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Implications for REDUCE IT in clinical practice

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ABSTRACT

Statin therapy is effective in primary and secondary prevention, but substantial residual risk remains on statin treatment, especially among high risk and very high risk patients. Add-on therapy with ezetimibe and proprotein convertase subtilisin /kexin type 9 (PCSK9) inhibitors provides additional risk reduction through further reduction in low density lipoprotein cholesterol. Elevated triglycerides/triglyceride rich lipoproteins contribute to atherogenesis and to the residual risk on statin therapy. Addition of icosapent ethyl to statins has recently been shown to markedly lower risk of ASCVD events in patients with established atherosclerotic CVD (ASCVD) and high risk patients with type II diabetes mellitus. These data are discussed in the context of current guidelines and synthesized in a decision pathway to guide combination lipid-lowering therapy in patients at high ASCVD risk.

Contents

Introduction

Statins reduce risk of ASCVD events across the spectrum of ASCVD risk in secondary and primary prevention.[1] Benefit increases with intensity and duration of statin treatment. While relative risk reductions per mmol of low-density lipoprotein (LDL) cholesterol (LDL-C) lowering for one year are consistent across different risk strata, absolute risk reduction is greater among individuals at higher risk translating to a lower number needed to treat to prevent one event. Risk, however, does not return to zero on statin treatment. This "residual risk" is a function of the severity of established atherosclerosis, non-lipid risk factors (e.g. smoking, diabetes, hypertension), inflammation, pro-thrombotic milieu, as well as risk due to atherogenic lipoproteins other than LDL.[2]

Abbreviations and acronyms: ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; Hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; LDL-C, low- density lipoprotein cholesterol; MI, myocardial infarction; PCSK9I, proprotein convertase subtilisin/kexin type 9 inhibitor; QALY, quality-adjusted life year; TG, triglyceride.

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The degree to which these factors contribute in an individual patient is quite heterogeneous and we, as treating clinicians, rarely know the proportional contribution of all these factors.

Recent trials with ezetimibe or PCSK9 inhibitors added to statins suggest that the risk of ASCVD events can be lowered further with more intensive LDL-C lowering therapy.[3–5] In contrast, trials that added a fibrate or niacin to statins did not show any reduction in residual risk[6–8] and, with the exception of a single trial,[9] addition of cholesterol ester transfer protein inhibitors to statins also did not favorably affect event rates.

This review will briefly summarize the current American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety cholesterol guidelines,[10] and review the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT)[11] (published subsequent to these guidelines) in the context of other recent trials that have shown that add-on lipid-lowering therapy to statins can further reduce risk. The review will also compare conclusions drawn by other medical societies based on data from REDUCE-IT, suggest a potential decision pathway for high risk and very high risk ASCVD patients, and then close with a discussion of areas of uncertainty and potential future investigation.

Current AHA/ACC/multisociety cholesterol guidelines – recommendations for non-statin therapy.

The 2018 AHA/ACC/Multisociety Guidelines[10] recommend non-statin add-on therapy to statin therapy in selected very high risk and high risk patients to achieve additional LDL-C lowering: 15–30% additional lowering by bile acid sequestrants, 13–20% by ezetimibe, and 43–64% by PCSK9Is. Recommendations for combination therapy as presented by the 2018 guidelines are summarized in Table 1. In a departure from prior guidelines, the current guideline also makes value statements based on an assessment of cost-effectiveness. The guideline writers concluded that PCSK9Is at mid-2018 list prices had a low cost value i.e. >$150,000 per quality-adjusted life year (QALY); a good cost value was defined as <$50,000. More recent economic evaluations of statin add-on therapy are summarized later in this review.

