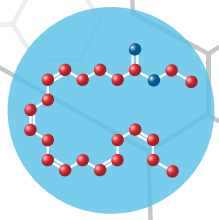
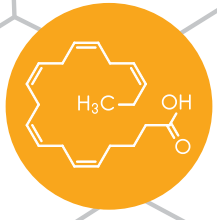
ALGORITHM

Biologix FZCO

MIND ON SCIENCE

EVOLUTION OF CARDIOVASCULAR RISK MANAGEMENT: FOCUS ON STATIN-ADJUNCT THERAPIES AND GUIDELINE UPDATES





Content

Introduction

Cardiovascular disease (CVD), a leading cause of mortality worldwide, represents a substantial economic burden. Several epidemiological studies across the globe have demonstrated a strong association between elevated low-density lipoprotein cholesterol (LDL-C) levels and an increase in the risk of CVD incidence.[1] Statins are the mainstay of lipid-lowering therapy (LLT)[1] and have been shown to be effective in lowering the cardiovascular (CV) risk and retarding the progression of atherosclerosis. A persistent CV risk remains elevated despite statin therapy in patients at high risk and those with atherosclerotic cardiovascular disease (ASCVD); this persistent risk tends to be higher in individuals with elevated triglycerides (TGs; 135–499 mg/dL). Event rates have been observed to be high despite being on maximally tolerated doses of statins.[2]

Residual Risk Beyond Statin Therapy

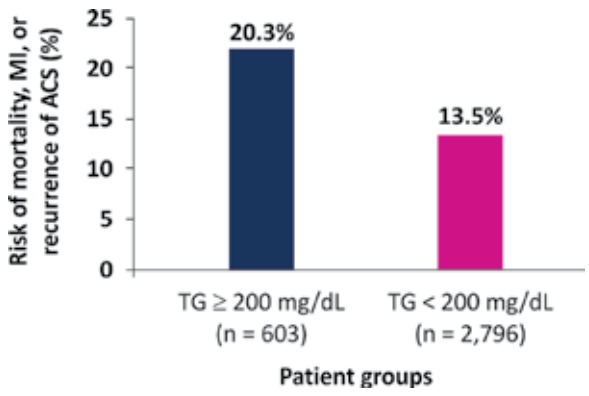
The CV risk can be determined by several non-lipid factors, such as age, alcoholism, diabetes mellitus (DM), hypertension, obesity, sedentary lifestyle, sex, and smoking; and lipid factors, such as raised LDL-C levels, elevated TGs, and/or low high-density lipoprotein cholesterol (HDL-C) levels. The residual CV risk, which is partly dependent on lipid abnormalities other than the LDL-C levels, has been defined by the Residual Risk Reduction Initiative as "the risk of CV events that persists in people despite the achievement of treatment goals for LDL-C, blood pressure, and glycemia according to the current standards of care."[3]

A study assessed subclinical carotid atherosclerosis in 3,012 Framingham Study participants who were free of CVD and whose mean age was 58.4 years. Fifty-five percent of the participants were women. It estimated the absolute CV risks by age and gender for various categories of LDL-C levels, stratified by LLT status and categorizing the subjects into five groups, namely LDL-C < 100 mg/dL without LLT (group 1), LDL-C ≥ 100 mg/dL to < 130 mg/dL without LLT (group 2), LDL-C < 130 mg/dL on LLT (group 3), LDL-C ≥ 130 mg/dL without LLT (group 4), and LDL-C ≥ 130 mg/dL on LLT (group 5). Significantly more carotid atherosclerosis was detected in group 3 to 5 participants, as compared to those in group 1. The number of CV events that occurred during follow-up (median, 13.7 years) was 548. The residual CV risk was found to be substantially high at 26.7 and 24.1 per 1000 person-years, respectively, in group 3 and group 5 individuals. This was nearly three times the risk in untreated individuals with an LDL-C level < 100 mg/dL. The absolute CV risks were found to increase with age and were slightly higher in males compared to females.[4]

Hypertriglyceridemia Despite Statin Therapy – A Biomarker of High CV Risk

The PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial had shown that after acute coronary syndrome (ACS), an LDL-C level < 70 mg/dL was associated with a greater decrease in coronary heart disease (CHD) events compared to an LDL-C level < 100 mg/dL. A study that assessed the impact of on-treatment TG levels on the risk of CHD following an episode of ACS, mortality, myocardial infarction (MI), or a subsequent ACS event found that the risk was lower in patients with a TG level < 200 mg/dL (Figure 1).[5]

Figure 1: Hypertriglyceridemia associated with residual risk despite LDL-C being < 70 mg/dL on statin therapy[5]



