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Efficacy and safety of icosapent ethyl in hypertriglyceridaemia: a recap

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Although low-density lipoprotein cholesterol lowering is effective in atherosclerotic cardiovascular disease (ASCVD) prevention, considerable 'lipid-associated' residual risk remains, particularly in patients with mild-to-moderate hypertriglyceridaemia (2–10 mmol/L; 176–880 mg/dL). Triglyceride (TG)-rich lipoproteins carry both TGs and cholesterol (remnant-cholesterol). At TG levels >5 mmol/L (440 mg/dL) vs. <1 mmol/L (88 mg/dL) or remnant-cholesterol >2.3 mmol/L (89 mg/dL) vs. <0.5 mmol/L (19 mg/dL), risk is ~1.5-fold elevated for aortic stenosis, 2-fold for all-cause mortality, 3-fold for ischaemic stroke, 5-fold for myocardial infarction (MI), and 10-fold for acute pancreatitis. Furthermore, Mendelian randomization studies indicate that elevated TG-rich lipoproteins are causally related to increased risk of ASCVD and even all-cause mortality. While genetic and epidemiological data strongly indicate that TG-rich lipoproteins are causally linked to ASCVD, intervention data are ambiguous. Fibrates, niacin and low-dose omega-3 fatty acids have all been used in outcome trials, but have failed to demonstrate clear benefit in combination with statins. Whether the lack of additional benefit relates to methodological issues or true failure is indeterminate. Importantly, a recent intervention trial evaluating a high dose of eicosapentaenoic-acid showed clear benefit. Thus, REDUCE-IT evaluated the effect of icosapent ethyl (4 g/day) on cardiovascular outcomes in 8179 high-risk patients with moderate TG elevation on statin therapy. Over a median duration of 4.9 years, the relative risk for the primary endpoint (composite of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina) was reduced by 25% (absolute risk 17.2% vs. 22.0%; $P < 0.0001$; number needed to treat 21). High-dose icosapent ethyl intervention therefore confers substantial cardiovascular benefit in high-risk patients with moderate hypertriglyceridaemia on statin therapy.

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Current strategies to address hyperlipidaemia for atherosclerosis prevention

European and US guidelines on prevention of atherosclerotic cardiovascular disease (ASCVD) focus on reduction of low-density lipoprotein (LDL) cholesterol in high-risk individuals.[1,2] Such individuals include those with ASCVD, familial hypercholesterolaemia, diabetes, chronic kidney disease, and those with 10-year risk of future ASCVD above certain thresholds. These diseases and risk thresholds are generally coupled with LDL cholesterol above certain levels before LDL cholesterol-lowering therapy is recommended. In other words, reduce LDL cholesterol in those with both high ASCVD risk and high LDL cholesterol.

Such evidence-based medical practice is founded on a substantial scientific database documenting the observation that elevated LDL cholesterol is causally related to ASCVD, and that reduction of LDL cholesterol leads to reduced ASCVD.[3-5] Key evidence in man, summarized in the current European guidelines[2] includes findings derived from familial hypercholesterolaemia, from the epidemiology of hypercholesterolaemia and premature ASCVD, from human genetics, and from randomized, placebo-controlled trials involving reduction of LDL cholesterol using statins, ezetimibe, and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors.

Residual risk—the role of triglyceride-rich lipoproteins

Although LDL cholesterol lowering is successful in ASCVD prevention, there remains a considerable 'lipid-associated' residual risk, particularly if LDL cholesterol elevation is not the only lipid abnormality. This is the case in patients with hypertriglyceridaemia or combined hyperlipidaemia [elevation of both triglycerides (TGs) and cholesterol]. Here, the role of TG-rich lipoproteins during mild-to-moderate hypertriglyceridaemia (2–10 mmol/L; 176–880 mg/dL) is discussed.

What are triglyceride-rich lipoproteins?

Triglyceride-rich lipoproteins are the largest fat particles in plasma, those that carry most TGs; however, all lipoproteins contain some TGs.[6,7] Indeed, all lipoproteins contain hydrophobic TGs and esterified cholesterol in the core. These fat molecules are kept in solution in the water phase of plasma through a surface layer of phospholipids, free cholesterol, and apolipoproteins, each of which have hydrophobic and lipophilic parts towards the centre of the lipoprotein and hydrophilic parts towards the water phase securing the spherical form of lipoproteins in water.

All lipoproteins causing ASCVD have one molecule of the huge apolipoprotein B (apoB), the ligand for the LDL receptor.[8] This is the by far the most dominant protein in LDL, while TG-rich lipoproteins in addition carry several other proteins like apolipoproteins C and E and while lipoprotein(a) have an additional apolipoprotein(a) attached to apoB via a disulphide bridge.

