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Icosapent ethyl: Where will it fit into guideline-based medical therapy for high risk atherosclerotic cardiovascular disease? ☆

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ABSTRACT

Patients who are at high or very high risk for atherosclerotic cardiovascular disease (ASCVD) events derive the greatest benefit when clinicians prescribe evidence-based preventive therapies. The writing process used in the creation of the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol employed a thorough evaluation of the highest quality evidence, and synthesis of this evidence into actionable recommendations for ASCVD risk reduction. Clinical trials supporting the addition of ezetimibe, PCSK9 inhibitors, or both to evidence-based statins provide the basis for the updated recommendations for the preventive care of these patients. The publication in late 2018 of a randomized controlled trial supporting the net ASCVD risk reduction benefit of adding icosapent ethyl to statins in selected hypertriglyceridemic patients with clinical ASCVD and/or type 2 diabetes with multiple additional risk markers provides the rationale for incorporation of icosapent ethyl therapy into future ASCVD preventive care regimens.

Introduction

Guideline-based medical therapy is considered the gold standard for the provision of preventive therapy for patients with, or at risk for atherosclerotic cardiovascular disease (ASCVD). Patients at high and very high risk benefit from the receipt of therapies supported by high-quality evidence. The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol [1] (the 2018 Guideline) updated the evidence base used in the 2013 ACC/AHA Cholesterol Guideline [2] to make more contemporary recommendations for the preventive care of these patients. This article reviews the evidence supporting the 2018 Guideline's new management recommendations for high- or very-high risk patients with clinical ASCVD or primary severe hypercholesterolemia, examines the potential role of long-chain omega 3 marine fatty acids for ASCVD risk reduction, and discusses the results of a randomized controlled trial (RCT), published after closure of the evidence review for the Guideline, supporting the use of icosapent ethyl in preventive therapy for selected high-risk hypertriglceridemic patients. The results of this study will require future lipid guideline writers to consider an expansion of current recommendations to provide optimal preventive care for these patients.

Guideline recommendations for patients with clinical ASCVD

The 2018 Guideline definition of clinical atherosclerotic cardiovascular disease (ASCVD) includes patients with acute coronary syndrome and those with history of myocardial infarction, stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease including aortic aneurysm, all of atherosclerotic origin. The Guideline separates individuals with ASCVD into very high versus high risk categories. Very high risk individuals are defined as having a history of two major ASCVD events or one major ASCVD event and two or more high risk conditions. Major ASCVD events and high risk conditions are defined in Fig. 1. High risk ASCVD is defined as clinical ASCVD in patients who do not meet the criteria for very high risk categorization.

Because moderate- or high-intensity statin therapy has been demonstrated to be associated with ASCVD risk reduction [3], the Guideline advises that the clinician-patient discussion in such patients begin with an explanation of the anticipated benefits versus potential adverse effects of statin therapy, reassurance that benefits greatly outweigh the risks, and affirmation that long term adherence to therapy is associated with the best results [4]. It

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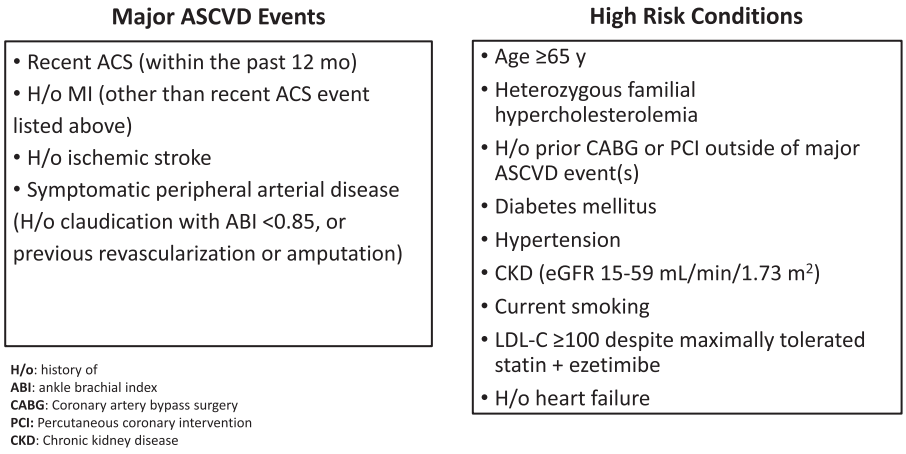