Adjusted hazard ratio (95% CI) 0.60 (0.45–0.81); $p = 0.001$

CV Outcomes with Fibrates as an Add-on to Statin Therapy

Table 1 summarizes major clinical trials and epidemiological studies on fibrate therapy with or without statins, along with their CV outcomes. It is evident that only the HHS (Helsinki Heart Study) and the VA-HIT (Veteran Affairs HDL Intervention Trial) on gemfibrozil achieved the primary endpoint. A statistically significant reduction in CHD, stroke, and CV death was also witnessed in the ECLIPSE-REAL (Effectiveness of Fenofibrate Therapy in Residual Cardiovascular Risk Reduction in the Real-World Setting) study, while all the remaining studies on CV protection with fibrates failed to do so.[6]

Table 1: CV outcomes of fibrate therapy with or without statins[6]

Name of the study	Patient population	Number	Treatment groups	Primary outcome	Results	Additional findings
HHS (1987)	Dyslipidemia (asymptomatic middle-aged men with primary dyslipidemia [non-HDL-C ≥ 200 mg/dL] without CVD)	4,081	Gemfibrozil 1,200 mg/day versus placebo	Fatal and non-fatal MI or cardiac death	34% ↓	
VA-HIT (1999)	CHD	2,531	Gemfibrozil 1,200 mg/day versus placebo	Non-fatal MI or coronary death	22% ↓	
BIP (2000)	CHD	3,090	Bezafibrate 400 mg/day versus placebo	Fatal or non-fatal MI or sudden death	9.4% ↓	41.8% ↓ in subgroup (HDL-C < 35 mg/dL, TG ≥ 200 mg/dL)
FIELD (2005)	Type 2 DM	9,795	Fenofibrate 200 mg/day versus placebo	CHD death or non-fatal MI	11% ↓	24% ↓ in non-fatal MI
ACCORD-Lipid (2010)	Type 2 DM	5,518	Simvastatin plus fenofibrate 160 mg/day versus simvastatin alone	Non-fatal MI, non-fatal stroke, CV death	8% ↓	28.6% ↓ in subgroup (HDL-C ≤ 34 mg/dL, TG ≥ 204 mg/dL)
ACCORDION (2017)	Type 2 DM	4,644	Simvastatin plus fenofibrate 160 mg/day versus simvastatin alone	Non-fatal MI, non-fatal stroke, CV death	7% ↓	27% ↓ in subgroup (HDL-C ≤ 34 mg/dL, TG ≥ 204 mg/dL)
ECLIPSE-REAL (2019)	Metabolic syndrome	10,705	Statin plus fenofibrate 160 mg/day versus statin alone	CHD, stroke, CV death	26% ↓	36% ↓ in subgroup (HDL-C < 34 mg/dL, TG ≥ 204 mg/dL)

HHS, Helsinki Heart Study; VA-HIT, Veterans Affairs HDL Intervention Trial; BIP, Bezafibrate Infarction Prevention; LEADER, Lower Extremity Arterial Disease Event Reduction; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACCORDION, ACCORD Follow-On; ECLIPSE-REAL, Effectiveness of Fenofibrate Therapy in Residual Cardiovascular Risk Reduction in the Real-World Setting.

CV Outcomes with Proprotein Convertase Subtilisin/Kexin Type-9 (PCSK9) Inhibitors as an Add-on to Statin Therapy

PCSK9 inhibitors have been shown to reduce the lifetime risk of CV events, and these drugs are also known to reduce endothelial inflammation, the key factor in the pathogenesis of atherosclerosis. The efficacy and safety of these monoclonal antibodies in patients at risk of CV diseases due to dyslipidemia have been demonstrated by large phase II and III trials.[7] As compared to placebo, the use of evolocumab on a background of statin therapy in the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial — a randomized, double-blind, placebo-controlled trial involving 27,564 participants with a history of atherosclerotic disease — was associated with a mean percentage reduction in LDL-C levels of 59% at 48 weeks, from a median baseline value of 92 mg/dL (2.4 mmol/L) to 30 mg/dL (0.78 mmol/L) [$p < 0.001$]. The risk of the primary endpoint significantly reduced in the evolocumab group (1,344 patients; 9.8%) compared to the placebo group (1,563 patients; 11.3%); hazard ratio (HR): 0.85; 95% confidence interval (CI): 0.79 to 0.92; $p < 0.001$. The key secondary endpoint was reported in 816 (5.9%) patients in the former group versus 1,013 (7.4%) patients in the latter group (HR: 0.80; 95% CI: 0.73 to 0.88; $p < 0.001$).[8] In a post hoc analysis of the ODYSSEY LONG-TERM (Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy) trial, the rate of major adverse cardiovascular events (MACE; death from CHD, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization) in 2,341 patients at high risk of CV events who had LDL-C levels of 70 mg/dL or more and were on maximally-tolerated statin therapy, with or without other LLT, was found to be 1.7% in the alirocumab group (given 150 mg SC every 2 weeks for 78 weeks) and 3.3% in the placebo group (HR: 0.52; 95% CI: 0.31 to 0.90; nominal $p = 0.02$).[9]