After fatty meals, TG-rich lipoproteins come from the intestine via lymph as chylomicrons that during TG hydrolysis in plasma are converted to cholesterol-enriched chylomicron remnants to be taken up by liver cells.[9] Liver cells then repackage TGs together with esterified cholesterol into very low-density lipoproteins (VLDL) that during TG hydrolysis in plasma are converted first into intermediate-density lipoproteins and then further into LDL. This process is rather complex and not only involves TG hydrolysis by lipoprotein lipase but also cholesterol enrichment by cholesterol ester transfer protein. The different lipoprotein fractions are important for understanding human physiology, but likely much less important when it comes to clinical relevance.

For clinical use it is generally enough to lump all TG-rich lipoproteins into one group, to differentiate this class from LDL, lipoprotein(a), and high-density lipoprotein (HDL).[8,9] Triglyceride-rich lipoproteins are also for simplicity sometimes referred to collectively as remnants.[10] A remnant means a breakdown product, and all chylomicrons and VLDL are immediately partly broken down due to TG hydrolysis by lipoprotein lipase after entering the plasma space. In hypertriglyceridaemia, TG-rich lipoproteins usually represent a mixture of liver-derived VLDL remnants and intestine-derived chylomicron remnants.[11] The only exception from this scenario is familial chylomicronemia syndrome (seen in one in a million), characterized by a total lack of lipoprotein lipase.

For LDL in clinical use we measure the cholesterol content, as after degradation of TGs, proteins, and phospholipids the remainder undegradable cholesterol is what is deposited in the arterial intima to cause atherosclerosis. In analogy, for clinical use one should examine TG-rich lipoprotein cholesterol, also referred to as remnant cholesterol.[7,9,10] Plasma TGs represent a less precise marker of TG-rich lipoproteins as these lump TGs in all lipoproteins and not only TGs in remnants/TG-rich lipoproteins.

Epidemiology

In the population at large studying the Copenhagen General Population Study and the Copenhagen City Heart Study, higher and higher levels of TG-rich lipoproteins measured either as plasma TGs above vs. below 1 mmol/L (88 mg/dL) or remnant cholesterol above vs. below 0.5 mmol/L (19 mg/dL) are associated with higher and higher risk of ASCVD, aortic valve stenosis, and all-cause mortality (*Figure 1*).[12-15] At TG levels above 5 mmol/L (440 mg/dL) vs. below 1 mmol/L (88 mg/dL) or remnant cholesterol above 2.3 mmol/L (89 mg/dL) vs. below 0.5 mmol/L (19 mg/dL), risk is ~1.5-fold for aortic stenosis, 2-fold for all-cause mortality, 3-fold for ischaemic stroke, 5-fold for myocardial infarction (MI), and 10-fold for acute pancreatitis.

Interestingly, with the same increase in plasma TGs the relative risk of acute pancreatitis is double that of MI (*Figure 1*);[16] however, the absolute risk of MI was much higher than that of acute pancreatitis as roughly 10 times as many MIs compared to acute pancreatitis events developed during 7 years of follow-up. In *Figure 1* we only show risk of acute pancreatitis as a function of elevated plasma
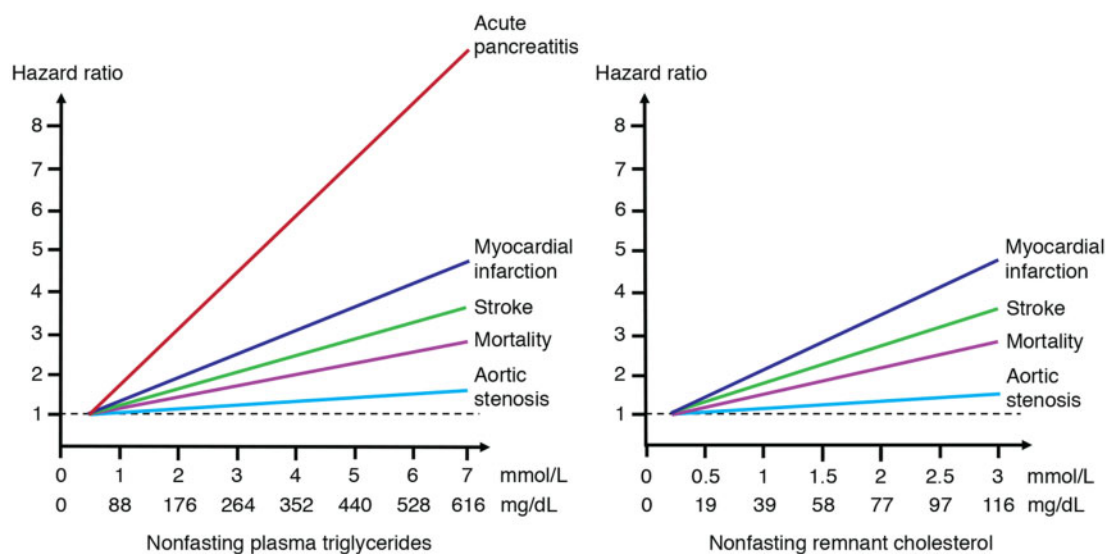
Figure 1 Relationship of progressive increase in non-fasting plasma triglycerides and remnant cholesterol with progressive increase in risk of morbidity and mortality. Observational relationships are shown; however, using a genetic instrument in Mendelian randomization analysis, such associations are confirmed to represent causal relationships. For acute pancreatitis, only the relationship with plasma triglycerides is depicted, as remnant cholesterol is not thought to play a causal role in this disease. Figure produced by Professor B. G. Nordestgaard based on data from roughly 100 000 individuals participating in the Copenhagen General Population Study and the Copenhagen City Heart Study as published previously.[12-17]