Hypertriglyceridemia and ASCVD risk

It is estimated that about one quarter of United States adults aged 20 and over have hypertriglyceridemia, defined as a triglyceride (TG) level ≥ 150 mg/dL.[12] Prevalence rates are substantially higher among individuals who are overweight and obese even in the absence of diabetes.[13] Hypertriglyceridemia is common among individuals with poorly controlled diabetes, renal disease, other metabolic disorders, and among patients with ASCVD.[14]

Fasting and nonfasting TGs are associated with ASCVD in many, but not all prospective epidemiologic studies, and recent Mendelian randomization analyses suggest that this relationship is causal.[15,16] While it is possible that TGs directly affect the development of ASCVD (e.g. through increased free fatty acid levels at the vascular surface),[17] there is growing consensus that TGs are a marker for levels of circulating apo B-containing TG-rich lipoproteins and remnants, which in turn are causally related to atherogenesis.[16] Further support for this notion comes from a recent Mendelian randomization study that showed that genetic lipoprotein lipase variants associated with lower TG levels and LDL receptor variants associated with lower LDL-C levels had the same association with reduced coronary heart disease when standardized per unit change of apolipoprotein B.[18]

Several analyses of clinical trial populations suggest that hypertriglyceridemia remains a risk factor for future ASCVD events among statin treated patients with ASCVD.[19,20] Yet blinded randomized controlled clinical trials designed to test the hypothesis that adding a TG lowering agent (nicotinic acid or fibrate) to statin therapy would reduce ASCVD risk failed to show such a benefit.[6–8]

Table 1
Recommendations for combination lipid-lowering therapy – AHA/ACC/multisociety guideline on the management of blood cholesterol.

	Class of recommendation	Level of evidence
Clinical ASCVD		
In patients with clinical ASCVD who are judged to be **very high risk** and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe	I	B-NR
In patients with clinical ASCVD who are judged to be **very high risk** and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non–HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost	IIa	A^{SR}
In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at **very high risk** and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy	IIa	B-R
In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe	IIb	B-R
Severe hypercholesterolemia (LDL-C ≥ 190 mg/dL)		
In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, ezetimibe therapy is reasonable	IIa	B-R
In patients 20 to 75 years of age with a baseline LDL-C level ≥ 190 mg/dL (≥4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL (≤3.4 mmol/L). while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered	IIb	B-R
In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered	IIb	B-R
In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL (≥5.7 mmol/L) or higher and who achieve an on-treatment LDL-C level of 130 mg/dL (≥3.4 mmol/L) or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered	IIb	C-LD
Diabetes mellitus		
In adults with diabetes mellitus and **10-year ASCVD risk of 20%** or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C levels by 50% or more	IIb	C-LD
Primary prevention		
In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin	IIb	B-R
Adults with chronic kidney disease		
In adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.7 to 4.8 mmol/L) who are at 10-year ASCVD risk of 7.5% or higher, CKD not treated with dialysis or kidney transplantation is a risk-enhancing factor and initiation of a	IIa	B-R

Table 1 (*continued*)

	Class of recommendation	Level of evidence
moderate-intensity statin or moderate-intensity statins combined with ezetimibe can be useful		

This table summarizes recommendations for combination therapy from the AHA/ACC Multisociety Cholesterol Guideline. Recommendations are quoted from tables in Sections 4.1, 4.2, 4.3, and 4.5.4.[10]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; LDL-C, low density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; TG, triglyceride.

Approach to hypertriglyceridemia in the 2018 AHA/ACC/ multisociety guidelines

For individuals with severe hypertriglyceridemia (fasting TG ≥ 500 mg/dL and, especially, ≥1000 mg/dL), the guidelines recommend a thorough search for and treatment of secondary causes of hypertriglyceridemia, intensive lifestyle change, consumption of omega-3 fatty acids in the diet and, if necessary to prevent acute pancreatitis, fibrate therapy.[10] For individuals with moderate hypertriglyceridemia (fasting triglyceride 175–499 mg/dL), lifestyle change and management of secondary causes are the mainstay of therapy. For individuals age 40–75 years old and ASCVD risk ≥7.5%, persistently elevated TGs are considered a risk-enhancing factor favoring initiation or intensification of statin therapy to lower atherogenic lipoproteins including LDL and very low density lipoprotein particles.