Fig. 1. Very high risk ASCVD: 2 or more major events or 1 major event and ≥2 high risk conditions.

recommends the concomitant initiation of lifestyle therapy, and for those who are 75 years of age or younger, the prescription of high-intensity statins, including atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg daily. The lipoprotein-reducing objective of high-intensity therapy is to achieve a ≥50% reduction from baseline LDL-C levels.

For those not able to tolerate a high-intensity statin, a moderate-intensity statin should be initiated with a goal of achieving a 30–49% reduction. For patients older than 75 years of age, initiation of moderate or high-intensity statins, or continuation of such therapy is reasonable after evaluation of the potential for ASCVD risk reduction, adverse effects, drug-drug interactions, patient frailty and patient preferences.

The 2013 Guideline provided no recommendation for lipid-lowering preventive therapy in patients with heart failure. Since the publication of that guideline, a patient-level meta-analysis of two trials of statin therapy in heart failure, neither of which met its primary endpoint [5,6], showed that when accounting for competing causes of death [7], rosuvastatin therapy was associated with a small, but statistically significantly reduced risk of myocardial infarction in those with less severe heart failure. Based on this result, the 2018 Guideline suggests that in patients with coronary artery disease, reduced ejection fraction, less severe heart failure and a 3–5 year life expectancy, the initiation of moderate-intensity statin therapy may be considered.

Based upon the publication of randomized controlled trials supporting the net ASCVD risk reduction benefit of adding ezetimibe [8] and the PCSK9 inhibitors evolocumab [9] and alirocumab [10] to evidence-based statin therapy, the Guideline authors support consideration of these agents in selected high or very high risk individuals 75 years of age or younger taking maximal tolerated statins. Ezetimibe treatment is deemed reasonable as additive therapy in very-high risk patients who have an LDL-C ≥ 70 mg/dL, and may be considered in high-risk patients with a similar LDL-C level.

Ezetimibe is recommended as the initial add-on agent to statins in those very-high risk patients being considered for treatment with a PCSK9 inhibitor. For those with an LDL-C ≥ 70 mg/d or non-HDL-C ≥ 100 mg/dL despite maximal tolerated statin and ezetimibe, it is reasonable to add a PCSK9 inhibitor following a clinician-patient discussion about net-benefit, safety and cost. In view of an estimated cost-value of >$150,000 per quality-adjusted life year at mid-2018 prices at the time of the evidence review for the Guideline, PCSK9 inhibitors were deemed low economic value therapeutic agents [11]. PCSK9 inhibitor retail price reductions reported since the publication of the 2018 Guideline may alter cost value estimates for the use of these agents [12].

The strength of recommendations and levels of evidence employed in the Guideline is summarized in Fig. 2. A summary of the management recommendations for patients with clinical ASCVD is provided in Fig. 3.

Guideline recommendations for patients with primary severe hypercholesterolemia (LDL-C ≥ 190 mg/dL)

Patients with LDL-C ≥ 190 mg/dL should first have a repeat lipid panel for confirmation and then undergo testing to exclude secondary metabolic causes, including hypothyroidism, chronic kidney disease and obstructive liver disease. When present, these disorders should be addressed. Those with primary severe hypercholesterolemia are at high or very high risk of clinical ASCVD [13]. A study using individual pooled data from 6 large US epidemiological cohorts showed that those with LDL-C ≥ 190 mg/dL had a 30 year hazard ratio of up to 5.0 for coronary heart disease and of up to 4.1 for total ASCVD as compared to those with LDL-C < 130 mg/dL [14]. Those with clinical or molecularly-confirmed familial hypercholesterolemia harbor a particularly high risk for premature and recurrent coronary events, due to a lifetime exposure of the endothelium to high circulating LDL-C levels [15,16].

