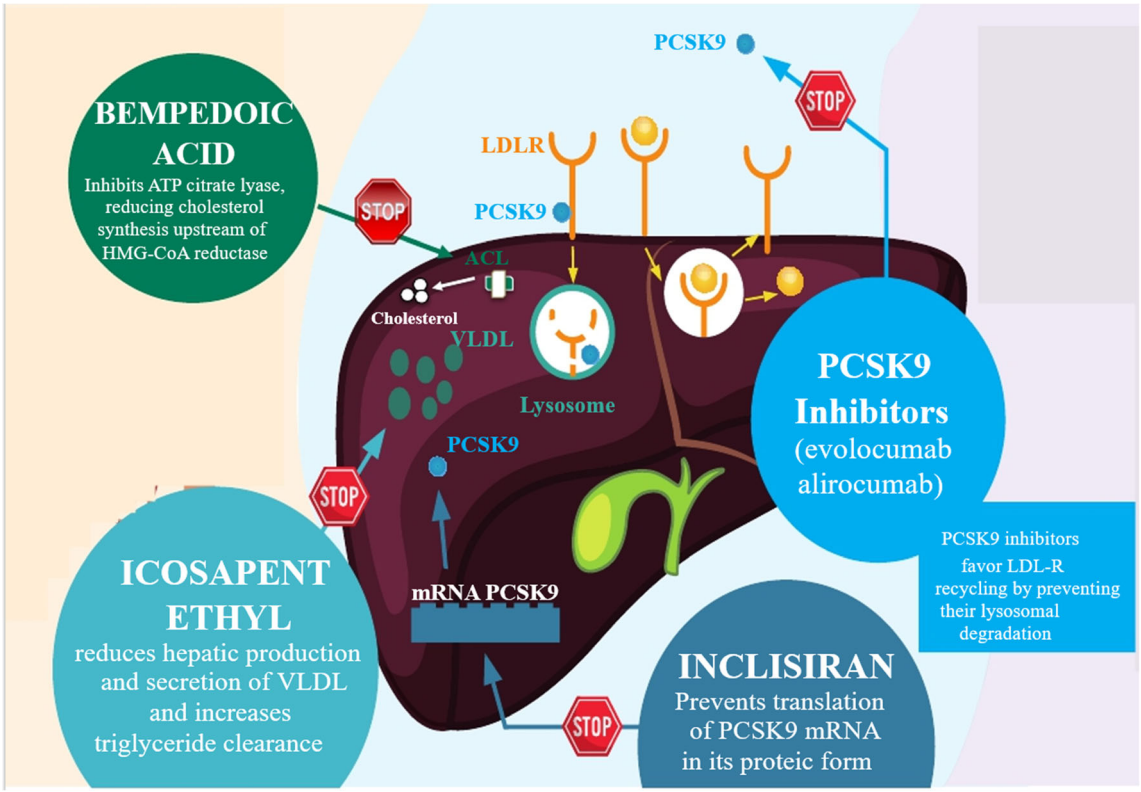

Fig. 1 Novel therapeutic strategies to reduce lipid-related cardiovascular risk

therapy, with top-line results reported in May 2018 and October 2018, respectively.

CLEAR Harmony [23••] was a phase III double-blind RCT aimed to assess long-term safety and efficacy of BA in patients with pre-existing ASCVD and/or heterozygous familial hypercholesterolemia (HeFH), with baseline LDL-C ≥ 70 mg/dL while receiving maximally tolerated statin dose. CLEAR Harmony trial enrolled 2230 patients, of whom 1488 were assigned to receive BA 180 mg daily and 742 to receive placebo, with baseline mean (± SD) LDL-C level of 103 ± 29 mg/dL and followed for 52 weeks. The primary endpoint was safety and the principal efficacy endpoint was the percent change from baseline to 12 weeks in LDL-C. BA was demonstrated to be safe. The incidence of adverse events did not differ substantially between both groups during the intervention period, but the adverse events leading to discontinuation of the regimen was higher in the BA group compared with the placebo group (162 patients [10.9%] vs. 53 [7.1%]), as was the incidence of gout (18 patients [1.2%] vs. 2 [0.3%]). At week 12, BA reduced the mean LDL-C level by 19.2 mg/dL, representing a change of − 16.5% from baseline. The difference in percent change from baseline between BA vs. placebo was − 18.1%; (95% CI − 20.0 to − 16.1; $P < 0.001$). Significant reductions in LDL-C were maintained through week 52. BA also significantly lowered the secondary endpoints of non-HDL-C, total cholesterol, apoB, and hsCRP. Safety and efficacy findings were consistent across various intensity of background statin therapy. Although CLEAR Harmony was not a CVOT, the findings support that BA can represent a therapeutic option to lower LDL-C in high ASCVD risk patients in combination with statins [23••].