REDUCE-IT

The REDUCE-IT,[11] presented and published in late 2018, was a multicenter, randomized, controlled, double-blind trial in 8179 participants who either had ASCVD (≥45 years old; 70.7% of the cohort) or had diabetes with other risk factors (≥50 years old; 29.3% of the cohort). These study participants who were already on evidence-based statin therapy with or without ezetimibe therapy (just over 30% were on high intensity statins; 6.4% were on ezetimibe) were randomized to either 2 g twice daily of icosapent ethyl (purified eicosapentaenoic ethyl ester) or 2 g twice daily of a refined mineral oil placebo. Median LDL-C was 74 mg/dL in the treatment group and 76 mg/dL in the placebo group. Baseline TG distributions were also comparable in the two groups with 10% of study subjects <150 mg/dL, 29% between 150 and < 200 mg/dL and 61% of ≥200 mg/dL, resulting in a median TG level of 216 mg/dL. The primary composite end point included cardiovascular disease death, nonfatal myocardial infarction (MI), non-fatal stroke, coronary revascularization, or unstable angina; the key secondary end point was a composite of cardiovascular disease death, nonfatal MI or nonfatal stroke. Participants were followed for a median of 4.9 years.

A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, compared to 22.0% of the patients in the placebo group (hazard ratio (HR), 0.75; 95% confidence interval [CI], 0.68–0.83; $P < .001$). The high event rate in the placebo group indicates that the patients enrolled in REDUCE-IT were on average at very high ASCVD risk, about 4% per year. The absolute risk reduction of 4.8% translated to a number needed to treat of 21 (95% CI 15–33) over 4.9 years. There was a similarly significant reduction in the key secondary end point from 14.8% to 11.2% (absolute risk reduction 3.6%, HR, 0.74; 95% CI, 0.65–0.83; $P < .001$), translating to a number needed to treat of 28 (95% CI 20–47). Icosapent ethyl therapy reduced cardiovascular disease death by 20%, but did not reduce total mortality. Treatment benefits were seen across all pre-specified subgroups defined by demographics, clinical characteristics, intensity of statin therapy or laboratory parameters.

In the primary endpoint paper, the REDUCE-IT investigators stratified by baseline TG level of 150 mg/dL (original entry criterion) and 200 mg/dL (entry criterion in the revised protocol) and reported that there were no significant interactions of treatment effect by baseline TG level. Similarly, there was no interaction by achieved TG level at 1 year.[11] In a subsequent research letter, the authors investigated treatment effects across TG tertiles for time to primary endpoint and for total primary endpoint events.[21] Cross-tertile interaction *p*-values were again non-significant. When examining absolute risk, the investigators observed an interaction *p* value of 0.12 for first events and of 0.03 for total events, with greater absolute benefit in the top tertile of the TG distribution, i.e. the tertile with the highest baseline ASCVD risk. The authors concluded that the effect of icosapent ethyl was "tied primarily to baseline risk and non-TG-related effects".[21] Using estimates of TG-associated risk derived from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE-IT) trial, a recent editorial estimated that the TG lowering achieved with icosapent ethyl observed in REDUCE-IT explained <25% of the observed benefit.[22] Potential pleiotropic mechanisms include improvement in endothelial function, reduced inflammation, greater functionality of high density lipoprotein particles and suppression of platelet aggregability through inhibition of thrombin generation.[22,23] A beneficial effect on ventricular arrhythmias through increase in eicosapentaenoic acid (EPA) incorporation into membranes is also possible and may explain the observed reduction in cardiac arrest and sudden cardiac death.[11]

Treatment with icosapent ethyl was well tolerated overall with comparable treatment emergent adverse event rates in the two treatment arms.[11] Gastrointestinal symptoms were common in both groups with greater rates of diarrhea in the mineral oil placebo group (11.1% vs 9%) and greater constipation in the icosapent ethyl group (5.4 vs 3.6%). Bleeding related disorders were numerically more common in the icosapent ethyl group (2.7% vs 2.1%), but the difference was not statistically significant ($p = .06$). Of concern was a higher frequency of atrial fibrillation (AF) (5.3% vs 3.9%, $p < .001$) and adjudicated hospitalized AF (3.1 vs 2.1%, $p = .004$) in the icosapent ethyl group compared to the placebo group. In contrast, sudden cardiac death (1.5% vs 2.1%, HR 0.69, 95% CI 0.50–0.96) and cardiac arrest (0.5% vs 1.0%, HR 0.52, 95% CI 0.31–0.86) were significantly less common in the icosapent ethyl group. Edema was more common in the icospent ethyl group, but adjudicated heart failure was comparable in the two groups.