The SPIRE trials that were evaluating the efficacy of bococizumab were terminated early due to concerns about immunogenicity. However, the immunogenicity of evolocumab was found to be very low, and the neutralizing anti-drug antibody was observed only in 1.3% of patients who were treated with alirocumab.[7]

CV Outcomes With Eicosapentaenoic Acid (EPA)

The effects of EPA on CV outcomes in patients with dyslipidemia have been evaluated in a few studies. In the JELIS (Japan EPA Lipid Intervention Study), 18,645 patients with hypercholesterolemia, with or without coronary artery disease (CAD), were randomized to receive EPA 1.8 g/day plus a statin (pravastatin 10 mg or simvastatin 5 mg once daily; n = 9,326) or statin monotherapy (n = 9,319); the follow-up period was 5 years. While the 5-year cumulative rate of major coronary events in the EPA/statin group was 2.8%, the rate in the statin monotherapy group was 3.5%. The EPA/statin group demonstrated a 19% relative reduction in the risk of major coronary events compared with the statin monotherapy group.[10]

Mechanisms by which EPA Reduces the Risk of CVD

EPA positively influences the pathophysiologic cascade right from the onset of plaque formation through its rupture once it gets incorporated into the membrane phospholipids and atherosclerotic plaques. It seems to have beneficial effects regarding endothelial function, foam cell formation, inflammation, oxidative stress, platelet aggregation and thrombus formation, and the formation, progression, and rupture of plaques. It reduces the TG level without raising the LDL-C level, thereby decreasing atherogenic dyslipidemia. Other benefits of EPA include improving membrane fluidity and lowering blood pressure by producing vasodilation. The protective role of EPA against atherosclerotic CVD has been shown in Table 2.[11]

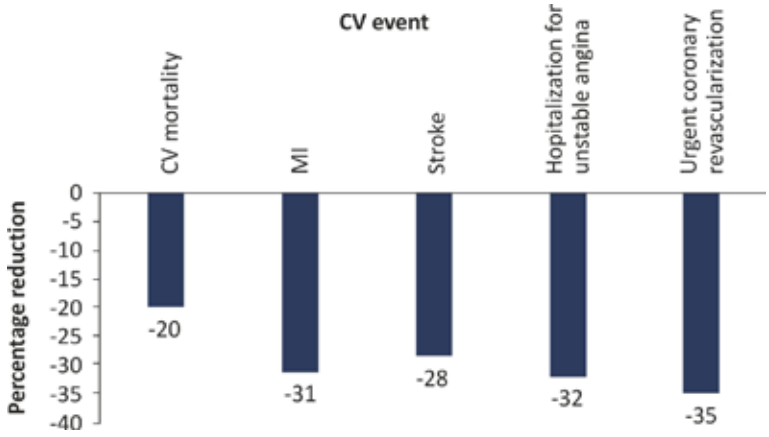
Table 2: Protective role of EPA against atherosclerotic CVD[11]

Mechanisms of atherosclerotic CVD	Protective role of EPA
In the subendothelial space, LDL-C undergoes oxidative alterations, progressing from minimally modified LDL (mm-LDL) to extensively oxidized LDL (ox-LDL). Inflammatory cytokines and mm-LDL cause the endothelial cells to express cell adhesion molecules that attract monocytes to migrate here and adhere to the cells. These monocytes then differentiate into macrophages. Foam cell formation takes place because of uptake of ox-LDL via scavenger receptors. This ox-LDL gets esterified and stored in lipid droplets before being converted to more soluble forms or being exported to extracellular HDL acceptors via cholesterol transporters.	↓ Adhesion of monocytes ↑ Antioxidant effects ↓ Cholesterol crystalline domains ↓ Foam cells ↑ Improved endothelial function ↓ Oxidized LDL ↓ Macrophages ↓ Remnant-like lipoparticle cholesterol
A chronic inflammatory process gets established owing to interactions between the macrophage foam cells, T helper (Th) 1 cells, and Th2 cells. The cellular components of the vascular wall are subjected to pro-atherogenic as well as anti-atherogenic effects of cytokines secreted by lymphocytes and macrophages. Migration of smooth muscle cells from the medial portion of the arterial wall is followed by their proliferation. Fibrous plaque formation occurs due to the secretion of the extracellular matrix proteins by the smooth muscle cells.	↑ EPA/arachidonic acid ↓ High-sensitivity C-reactive protein ↓ Inflammation ↓ Intercellular adhesion molecule 1 ↓ Interleukin 6 ↓ Interleukin 10 ↓ Lipoprotein-associated phospholipase A2 ↓ Matrix metalloproteinases
The foam cells derived from the macrophages and SMCs undergo necrosis, which results in the formation of a necrotic core and accumulation of extracellular cholesterol. Secretion of matrix metalloproteinases by the macrophages and neovascularization weaken the fibrous plaque. Rupture of the plaque leads to exposure of the blood components to tissue factors, thereby triggering the coagulation process, recruiting platelets, and forming a thrombus. If the thrombus is large enough to obstruct the lumen of the coronary artery, symptoms of ischemia manifest and ACS appears clinically.	↓ Arterial stiffness ↑ Fibrous cap thickness ↑ Lumen diameter ↑ Plaque stability ↓ Plaque volume ↓ Plaque vulnerability ↓ Platelet response ↓ Thrombosis