No RCT's of statin therapy have been done in populations of patients enrolled whose enrollment was limited exclusively to those with LDL-C greater than or equal to 190 mg/dL. However, a large RCT of Scottish primary and secondary prevention patients with a mean entry LDL-C of 192 ± 17 mg/dL [17], and a subsequent post-hoc analysis of 2560 exclusively primary prevention patients in the original trial [18] demonstrated a reduced incidence of myocardial infarction and cardiovascular death in those who received pravastatin 40 mg daily versus placebo. Retrospective cohort studies of patients who meet clinical criteria for familial hypercholesterolemia have shown that statin therapy reduces the risk for clinical coronary heart disease [19,20] and coronary heart disease mortality [20].

The 2018 Guideline recommends that for patients with severe hypercholesterolemia, the initial goal is to achieve a ≥50% LDL-C reduction from baseline LDL-C using a high-intensity statin, or the maximal tolerated statin intensity. When less-than-anticipated LDL-C lowering is encountered, and LDL-C remains >100 mg/dL, a level at which an increased odds of clinical ASCVD is encountered in patients with familial hypercholesterolemia [21], the addition of a second LDL-C lowering drug is reasonable. A randomized controlled trial of 720 patients with familial hypercholesterolemia treated with moderate-intensity statin plus ezetimibe vs. placebo showed greater LDL-C lowering with

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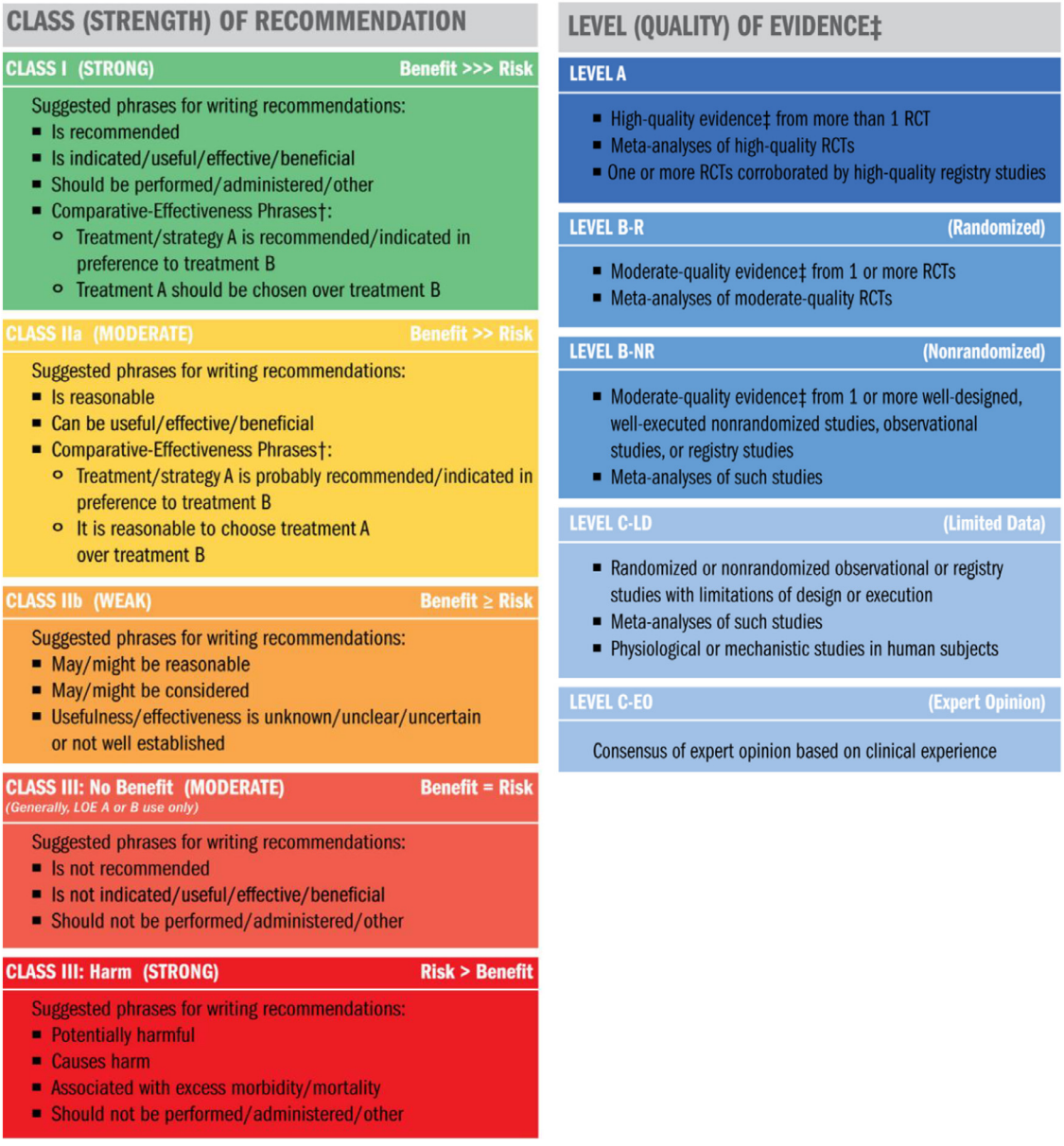