Concerns have been raised about the impact of the mineral oil placebo.[24] Mineral oil is believed to be metabolically inert due to lack of carboxyl groups. At higher doses, mineral oil is a laxative, available without prescription in the United States. These laxative properties even at the lower dose used in REDUCE-IT may explain the greater frequency of diarrhea in the placebo group.[11] Statin malabsorption, one possible mechanism by which mineral oil could adversely affect ASCVD risk, is not believed to have had a significant impact on ASCVD outcomes – in a post-hoc analysis of REDUCE-IT, benefits of icosapent ethyl were similar regardless of whether LDL-C increased during the trial.[11] It is less clear whether differential changes in high sensitivity C-reactive protein (hs-CRP) in the two treatment groups influenced the trial results. Baseline hs-CRP levels were comparable in the two groups (median 2.2 mg/L in the icosapent-ethyl group and 2.1 mg/L in the placebo group), but corresponding median on-trial levels were 1.8 mg/L in the icosapent ethyl group and 2.8 mg/L in the placebo group. It is unknown whether mineral oil supplementation results in hs-CRP elevation – hs-CRP was not measured in prior trials that used a mineral oil placebo compared to icosapent ethyl.[25–27] Data from several clinical trials of ASCVD prevention suggest that higher on-treatment hs-CRP levels are associated with higher ASCVD event rates.[28,29] It is thus possible, that a similar increase in event rates in the placebo group in REDUCE-IT may have inflated the apparent benefit of icosapent-ethyl.

Estimating the generalizability of clinical trial results is important. Picard et al. analyzed data from the ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY) registry from 45 countries to determine how many participants would have qualified for REDUCE-IT.[30] Only 15.5% met REDUCE-IT inclusion

criteria. However, given a prevalence of 16.5 million individuals with coronary artery disease in the United States (National Health and Nutrition Survey 2011–2014), the actual number of eligible patients would be substantial. Jia et al. found 14.5% eligibility among ASCVD patients and 17.1% eligibility among patients with diabetes in the Veterans Administration database, but suggested that actual eligibility would be somewhat lower, if all patients had been on statins of appropriate intensity.[31] Lan and colleagues evaluated a "real-world" cohort of patients with diabetes and acute coronary syndrome in Australia and found that 17.1% would have met REDUCE-IT eligibility criteria.[32]

REDUCE-IT results are consistent with findings from the Japan EPA lipid intervention study (JELIS) published in 2007.[33] This open label study included both primary and secondary prevention patients, randomized to 1.8 g daily of EPA with statin compared to statin only. Event rates were lower in JELIS than in REDUCE-IT: the primary endpoint of major coronary events occurred in 3.5% of controls overall, 1.7% among primary prevention patients, 10.7% among secondary prevention patients. Over a mean follow-up of 4.6 years, there was a statistically significant 19% relative risk reduction and 0.7% absolute risk reduction in the primary endpoint of major coronary events overall, primarily driven by a reduction in angina; subgroup analyses showed benefit in primary and secondary prevention patients, but only the latter was statistically significant. Patients in JELIS were quite different from those enrolled in REDUCE-IT: LDL-C was substantially higher (mean 182 mg/dL), TGs lower (median 154 mg/dL) and high- density lipoprotein cholesterol (HDL-C) higher (mean 58 mg/dL). Saito et al. subsequently analyzed outcomes in JELIS by TG/HDL-C subgroup.[34] Individuals with TGs ≥ 160 mg/dL and HDL-C < 40 mg/dL had the highest event rate (3.3% over 5 years) and the greatest benefit from EPA: an absolute 1.9% risk reduction and a 53% relative risk reduction after adjustment for age, sex, smoking, diabetes and hypertension (HR 0.47, 95% CI 0.23–0.98).