CV Outcomes with Icosapent Ethyl (IPE)

A new standard of care in addressing the residual risk in patients with elevated TG levels already treated with statins has been established by the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial). In this study, IPE, a highly purified n-3 fatty acid, was found to reduce by 25% the time from randomization to the first occurrence of an MACE, where the primary endpoint (a 5-point composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization) reduced from 22% to 17.2% (HR: 0.75; 95% CI: 0.68 to 0.83; p = 0.00000001; number needed to treat [NNT]: 21), and the key secondary endpoint (a 3-point composite of CV death, non-fatal MI, or non-fatal stroke) reduced from 14.8% to 11.2% (HR: 0.74; 95% CI: 0.65 to 0.83;

Figure 2: Reduction in MACE with IPE[13]

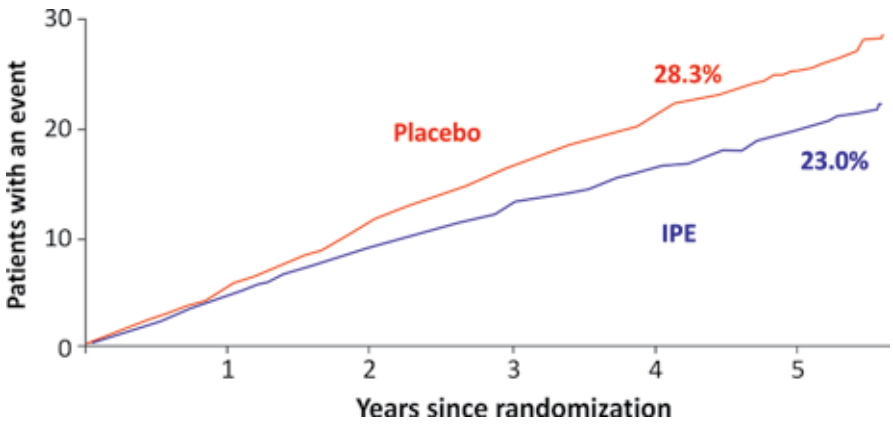


p = 0.0000006; NNT: 28).[12,13] As is evident from Figure 2, statistically significant reductions were reported in CV mortality as well as a variety of other prespecified endpoints.[13]

CV event reduction in the REDUCE-IT

Figure 3 shows Kaplan–Meier event curves for the primary efficacy composite endpoint of CV mortality, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina in patients treated with IPE or placebo in a time-to-event analysis. In the placebo group, 28.3% of the patients experienced a primary endpoint event. The incidence rate was found to be significantly lower at 23% in the IPE group. Additionally, a 25% residual risk reduction (RRR) of MACE was observed in the IPE group (HR: 0.75; 95% CI: 0.68 to 0.83; p = 0.00000001; absolute risk reduction [ARR]: −4.8%; NNT: 21; 95% CI: 15 to 33).[14]

Figure 3: Primary endpoint in the IPE and placebo groups[14]



Total event analysis in the REDUCE-IT

An analysis of the total number of CV events that occurred in the REDUCE-IT showed that approximately one CV event was prevented in every six patients treated with IPE for 5 years. On comparing the placebo and IPE groups, the total (first and subsequent) primary endpoint event rates were found to reduce from 89 to 61 per 1,000 patient-years, respectively (rate ratio [RR]: 0.70; 95% CI: 0.62 to 0.78; $p < 0.0001$). The first occurrence of a primary composite endpoint was reduced with IPE versus placebo (HR: 0.75; 95% CI: 0.68 to 0.83; $p < 0.0001$) as was the second occurrence (HR: 0.68; 95% CI: 0.60 to 0.78; $p < 0.0001$). With the use of IPE, a 30% relative risk reduction was observed in the total (first and subsequent) ischemic events for the primary composite endpoint. While first events were reduced by 25%, the second, third, and fourth or more events were found to decrease by 32%, 31%, and 48%, respectively.[15]