Fig. 2. ACC/AHA recommendation system.

Patient characteristics	Statin intensity	Ezetimibe	PCSK9 inhibitor
Clinical ASCVD ≤ age 75 years	Hi or max. tolerated (IA)	Reasonable if LDL-C ≥ 70 mg/dL (IIb B-R)	No recommendation
Very high risk ASCVD ≤ age 75 years	Hi or max. tolerated (IA)	Reasonable if LDL-C ≥ 70 mg/dL (IIa B-R)	Reasonable if LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL on max. tolerateed statin and ezetimibe (IIa, A)
ASCVD >75 years	Reasonable to use moderate, or high if tolerated (IIa B-R)	No recommendation	No recommendation
ASCVD with heart failure >3-5 yr. life expectancy	May be reasonable to use moderate (IIb B-R)	No recommendation	No recommendation

Fig. 3. Management of high or very high risk ASCVD.

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Patient characteristics	Statin intensity	Ezetimibe	PCSK9 inhibitor	Bile acid sequestrant
Severe 1º hypercholesterrolemia	Age 20-75 years: Hi or max. tolerated (I B-R)	Age 20-75 years: Reasonable if <50% LDL -C↓ and/or LDL-C ≥100 mg/dL (IIa B-R)	Age 40-75 years: May be reasonable if baseline LDL-C ≥ 220 mg/dL and on-treatment LDL-C ≥ 130 mg/dL on max. tolerated statin and ezetimibe (IIb C-LD)	Age 20-75 years: May be reasonable if <50% LDL-C ↓ from baseline and TG ≤300 on max. tolerated statin and ezetimibe (IIb B-R)
Heterozygous FH, age 30-75 years	Hi or max tolerated	If <50% LDL-C and/or LDL-C ≥ 100 mg/dL	May be reasonable if LDL-C ≥ 100 mg/dl on max. tolerated statin and ezetimibe (IIb B-R)	No recommendation

Fig. 4. Management of severe primary hypercholesterolemia.

combination therapy than with statin monotherapy and that ezetimibe was well-tolerated [22]. As the addition of ezetimibe to a moderate-intensity statin in adults who have suffered a recent acute coronary syndrome was associated with greater ASCVD risk reduction than statin monotherapy [8], and as ezetimibe is well tolerated and available as a generic drug, the addition of this drug is reasonable in those with severe hypercholesterolemia whose LDL-C remains ≥100 mg/dL despite maximal tolerated statin therapy.

For patients with severe primary hypercholesterolemia and LDL-C ≥ 100 mg/dL despite maximal tolerated statins and ezetimibe, two additional drug therapy options, bile acid sequestrants and PCSK9 inhibitors are available. There are limited safety and efficacy data on the use of bile acid sequestrants in these patients, although a Mendelian randomization analysis [23] as well as a small, placebo controlled RCT in patients meeting clinical or genetic criteria for heterozygous familial hypercholesterolemia and receiving maximal tolerated statin and ezetimibe showed that the addition of colesevelam 3.75 g daily was well-tolerated and associated with an additional 18.5% reduction over 12 weeks [24]. The use of generic bile acid sequestrants is limited by gastrointestinal side effects, inconvenient dosing, the absence of well-tolerated generic formulations and drug interactions.