Marston and colleagues[35] summarized data from 24 TG-lowering randomized controlled trials in a systematic review and meta-regression analysis (9 fibrate trials, 3 niacin trials and 13 omega-3 fatty acid trials) together with data from 25 statin trials. Risk reduction was similar per 1 mmol of non-HDL-C reduction for fibrates, niacin and statins, but more pronounced for omega-3 fatty acids; this apparent difference was markedly attenuated when REDUCE-IT was removed from the analysis, suggesting that REDUCE-IT is an outlier. Findings were similar when LDL-C reduction and TG reduction were modeled jointly: the risk ratio changed from 0.84 per 1 mmol/L TG reduction with REDUCE-IT included to 0.91 per 1 mmol/L TG reduction when REDUCE-IT was excluded from the analysis. Meta-regressions by type of omega-3 fatty acid suggested a strong dose dependency with greater effect at higher doses for EPA (7% lower relative risk for each 1 g/day of EPA), while a 1 g/day dose of docosahexaenoic acid (DHA) was associated with a non-significant 4% lower risk of major CVD events.

More data are needed to better understand the mechanism of action of icosapent ethyl, the potential impact of the mineral oil placebo, and to determine whether benefits seen in REDUCE-IT are confined to this specific compound or can be reproduced with other omega-3 fatty acid preparations. While the Vitamin D and Omega-3 Trial (VITAL), a recent primary prevention study in a population with low absolute risk of ASCVD events, saw no reduction in the primary ASCVD endpoint among participants treated with a combination of 460 mg of EPA and 380 mg of DHA, the investigators observed a statistically significant 28% reduction in MI (absolute risk reduction: 0.32%).[36] Whether a combination of EPA and DHA would benefit a contemporary population at high or very high ASCVD risk is unknown. One such compound, Epanova (a combination product of EPA and DHA as omega-3 carboxylic acids), is currently under evaluation in the STRENGTH trial (A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia).[37] This trial is scheduled to complete in September 2020 (clinicaltrials.gov, accessed 9/29/2019).

Guidelines after publication of REDUCE-IT

The European Society of Cardiology Dyslipidemia Guidelines issued in 2019 limit drug therapy of elevated TGs to high-risk patients with hypertriglyceridemia despite lifestyle measures.[38] Statin treatment received a Class I—B indication for ASCVD risk reduction in high risk patients with hypertriglyceridemia. In high risk patients with TG levels mirroring the entry criteria for REDUCE-IT (135–499 mg/dL despite statin therapy), addition of icosapent ethyl at 2 g twice daily received a Class IIa-B recommendation. Addition of fibrates added to statins in primary prevention patients and high risk patients at LDL-C goal, but with TGs over 200 mg/dL, is a IIb recommendation.

The American Diabetes Association updated its Standards of Care in March 2019 based on the results of REDUCE-IT. For patients with diabetes and ASCVD or other ASCVD risk factors on a statin with controlled LDL-C, but with elevated TG(135–499 mg/dL, mirroring the entry criteria for REDUCE-IT), there is now a recommendation to consider icosapent ethyl to reduce ASCVD risk [https://www.diabetes.org/newsroom/press-releases/2019/ada-issues-critical-updates-to-2019-standards-of-care; accessed 9/24/2019].

The full National Lipid Association Statement on the Use of Icosapent Ethyl is not in print at the time of this writing. The single slide available on the National Lipid Association website (https://www.lipid.org/communications/news-stories; accessed 9/23/2019), recommends icosapent ethyl therapy for patients similar to the REDUCE-IT patients with a Class I-B-R recommendation.

Clinical implications

Across current guidelines, there is general consensus that combination lipid-lowering therapy is appropriate for individuals at very high risk and selected individuals at high risk. It is less clear which add-on option is best for which patient. We currently have 3 interventions with randomized placebo-controlled clinical trial-documented event reduction when added to statin therapy: statin plus ezetimibe,[3] statin plus PCSK9I (either evolocumab or alirocumab),[4,5] or statin and icosapent ethyl.[11] So how are we going to choose among these interventions?