REDUCE-IT EPA subanalysis

In patients with baseline serum EPA tertiles ≤ 20 µg/mL, the primary composite endpoint occurred in 17.2% of the patients in the IPE group and 22% in the placebo group (HR: 0.75; CI: 0.68 to 0.83; p = 0.91). In patients with tertiles between 20 µg/mL and 34 µg/mL, these percentages were 17.9% and 21.6% in the IPE and placebo groups, respectively (HR: 0.79; CI: 0.66 to 0.95; p = 0.91); and in those with tertiles above 34 µg/mL, the percentages were 17% and 22.1% in the IPE and placebo groups, respectively (HR: 0.75; CI: 0.63 to 0.91; p = 0.91). The benefits of IPE 4 g per day were found to be beyond what could be explained by the extent of changes in the TG or other biomarker levels. The on-treatment EPA levels due to the IPE therapy strongly correlated with the primary endpoint, the key secondary endpoint, all-cause mortality, cardiac arrest, coronary revascularization, CV mortality, MI, new heart failure, stroke, sudden cardiac death, and unstable angina.[16]

REDUCE-IT REVASC subanalysis

In this subanalysis, IPE 4 g per day significantly decreased the first and total revascularization events by 34% and 36% (RR: 0.64; 95% CI: 0.56 to 0.74; p = 0.0000000005), respectively, compared with placebo. When analyzing the time to coronary revascularization in the two groups, the percentage of patients who required revascularization by the fifth year of randomization was found to be 16.7% in the placebo group and 11.4% in the IPE group (HR: 0.66; 95% CI: 0.58 to 0.76; RRR: 34%; ARR: 4.1%; NNT: 24; p = 0.0000000008). Compared with the placebo group, the number of first,

second, and third and more revascularization events in the IPE group was lesser by 168 (HR: 0.67; 95% CI: 0.58 to 0.76; $p = 0.000000001$), 64 (HR: 0.49; 95% CI: 0.37 to 0.66; $p = 0.000003$), and 26 (HR: 0.51; 95% CI: 0.27 to 0.99; $p = 0.05$), respectively. Consistency in reduction was reported across various revascularization categories, irrespective of whether they were urgent, emergent, or elective; and included percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) as well. Further, it is worth noting that this was the first non-LDL-C intervention in a major randomized trial in which patients treated with statins underwent fewer CABG surgeries.[17]

REDUCE-IT DIABETES subanalysis

This subanalysis found that IPE 4 g/day significantly decreased the first as well as the total primary endpoint events compared with placebo in 4,787 patients with diabetes at baseline by 23% and 24%, respectively. In patients without established CVD with diabetes and other risk factors, the percentage of patients who had first events by the fifth year of randomization was 18.5% in the placebo group and 14.3% in the IPE group (HR: 0.88; 95% CI: 0.70 to 1.10; $p = 0.24$). Considering the total events, the percentage was 25.4% in the former group and 22.1% in the latter group (RR: 0.88; 95% CI: 0.68 to 1.15; $p = 0.35$). In patients with established CVD with diabetes, the percentage of patients with first events by the fifth year of randomization was 40.9% in the placebo group and 30.8% in the IPE group (HR: 0.72; 95% CI: 0.62 to 0.84; $p = 0.00003$). In terms of total events, the percentage was 82% in the former group and 58% in the latter group (RR: 0.70; 95% CI: 0.59 to 0.84; $p = 0.00009$). In patients with established CVD without diabetes, the percentage of those with first events by the fifth year of randomization was 27.1% in the placebo group and 21.2% in the IPE group (HR: 0.73; 95% CI: 0.62 to 0.85; $p = 0.00006$). Total event analysis showed a percentage of 53.3% in the former group and 31.5% in the latter group (RR: 0.59; 95% CI: 0.49 to 0.70; $p = 0.000000007$). Thus, these reductions were statistically significant and consistently observed across the hierarchy of endpoints, irrespective of whether patients with diabetes had CVD or vice versa.[18]

REDUCE-IT RENAL subanalysis

The baseline eGFR ranged between 17 and 123 mL/min/1.73 m^2 (median = 75 mL/min/1.73 m^2) among the 8,179 patients who participated in the REDUCE-IT. Benefits in terms of the primary and key secondary endpoints were consistently observed with IPE. Patients with an eGFR < 60 mL/min/1.73 m^2 demonstrated the greatest numerical reduction in CV mortality (IPE: 7.6%; placebo: 10.6%; HR: 0.70; 95% CI: 0.51 to 0.95; $p = 0.02$). Adverse event reporting of microalbuminuria was lower in the IPE group (0.1%) compared with the placebo group (0.3%; $p = 0.01$). Thus, in the REDUCE-IT RENAL subanalysis, the number of ischemic events (both fatal and nonfatal) reduced with IPE across a wide range of baseline eGFR categories.[19]

REDUCE-IT PCI subanalysis

Out of the 8,179 patients who were included in the REDUCE-IT and followed for an average of 4.9 years, 3,408 (41.7%) had a previous PCI, the median time being 2.9 years (0.4 months to 30.7 years) from PCI to randomization (in the 2,559 patients who had records of the same). The reduction rate was found to be 34%, with the occurrence of the primary endpoint being 20.8% in the IPE group and 29.4% in the placebo group. Thus, the rate of reduction was 34% (HR: 0.66; 95% CI: 0.58 to 0.76; $p < 0.0001$; ARR: 8.5%; NNT: 12). Thus, the addition of IPE to the therapeutic regimen of statin-treated patients with elevated TGs and a history of PCI significantly decreased the number of ischemic events, and substantially reduced relative as well as absolute risk.[20]