PCSK9 inhibitors have been studied in patients with familial hypercholesterolemia. Safety and efficacy RCT's of the PCSK9 inhibitors, evolocumab [25] and alirocumab [26] administered to patients with genetic and/or clinical criteria for heterozygous familial hypercholesterolemia who are taking stable doses of statins, with or without concomitant additional lipid lowering therapy, showed that treatment with these agents results in a ≥50% additional LDL-C reduction and is well tolerated. A large registry of 2404 Spanish patients with molecularly defined heterozygous FH demonstrated, in multivariate analysis, that the hazard ratio for incident ASCVD is higher in patients >30 years of age as compared to those who are younger and in patients with LDL-C ≥ 100 mg/dL as compared to those with higher LDL-C values [21]. The 2018 Guideline states that the addition of either evolocumab or alirocumab to the medical regimen of heterozygous familial hypercholesterolemia patients, 30–75 years of age, taking maximal tolerated statin and ezetimibe with an LDL-C ≥ 100 mg/dL may be reasonable. As a corollary, those with severe primary hypercholesterolemia who do not meet the criteria for familial hypercholesterolemia, but have a baseline LDL-C ≥ 220 mg/dL and an LDL-C ≥ 130 mg/dL while taking maximal tolerated statin and ezetimibe, may be considered for the addition of a PCSK9 inhibitor. The management recommendations of the 2018 Guideline for patients with severe primary hypercholesterolemia are summarized in Fig. 4.

Hypertriglyceridemia, triglyceride-lowering therapy and ASCVD risk

Observational epidemiological studies have demonstrated that moderate fasting or non-fasting hypertriglyceridemia (175–499 mg/dL) is associated with increased ASCVD risk [27–29]. The increased risk, supported by Mendelian randomization and genome-wide association studies, is likely mediated via the unregulated delivery to arterial wall macrophages of cholesterol transported via triglyceride-rich remnant particles [30] in the setting of a pro-inflammatory, pro-thrombotic milieu [31]. The 2018 Guideline identifies moderate hypertriglyceridemia as "risk-enhancing factor" in the clinician-patient risk discussion, favoring the initiation or intensification of statin therapy.

An apolipoprotein that resides on the surface of triglyceride-rich lipoproteins, apolipoprotein C3, inhibits lipoprotein lipase-mediated lipolysis of triglyceride-rich lipoproteins, raising circulating triglyceride levels. Exome sequencing studies of individuals of European or African American descent have identified mutations in the gene encoding apolipoprotein C3, APOC3, and determined that heterozygous carriers of one of 4 loss-of-function mutations had circulating triglyceride levels that were 39% lower than non-carriers. Coronary heart disease risk was 40% lower in those with any of 4 APOC3 mutations than in non-carriers [32]. Despite these observations, RCT's of triglyceride-lowering treatments, including niacin [33,34] and fibrates [35], have not achieved their primary endpoints of ASCVD risk reduction.

The potential role of long-chain marine omega 3 fatty acids for ASCVD risk reduction

Over the counter omega-3 fatty acid supplements have been widely used with the hope that they can reduce the risk of clinical ASCVD. However, a meta-analysis of 10 trials involving 77,917 individuals treated with low-dose mixtures of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) demonstrated no effect on the risk of coronary heart disease, stroke, coronary or non-coronary revascularization or any major vascular event [36]. In addition, two large recent ASCVD outcomes RCT of low dose EPA and DHA, one of 15,480 type 2 diabetics without clinical ASCVD treated with 840 mg/day of omega 3 fatty acids versus an olive oil placebo [37], and the other of 25,871 apparently healthy primary prevention patients treated with 840 mg/day of omega 3 fatty acids with and without vitamin D supplementation [38], did not meet their primary endpoints of ASCVD risk reduction. Although high-dose prescription omega 3 fatty acids are U.S. Food and Drug Administration approved options for triglyceride lowering therapy for patients with plasma triglycerides ≥500 mg/dL to reduce the

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risk of pancreatitis, none has received approval for ASCVD risk reduction.