A potential approach to the high risk or very high risk ASCVD patient is shown in Fig. 1, to be implemented in the context of shared decision making. Both lipid and non-lipid risk factors deserve attention. Management of the non-lipid risk factors is beyond the scope of the current paper, so not fleshed out further. Unless there are contra-indications, high risk and very high risk ASCVD patients should be on a high intensity or maximally tolerated statin. If the LDL-C remains above 100 mg/dL on this therapy, ezetimibe is less likely than a PCSK9I to reduce LDL-C to <70 mg/dL and a subgroup analysis of the ODYSSEY OUTCOMES trial suggests particular benefit of PCSK9Is in this group.[4] Addition of PCSK9I therapy as the next step seems reasonable. If the LDL-C is between 70 mg/dL and 100 mg/dL, a significant proportion of patients will achieve an LDL-C below 70 mg/dL after ezetimibe addition. An initial prescription of ezetimibe is thus reasonable, followed by PCSK9I therapy, if the LDL-C remains above 70 mg/dL. For very high risk patients, immediate addition of PCSK9I therapy is also reasonable. If LDL-C is below 70 mg/dL on a high intensity statin or maximally tolerated statin, TG levels will determine the next step. If the TG level matches the entry criteria for REDUCE-IT, then addition of icosapent ethyl is reasonable.

Only REDUCE-IT included patients at high risk, but without ASCVD. Thus any patient with type II diabetes requiring medications who is 50 years or older and has at least one additional risk factor would be eligible for icosapent ethyl therapy added to the statin.[11] Among patients with diabetes and CKD, combination therapy with statin and ezetimibe is also a consideration given 22% ASCVD reduction with simvastatin/ezetimibe compared to placebo in the Study of Heart and Renal Protection (SHARP).[39]