The CLEAR Wisdom trial randomized 779 patients to treatment with BA 180 mg or placebo once daily for 1 year in addition to maximally tolerated statins. A subset of 77 patients was not able to tolerate any statin dose. The primary endpoint was the percent change in LDL-C from baseline to week 12. A total of 740 patients completed the study (490 on BA and 250 on placebo). LDL-C levels in the BA group decreased from 119.4 mg/dL at baseline to 97.6 mg/dL at 12 weeks compared with no change from baseline in the placebo group (122.4 mg/dL vs 122.8 mg/dL). The mean percent change in LDL-C was 15.1% with BA vs. 2.4% with placebo ($p < 0.001$). Among the patients not taking statins, the mean percent change was more pronounced (− 24.6% with BA vs. − 2.6% with placebo). At 1 year, the LDL-C level was 99.6 mg/dL in the BA group vs. 116.9 mg/dL in the placebo group. The effect of BA was durable at 1 year and no increase in adverse effects from the addition of BA to statin therapy was reported.

The effect of BA on cardiovascular morbidity and mortality has not yet been determined but is currently being evaluated. Indeed, the CLEAR Outcomes trial is a double-blind, randomized CVOT which aims to assess the effects of BA on the occurrence of major cardiovascular events in patients with—or at high risk for—ASCVD, and who are only able to tolerate less than the lowest approved daily starting dose of a statin (NCT02993406). The primary endpoint is the time from randomization to first occurrence of one of the following composite endpoints: CV death, non-fatal MI, non-fatal stroke, or coronary revascularization, with an estimated average duration of 3.75 years. CLEAR Outcomes is expected to enroll approximately 12,600 patients with hypercholesterolemia (LDL-C ≥ 100 mg/dL) and high ASCVD risk or with statin intolerance at more than 600 sites in approximately 30 countries [6•]. Results are anticipated in 2022.

In addition to CLEAR Outcomes, there will be an extension of follow-up from CLEAR HARMONY to assess ASCVD events. These ongoing CVOTs will provide clinical efficacy evaluation to better define this agent's potential clinical role. In the meantime while awaiting for completion of these CVOTs, with all collected data on safety and biological efficacy on BA for LDL-C lowering, Esperion plans to submit in the next future New Drug Applications (NDAs) to the US Food and Drug Administration (FDA), for BA and BA plus ezetimibe fixed-dose combination, for LDL-C-lowering indications. Additionally, Esperion plans to submit Marketing Authorization Applications (MAAs) to the European Medicines Agency (EMA) also in 2019.

At this time, it seems that BA may be indicated for high-risk patients who need additional LDL-C despite use of maximally tolerated statin therapy and ezetimibe, and may have particular utility for those with SAMS or other reasons not to tolerate statin. Of note, the LDL-C lowering efficacy with BA is not as great as that conferred by monoclonal antibody inhibitors of PCSK9 (i.e., evolocumab and alirocumab), which lower LDL-C ~ 60% [11••, 12••]. However, the advantage of BA is its oral formulation and anticipated lower cost. Future studies should also determine whether BA is equally or more efficient to lower CV events compared to more potent lipid-lowering therapy, such as PCSK9 inhibitors, and the cost effectiveness of these various management strategies.

EPA

The marine-based omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to reduce hepatic production and secretion of very low-density lipoproteins (VLDL) and increase TRL clearance, with a good safety profile. An open label clinical trial conducted in Japan that enrolled patients with hypercholesterolemia, the JELIS trial, did previously show a benefit of MACE reduction with high-dose EPA at 1.8 g/day over a median of 4.6 years, with stronger benefit for secondary prevention patients [26]. However after that publication, a series of other RCTs and meta-

analyses failed to show a benefit of omega-3 PUFAs. These trials used dietary supplements (not pharmaceutical grade omega 3), at lower doses (generally ~ 1000 mg/day), and of mixed PUFA composition [27–29].

Icosapent ethyl is a highly purified EPA formulation, which had been demonstrated to lower triglyceride levels, but data were needed to determine its potential benefits on ischemic events. Therefore, a multicenter, randomized, double-blind, placebo-controlled trial was performed. This was a rather ambitious and risky study after the failure of several treatments acting on triglycerides when added to a background of statin therapy, such as fenofibrate in the ACCORD study [30] and the aforementioned negative omega-3 trials.