The Japan EPA Lipid Intervention Study (JELIS) was the first large study to assess the effects of EPA monotherapy on the risk for ASCVD events [39]. The physiologic rationale for considering the use of EPA monotherapy as opposed to a combination product containing EPA and DHA is that EPA is less likely to raise circulating LDL-C concentration, may have beneficial effects on platelet function, cholesterol crystalline domains and membrane bilayer structure [40,41].

JELIS was a randomized open-label study that enrolled 18,645 Japanese primary and secondary prevention patients, with a mean entry LDL-C level of 183 mg/dL and triglycerides 151 mg/dL, in which subjects were allocated to receive low intensity statin monotherapy (96–97% received simvastatin 5 mg or pravastatin 10 mg daily) versus low intensity statin plus EPA 1800 mg daily. The mean follow-up was 4.6 years. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. Therapy with statin plus EPA was associated with a 25% reduction in LDL-C in both groups, a 9% reduction in triglycerides in the EPA group and 4% triglyceride reduction in the control group. Among those receiving statin plus EPA, there was a statistically significant 19% reduction ($p = 0.011$) in the primary endpoint (2.8% versus 3.5%) as compared to the statin monotherapy group. Important limitations of this study included the use of an open-label interventional design, which could have affected physician-initiated endpoints such as coronary revascularization and hospitalization for unstable angina; the absence of a true placebo group; and a study size that was underpowered for subgroup analysis.

Results of an ASCVD outcomes randomized controlled trial employing icosapent ethyl

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) was a multicenter, randomized, double-blind, placebo-controlled trial of 8179 subjects with established cardiovascular disease or with diabetes and other risk factors, and was done to determine whether the addition of this highly purified and stable formulation of eicosapentaenoic ethyl ester could safely provide net ASCVD risk reduction benefit in patients already receiving evidence-based statin therapy [42]. Study subjects were men and women with established clinical ASCVD $\geq$ 45 years of age (secondary prevention cohort [70.7% of those enrolled]) or diabetics $\geq$50 years of age requiring medication for their diabetes, with additional risk factors (primary prevention cohort [29.3% of those enrolled]) on a stable dose of statin $\pm$ ezetimibe for at least 4 weeks, with fasting triglyceride levels of 135 to 499 mg and a median baseline level of 216 mg per deciliter. Study subjects were required to have low-density lipoprotein cholesterol levels of 41–100 mg per deciliter and had a median level of 75 mg/dL. Approximately 93% of subjects were receiving moderate- or high-intensity statin therapy. The patients were randomized to receive 2 g of icosapent ethyl twice daily or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina and the key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The median follow-up was 4.9 years.

A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, versus 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68–0.83; $P < 0.001$), representing a relative risk reduction of 24.8%, an absolute risk reduction of 4.8% and a number needed to treat of 21 (95% CI 15–33), $P = 0.00000001$. A key secondary end point was reported in 11.2% of those taking icosapent ethyl vs. 14.8% in those in the placebo group (hazard ratio, 0.74; 95% CI, 0.65–0.83; $P < 0.001$), representing a relative risk reduction of 26.5%, an absolute risk reduction of 3.6%, and a number needed to treat of 28 (95% CI 20–47), $P = 0.0000006$. With the exception of total mortality, all pre-specified individual endpoints were met in those taking icosapent ethyl.

Icosapent ethyl was generally well-tolerated. Treatment emergent adverse events occurred at similar rates in the icosapent ethyl and placebo groups. There was a trend toward more bleeding-related disorders in the icosapent ethyl group, but this did not reach statistical significance. There was more peripheral edema (6.5 vs 5.0, $P = 0.002$), constipation (5.4% vs. 3.6%, $P < 0.001$), atrial fibrillation (5.3 vs. 3.9%, $P = 0.003$) and atrial fibrillation requiring hospitalization (3.1% vs 2.1%, $P = 0.004$) with icosapent ethyl than placebo.