REDUCE-IT CABG subanalysis

Some 22.5% (1,837) of the 8,179 participants in the REDUCE-IT who were followed had a prior CABG. From the available CABG records of 1,263 patients, a median time value of 5.1 years (0.7 months to 33.3 years) from the date of CABG to randomization into the trial was obtained. IPE was found to decrease the occurrence rate of the primary endpoint by 24%, the occurrences being 22.0% in the IPE group and 28.2% in the placebo group (HR: 0.76; 95% CI: 0.63 to 0.92; $p = 0.004$; NNT: 16). Thus, in this subanalysis, add-on IPE significantly decreased ischemic events, whilst reducing large relative and absolute risk, in statin-treated patients with a history of prior CABG.[21]

The EVAPORATE study

The EVAPORATE (Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients With Elevated Triglycerides on Statin Therapy) was a randomized, double-blind, placebo-controlled study. This study was performed to evaluate the effects of IPE 4 g/d on atherosclerotic plaques in statin-treated patients with coronary atherosclerosis. As compared with placebo, IPE was found to slow the progression of low attenuation plaques by 21% (p = 0.469), total plaques by 42% (p = 0.0004), total non-calcified plaques by 19% (p = 0.010), fibrous plaques by 57% (p = 0.011), and calcified plaques by 89% (p = 0.001) at the prespecified time point of 9 months. However, no effect was evident on fibrofatty plaques (p = 0.650). IPE was found to be consistently efficacious across multiple subgroups, including those with baseline TG levels that ranged between 135 and 500 mg/dL.[22]

CV Outcomes With EPA/DHA Combinations

The GISSIP trial

The GISSIP (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione) trial had investigated the beneficial effects of foods rich in vitamin E (α-tocopherol), n-3 polyunsaturated fatty acids (PUFA), and their pharmacological substitutes as supplements in patients who had MI. The study found that treatment with n-3 PUFA, but not vitamin E, reduced the risk of the primary endpoint significantly (relative risk reduction: 10%; 95% CI: 1 to 18 by two-way analysis and relative risk reduction: 15%; 95% CI: 2 to 26 by four-way analysis). The benefit could be attributed to a reduction in the mortality risk (14%; 95% CI: 3 to 24 by two-way analysis and 20%; 95% CI: 6 to 33 by four-way analysis) and decrease in CV death (17%; 95% CI: 3 to 29 by two-way analysis and 30%; 95% CI: 13 to 44 by four-way analysis. Combined treatment yielded results that were similar to those for n-3 PUFA in terms of the primary endpoint (14%; 95% CI: 1 to 26) and for fatal events (20%; 95% CI: 5 to 33).[23]

The STRENGTH trial

In the STRENGTH (STatin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia) trial, which was a double-blind, randomized, multicenter trial, participants were randomized to receive omega-3 carboxylic acid (CA) 4 g/d (n = 6,539) or corn oil as an inert comparator (n = 6,539), in addition to usual background therapies, including statins. Compared with corn oil-treated patients, the statin-treated patients with a high CV risk who were given add-on omega-3 CA showed no significant difference in the composite outcome of MACE, namely CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina that needs hospitalization. The primary endpoint occurred in 795 corn oil-treated patients (12.2%) as against 785 omega-3 CA-treated patients (12.0%) [HR: 0.99; 95% CI: 0.90 to 1.09; p = 0.84]. The percentage of gastrointestinal adverse events was found to be higher in the latter group (24.7%) compared with the former group (14.7%).[24]

Guideline Updates

Recommendations made by various international guidelines regarding lowering the CV risk have been summarized in Table 3.

Table 3: International guidelines recommendations to lower the CV risk

Guidelines	Recommended pharmacological interventions
Cardiovascular Disease and Risk Management: ADA Standards of Medical Care in Diabetes—2020[25]	• The addition of ezetimibe or a PCSK9 inhibitor may be considered in patients with diabetes and ASCVD who are identified as being at very high risk based on specific criteria and if LDL-C ≥ 70 mg/dL despite maximally tolerated statin therapy. • To reduce the CV risk, one may consider adding IPE for patients with ASCVD or other CV risk factors on a statin with controlled LDL-C but elevated TGs (135–499 mg/dL).