The REDUCE-IT trial enrolled secondary prevention patients or patients with diabetes associated with other risk factors with the majority of participants (70.7%) being secondary prevention and diabetes was frequent (59%) [31••]. All patients were on statin therapy and had a fasting triglyceride level of 135 to 499 mg/dL, with well-controlled LDL-C level 41 to 100 mg/dL. Ezetimibe was used in only 6.4% of patients, whereas moderate- or high-intensity statin was prescribed for 94% of patients. The baseline lipid profile was a median triglyceride level of 216 mg/dL, LDL-C at 75 mg/dL, HDL-C at 40 mg/dL, and hsCRP at 2.2 mg/L. A total of 8179 patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total dose 4 g/day) or placebo with a median follow-up of 4.9 years. The primary 5-point MACE endpoint was a composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina. The secondary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

The primary endpoint event was reduced in the icosapent ethyl group with an ARR of 4.8% (17.2% vs. 22.0%) and RRR of 25% (HR 0.75 (95% CI 0.68–0.83); $p < 0.0001$)). The NNT with icosapent ethyl to prevent one primary outcome event was 21 over 4.9 years [31••]. The rates of the key secondary endpoint were reduced by 26% (11.2% vs. 14.8% in the placebo group (HR 0.74 (95% CI 0.65 to 0.83); $p < 0.001$)). Rates of additional ischemic endpoints pre-specified by hierarchical schema were also reduced such as CV death or MI (9.6% vs.12.4%, $p < 0.001$), CV death alone, MI alone, and stroke, with no impact of all-cause mortality: (6.7% vs. 7.6%, p = not significant).

Icosapent ethyl vs. placebo also provided a significant 1-year change in triglyceride levels of − 39.0 mg/dL vs. 4.5 mg/dL, in LDL-C of 2 mg/dL vs. 7 mg/dL. However, notably, the clinical efficacy of icosapent ethyl on MACE reduction was independent of achieved triglyceride levels suggesting alternate mechanisms for benefit [31••]. Concerning potential adverse events, more patients in the icosapent ethyl group than placebo were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, $p = 0.004$). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group ($p = 0.06$). A recent additional publication from REDUCE-IT reported that the rates of total ischemic events (beyond the initial event) were also reduced with icosapent ethyl [32•]. The total ischemic events of the primary outcome were reduced by 30% (rate ratio 0.70 (95% CI 0.62–0.78; $p < 0.0001$)), compared to placebo.

The results of REDUCE-IT indicate that the use of a highly purified, proprietary form of EPA (icosapent ethyl) at 4 g daily is superior to placebo in reducing CV events and CV death among statin-treated patients with elevated triglycerides and either known ASCVD or patients with diabetes at high risk for developing it. This makes it a promising option to reduce residual risk and has already been incorporated in the 2019 update for the Standards of Medical Care in Diabetes put forth by the American Diabetes Association. However, the exciting results of REDUCE-IT should not be extrapolated to dietary supplements or other formulations of omega 3's, which warrant further study.

There has been much discussion about why REDUCE-IT was a success compared to the several negative trials of omega-3 that proceeded it. The high dose (4 g/day) likely matters. It may also be due to the pure EPA formulation studied, as had been used in JELIS [26], as the biological effects of EPA and DHA differ. Questions also remain about the precise mechanisms explaining the observed benefits. Since the benefit of icosapent ethyl appears beyond its triglyceride lower effects, anti-thrombotic and anti-inflammatory mechanisms may be playing a key role. Whether other high-dose EPA formulations will confer the same benefit as icosapent ethyl remains to be seen. The STRENGTH trial is assessing the clinical efficacy of 4 g/day of omega-3 carboxylic acids on CV outcomes among high-risk statin-treated patients with elevated triglycerides and low HDL-C levels [33]. Also warranting study is whether icosapent ethyl or other high-dose omega-3 formulations will have benefit among patient populations not included in REDUCE-IT such as high-risk secondary prevention patients who do not have triglyceride elevation.

Conclusions

A healthy lifestyle remains the foundation for cardiovascular prevention throughout one's lifetime. Statins remain the mainstay for cardiovascular risk reduction in patients at elevated ASCVD risk. Nevertheless, residual risk in patients with established ASCVD, or at high risk for it, remains a crucial issue which has been attributed, in part, to insufficient LDL-C lowering and other lipid abnormalities such as high triglycerides. Emergence of new lipid-directed treatments allows for further optimization of high-risk patients' lipid profile together, with a good safety profile. Significant reduction in major CV events has already been demonstrated for the monoclonal

antibody PCSK9 inhibitors evolocumab and alirocumab and for the high-dose EPA formulation icosapent ethyl, and these therapies have been incorporated into current management guidelines. There are large CVOTs on going to evaluate the clinical effectiveness of other new strategies, which also have the potential to become important in cardiovascular disease prevention management.

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Compliance with Ethical Standards

Conflict of Interest P. Sabouret reports consulting/lecture fees or funding for conférence travel from Amgen, Astra-Zeneca, Bouchara-Recordati, Bristol-Myers Squibb, Merck Sharp and Dhome, Novartis, NovoNordisk, Pfizer, Sanofi, and Servier.

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- • Of importance
- •• Of major importance

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