The explanation for the highly beneficial observed outcomes is unclear. The relatively modest effects on blood lipids and lipoproteins (triglyceride reduction 19.7% from baseline ($P < 0.0001$), non-HDL-C reduction 13.1% ($P < 0.0001$), LDL-C reduction −6.6% ($p \leq 0.0001$) and apolipoprotein B 9.7% reduction) appears insufficient to explain the magnitude of the observed benefit. It is unlikely that the benefit was a function of baseline triglyceride levels, as reduction in risk of achieving either the primary or secondary efficacy composite endpoint was the same in those with baseline triglycerides $\geq$200 mg/dL and those with values $<$150 mg/dL. There was a 39.9% reduction in hs-CRP ($p < 0.0001$) consistent with an anti-inflammatory effect. There was a 358% increase in the concentration of EPA ($P < 0.0001$) and a statistically significant reduction in cardiac arrest (0.5 vs 1.0%, (hazard ratio 0.52, 95% CI 0.31–0.86) and in sudden cardiac death (1.5% vs 2.1% (hazard ratio 0.69, 95% CI 0.50–0.96), suggesting the possibility of an EPA-related anti-arrhythmic or membrane stabilizing effect.

Synthesis of the evidence on treatment of high and very high risk patients

Using data on 10-year ASCVD risk derived from randomized controlled trials, patients with uncomplicated coronary heart disease (with no diabetes, chronic kidney disease, cigarette smoking, severe hypercholesterolemia or metabolic syndrome) or uncomplicated stroke or TIA, or symptomatic peripheral arterial disease have an approximate 20–29% 10-year risk of clinical ASCVD events. Those with complicated ASCVD (ASCVD plus diabetes or chronic kidney disease or poorly controlled risk factors, or those with a recent acute coronary syndrome) have a 10-year risk estimated to be 30–39%. Those with the highest-risk ASCVD (ASCVD plus familial hypercholesterolemia or peripheral arterial disease; or recurrent ASCVD events) likely have a 10-year risk $>$40%. Individuals with heterozygous familial hypercholesterolemia between the ages of 40 and 80 have a 10-year risk of 20–40% [13,43]. All such patients are considered to be at high or very high ASCVD risk according the 2018 Guideline. Based on the 2018 Guideline evidence review, evidence-based pharmacological therapy for very high or high risk patients include high or the highest tolerated statin intensity, and when LDL-C is $\geq$70 mg/dL ezetimibe and PCSK9 inhibitors.

The results of REDUCE-IT, a high quality placebo-controlled ASCVD outcomes RCT, support the inclusion of icosapent ethyl as an additional evidence-based additive therapy to statins for selected hypertriglyceridemic patients with clinical ASCVD or type 2 diabetes with additional markers of increased risk. This well-tolerated therapy provides the first preventive therapeutic option with randomized controlled trial evidence of net ASCVD risk reduction benefit in hypertriglyceridemic patients, but it is unlikely that the observed benefit is mediated primarily via a triglyceride-lowering

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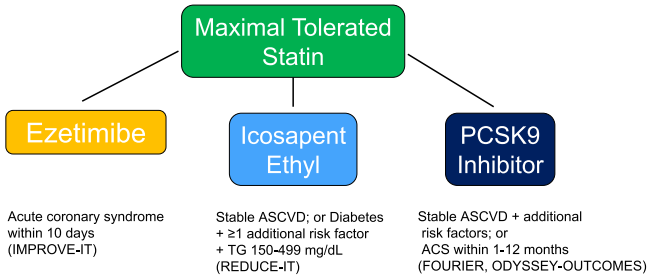

Fig. 5. RCT-proven non-statin additive therapies for ASCVD risk reduction in high-risk patients.

effect. It is the only currently available medicine to demonstrate this benefit independent of a LDL-cholesterol lowering mechanism. At the time of writing of this article, icosapent ethyl is approved only to treat patients with triglycerides ≥500 mg/dL to prevent acute pancreatitis. Current randomized controlled trial-supported treatments for ASCVD risk reduction in high and very high risk patients are summarized in Fig. 5. Pending US Food and Drug Administration approval of icosapent ethyl for ASCVD risk reduction, clinicians will look forward to future Guideline-based recommendations on its optimal use to prevent ASCVD events.

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