	• Combination therapy with a statin and fibrate/niacin is generally not recommended, as it has not been shown to improve ASCVD outcomes.
AACE/ACE 2020 Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm[26]	• Statin therapy is the cornerstone in the management of ASCVD risk. • If the risk persists despite statin therapy, its intensity must be increased or another agent like ezetimibe, a PCSK9 inhibitor, colesevelam, or niacin must be added for lowering LDL-C, TGs, apoprotein B, or non-HDL-C. • IPE 4 g/day can be added if the TG level ranges between 135 and 499 mg/dL and if the ASCVD risk is high despite being on maximally tolerated statin therapy.
AHA Science Advisory 2019[27]	• In patients with TG levels ranging between 200 and 499 mg/dL, prescription omega-3 fatty acids 4 g/day can produce about 20%–30% reduction in TGs without increasing LDL-C. • In patients with TGs ≥ 500 mg/dL, a TG reduction of ≥ 30% is produced. An increase in LDL-C is observed with DHA-containing, and not EPA-only, preparations. • They are efficacious and safe both as a monotherapy and as an add-on to other TG-lowering therapies. • In the REDUCE-IT, a 25% reduction in MACEs was observed with 4 g/day of EPA only.
AHA Scientific Statement on Clinical Management of Stable CAD in Patients with T2DM[28]	• High-intensity statin therapy is the mainstay of LLT and provides secondary prevention. • When LDL-C is > 70 mg/dL despite maximally tolerated statins, the use of ezetimibe and PCSK9 inhibitors can provide additional CV risk reduction. • The use of niacin is not recommended. • When TG levels stay elevated (> 135 mg/dL) despite maximally tolerated statin therapy, the addition of IPE should be considered to further reduce the CV risk.
2019 NLA (National Lipid Association) Position on the Use of Icosapent Ethyl in High and Very-High-Risk Patients[29]	• Treatment with IPE is recommended for ASCVD risk reduction in patients who are 45 years of age or older with clinical ASCVD, or 50 years of age or older with type 2 diabetes requiring medication and with one or more additional risk factors, and a fasting TG level between 135 and 499 mg/dL on a maximally tolerated statin, with or without ezetimibe.
2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk[30]	• The use of IPE 2 × 2 g/day should be considered in combination with a statin in high-risk patients with TG levels between 1.5 and 5.6 mmol/L (135 and 499 mg/dL) despite statin treatment.

References

1. Chiang C, Ferrières J, Gotcheva NN, *et al.* Suboptimal control of lipid levels: Results from 29 countries participating in the centralized pan-regional surveys on the undertreatment of hypercholesterolaemia (CEPHEUS). *J Atheroscler Thromb*. 2016 May 2;23(5):567–87.
2. Budoff MJ, Bhatt DL, Kinninger A, *et al*. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J.* 2020 Oct 21;41(40):3925–32.
3. Ferrari R, Aguiar C, Eduardo Alegria E, *et al*. Current practice in identifying and treating cardiovascular risk, with a focus on residual risk associated with atherogenic dyslipidaemia. *Eur Heart J Suppl.* 2016 Apr 12;18(Suppl C):C2–12.
4. Lieb W, Enserro DM, Larson MG, *et al.* Residual cardiovascular risk in individuals on lipid-lowering treatment: Quantifying absolute and relative risk in the community. *Open Heart*. 2018;5:e000722.
5. Miller M, Cannon CP, Murphy SA, *et al; PROVE IT-TIMI 22 Investigators.* Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2008 Feb 19;51(7):724–30.
6. Kim NH, Kim SG. Fibrates revisited: Potential role in cardiovascular risk reduction. *Diabetes Metab J*. 2020 Apr;44(2):213–21.
7. Bandyopadhyay D, Ashish K, Hajra A, *et al.* Cardiovascular outcomes of PCSK9 inhibitors: With special emphasis on its effect beyond LDL-cholesterol lowering. *J Lipids.* 2018 Mar 25;2018:3179201.
8. Sabantine MS, Giugliano RP, Keech AC, *et al*. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017 May 4;376(18):1713–22.

9. Robinson JG, Farnier M, Krempf M, *et al; ODYSSEY LONG TERM Investigators.* Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015 Apr 16;372(16):1489–99.

10. Nelson JR, Wani O, May HT, *et al.* Potential benefits of eicosapentaenoic acid on atherosclerotic plaques. *Vasc Pharmacol.* 2017 Apr;91:1–9.

11. Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. *Atherosclerosis*. 2015 Sep;242(1):357–66.

12. Bhatt DL, Steg PG, Brinton EA, *et al; REDUCE-IT Investigators.* Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol.* 2017 Mar;40(3):138–48.

13. Bhatt DL. Residual cardiovascular risk in statin-treated patients with elevated triglycerides: Now we can REDUCE-IT! *Eur Heart J.* 2019 Apr 14;40(15):1174–5.

14. Bhatt DL, Steg PG, Miller M, *et al*. Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial [Internet]. Available at: https://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=9509f58c47cc461c849846bd313ddedd. Accessed on Nov 25, 2020.

15. Bhatt DL, Steg PG, Miller M, *et al*. Effects of icosapent ethyl on total ischemic events: From REDUCE-IT. *J Am Coll Cardiol*. 2019 Jun 11;73(22):2791–802.