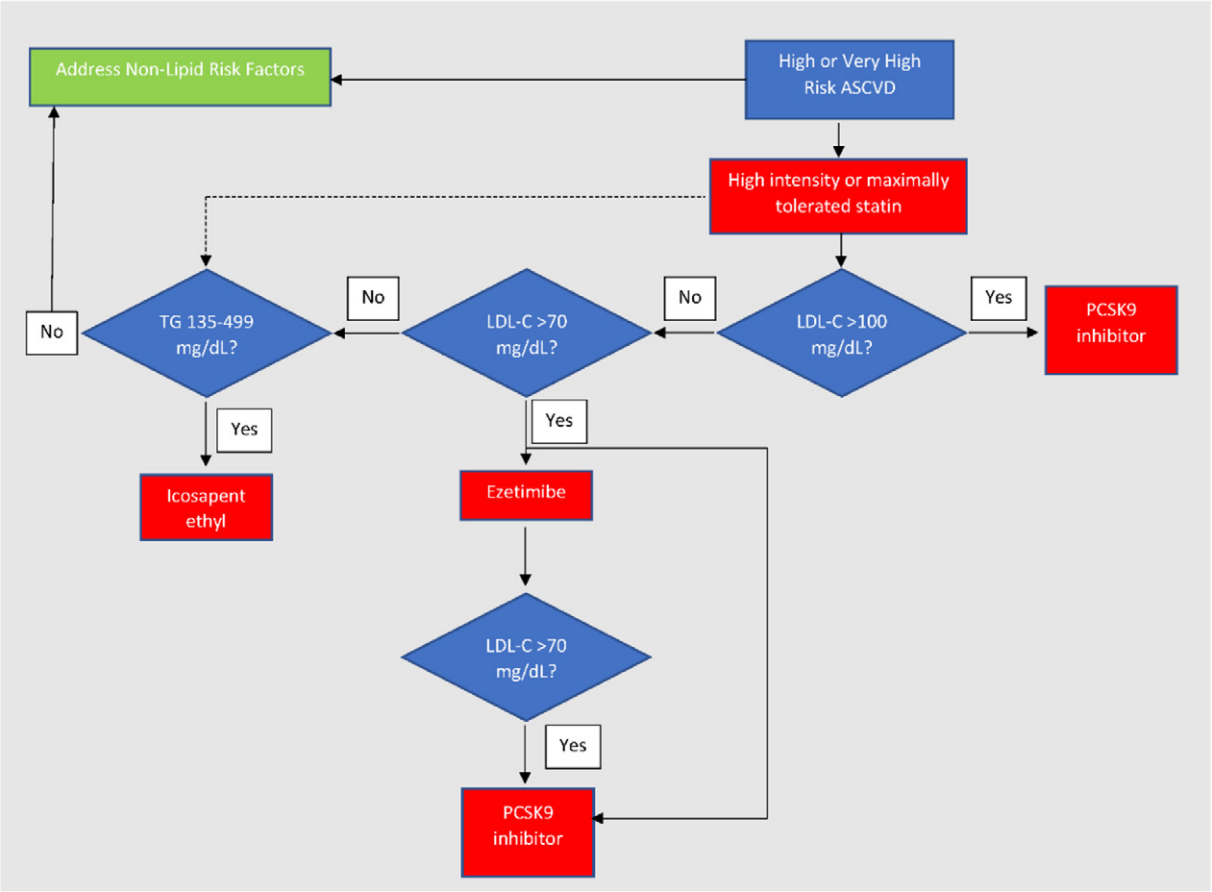

Fig. 1. Approach to the high risk or very high risk ASCVD patient. The figure shows a potential decision pathway for combination lipid-lowering therapy among high risk or very high risk ASCVD patients. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low density lipoprotein cholesterol; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; TG, triglyceride.

Outcomes trials to date have not raised any significant safety concerns for ezetimibe or currently available PCSK9Is, but follow-up has been short for the latter. We do not know whether the increased risk of AF among icosapent ethyl treated patients is causal or a chance finding and we do not have any predictors to identify increased susceptibility to AF in this cohort. At this time, it is thus not possible to quantify this risk for individual patients to further guide our decision making when choosing add-on lipid-lowering therapy in statin treated patients.

What about cost?

The Institute for Economic Review and Analysis (ICER) has performed several cost effectiveness analyses for PCSK9Is and, recently, for icosapent-ethyl. For icosapent ethyl, the cost per QALY gained was estimated at $18,000 and the cost per major adverse cardiovascular event avoided at $53,000.[40] This compares quite favorably to alirocumab and evolocumab used in unselected ASCVD patients, which remain well above $150,000 per QALY even after substantial price reductions over the last year.[41,42] Using the lowest available retail cost of ezetimibe in 2016 and data from IMPROVE-IT, Almalki et al. estimated the cost per QALY for ezetimibe add-on therapy at approximately $114,000 per QALY.[43]

Future directions

The current review is confined to optimizing lipid-lowering strategies among patients at high and very high risk. But residual risk, as stated in the introduction, is not confined to residual lipid risk. We now have evidence that anticoagulation on top of "standard of care" may benefit individuals with ASCVD (e.g. the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial[44]), we have evidence from several large clinical trials that novel agents used for the treatment of diabetes further improve ASCVD outcomes,[45] and, while not clinically available at this time, anti-inflammatory agents, such as canakinumab which showed benefit in the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)[46] may be in our armamentarium in the future. Randomized controlled clinical trials to test all possible permutations of therapies which individually improve prognosis cannot be performed. Whether sophisticated analyses of large databases culled from electronic health records or complex simulation studies could provide additional insights on benefits and risks of complex multi-drug therapy for primary and secondary prevention for individual patients is currently unknown. Pill burden and direct costs to the patient add additional complexity to the decision making. Even under the assumption that we can derive sound and evidence-based recommendations from novel analyses, how do we communicate such complex data to our patients in the process of shared decision making? Much work needs to be done before we can hope to optimize ASCVD risk for individual patients with a precision medicine approach.

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Dr. Bittner serves on the Executive Steering Committee of the ODYSSEY OUTCOMES trial (Sanofi) and as National Coordinator for

STRENGTH (Astra Zeneca), DalGene (Dalcor), CLEAR (Esperion), all contracted through the University of Alabama at Birmingham. She has served as site principal investigator for ARTEMIS (Astra Zeneca) and COMPASS (Bayer Healthcare) and is currently site principal investigator for the ORION IV Trial (The Medicines Company), all contracted through the University of Alabama at Birmingham. She has served as a consultant for Sanofi.

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