16. Bhatt DL, Steg PG, Miller M, *et al*. EPA Levels and Cardiovascular Outcomes in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial [Internet]. Available at: https://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=062fc9e4b3a74a9fb1c196a35dad8f3b. Accessed on Nov 25, 2020.

17. Peterson BE, Bhatt DL, Gabriel Steg PG, *et al*. Reduction of revascularization in patients with hypertriglyceridemia with icosapent ethyl: Insights from REDUCE-IT REVASC [Internet]. Available at: https://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=d756923c44de4d1487b540f5ad1e92a7. Accessed on Nov 25, 2020.

18. Bhatt DL, Brinton EA, Miller M, *et al*. Icosapent ethyl provides consistent cardiovascular benefit in patients with diabetes in REDUCE-IT [Internet]. Available at: https://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=ef9739685864453b84d5e26ac534a152. Accessed on Nov 25, 2020.

19. Majithia A, Bhatt DL, Friedman AN, *et al.* Benefits of icosapent ethyl across a range of baseline renal function in patients with established cardiovascular disease or diabetes: Results of REDUCE-IT RENAL. [Abstract FR-OR18]. *J Am Soc Nephrol*. 2020;31:21.

20. Peterson BE, Bhatt DL, Steg PG, *et al.* Treatment with icosapent ethyl to reduce ischemic events in patients with prior percutaneous coronary intervention: Insights from REDUCE-IT PCI. [TCT CONNECT Abstract 3]. *J Am Coll Cardiol.* 2020;76(17 Suppl B):1–2.

21. Verma S, Bhatt DL, Steg PG, *et al*. Icosapent ethyl reduces ischemic events in patients with prior coronary artery bypass grafting: REDUCE-IT CABG. [Abstract 14997]. *Circulation.* 2020 Nov 12;142:A14997.

22. Budoff M, Muhlestein JB, Bhatt DL, *et al*. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: The EVAPORATE study [Internet]. Available at: https://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=bb727249a4bd45dcb9ed91b45bd5957c. Accessed on Nov 25, 2020.

23. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. *Lancet*. 1999 Aug 7;354(9177):447–55.

24. Nicholls SJ, Lincoff AM, Garcia M, *et al.* Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: The STRENGTH randomized clinical trial. *JAMA.* 2020 Dec 8;324(22):2268–80.

25. American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2020. *Diabetes Care*. 2020 Jan;43(Suppl 1):S111–34.

26. Garber AJ, Handelsman Y, Grunberger G, *et al.* Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2020 executive summary. *Endocr Pract.* 2020 Jan;26(1):107–39.

27. Skulas-Ray AC, Wilson PWF, Harris WS, *et al.* Omega-3 fatty acids for the management of hypertriglyceridemia: A science advisory from the American Heart Association. *Circulation.* 2019 Sep 17;140(12):e673–691.

28. Arnold SV, Bhatt DL, Barsness GW, *et al.* Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus: A scientific statement from the American Heart Association. *Circulation*. 2020;141:e779–806.

29. Orringer CE, Jacobson TA, Maki KC. National Lipid Association Scientific Statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk. *Journal of Clinical Lipidology* [Internet] 2019;13(6):860–72. Available from: http://dx.doi.org/10.1016/j.jacl.2019.10.014

30. Mach F, Baigent C, Catapano AL, *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020 Jan 1;41(1):111–88.

ALGORITHM

Biologix FZCO

Summary

- Residual CV risk has been defined as the risk of CV events that persists in people despite the achievement of treatment goals for LDL-C, blood pressure, and glycemia according to the current standards of care.
- Hypertriglyceridemia, despite statin therapy, is a biomarker of high CV risk.
- Except for the HHS, VA-HIT, and ECLIPSE-REAL study, all the remaining studies on CV protection with fibrates failed to achieve the primary endpoint.
- While PCSK9 inhibitors have a role to play as an add-on to statin therapy in improving CV outcomes, there are concerns about their immunogenicity, especially with bococizumab.
- Various studies demonstrate the CV benefits of EPA in patients with dyslipidemia.
- EPA has beneficial effects regarding endothelial function, foam cell formation, inflammation, oxidative stress, platelet aggregation and thrombus formation, and the formation, progression, and rupture of plaques. It reduces the TG level without raising the LDL-C level, thereby decreasing atherogenic dyslipidemia. Other benefits of EPA include improving membrane fluidity and lowering blood pressure by producing vasodilation.
- In the REDUCE-IT, IPE – a highly purified ethyl ester of an n-3 fatty acid – was found to reduce the time from randomization to the first occurrence of a MACE by 25%.
- In the EVAPORATE study, IPE was found to slow the progression of atherosclerotic plaques in statin-treated patients with coronary atherosclerosis.
- Several international guidelines recommended the use of IPE to reduce TG levels for lowering the residual risk of CVD in various patients.

Insignia Learning FZC
Sign of Medical Excellence

MIND ON SCIENCE

Jan 2021