TGs, as this is the likely causal factor for acute pancreatitis through TG hydrolysis and inflammation,[18] and not remnant cholesterol which is more likely the cause of ASCVD.[13]

Importantly, in patients already on statins elevated TG-rich lipoproteins explain a large fraction of residual ASCVD risk.[13] Elevated TGs, remnant cholesterol, or TG-rich lipoprotein cholesterol associate with increased risk of ASCVD and/or all-cause mortality.

Genetics
Numerous studies now document that genetically elevated TG-rich lipoproteins, measured as plasma TGs or remnant cholesterol, are causally related to increased risk of ASCVD or even all-cause mortality.[13,14] These studies take advantage of the Mendelian randomization design where genetic variants generally are unconfounded and where reverse causation is not an issue, as genotypes are present from birth and therefore always precede ASCVD development.[19,20]

Genetic variants leading to lifelong high or low levels of TG-rich lipoproteins and corresponding high and low risk of ASCVD are observed in many single genes of direct importance for TG metabolism.[21-25] This is true for genetic variants in *LPL, APOA5, APOC3, ANGPTL3,* and *ANGPTL4,* all variants which influence plasma TGs through the lipoprotein lipase pathway. Apolipoprotein A5 enhances while apolipoprotein C3 and angiopoietin-like proteins 3 and 4 inhibit lipoprotein lipase activity.

Importantly, elevated TG-rich lipoproteins are a direct cause of ASCVD independent of levels of LDL, HDL, and lipoprotein(a).[26] While elevated LDL and lipoprotein(a) like TG-rich lipoproteins each are independent causal factors for ASCVD,[5,27,28] this is not the case for low HDL levels that rather should be considered a long-term marker of

elevated TG-rich lipoproteins just like elevated haemoglobin A1c is a long-term marker of elevated plasma glucose.[29]

What is the role of non-fasting or postprandial triglyceride-rich lipoproteins
The non-fasting or postprandial state predominates for most of a 24-h cycle.[7,8] In contrast, fasting for more than 8 h, as previously used before lipid profile testing, normally only occurs a few hours before breakfast. Therefore, because plasma only contains TG-rich lipoproteins of hepatic origin in the fasting state but additionally those of intestinal origin in the non-fasting state, the non-fasting state better capture the total amount of TG-rich lipoproteins in plasma during most of a 24-h period.

At 3-4 h after any last meal, non-fasting plasma TGs and remnant cholesterol are on average 0.3 mmol/L (26 mg/dL) and 0.2 mmol/L (8 mg/dL) higher than in the fasting state.[8] Therefore, using fasting lipid profiles may disguise the real residual risk in a patient due to elevated TG-rich lipoproteins.[7]

Non-fasting lipid profiles represent a simplification for patients, laboratories, and clinicians alike without negative implications for prognostic, diagnostic, and therapeutic options for cardiovascular disease prevention.[7-9] In accordance, European and US guidelines on prevention of ASCVD now endorse widespread use of non-fasting lipid profiles.[1,2]

Mechanism from triglyceride-rich lipoproteins to atherosclerotic cardiovascular disease
The most likely scenario is simple and straight forward (*Figure 2*).[13,14] At elevated levels in plasma and irrespective of hepatic or intestinal origin, TG-rich lipoproteins smaller than chylomicrons penetrate the arterial intima,
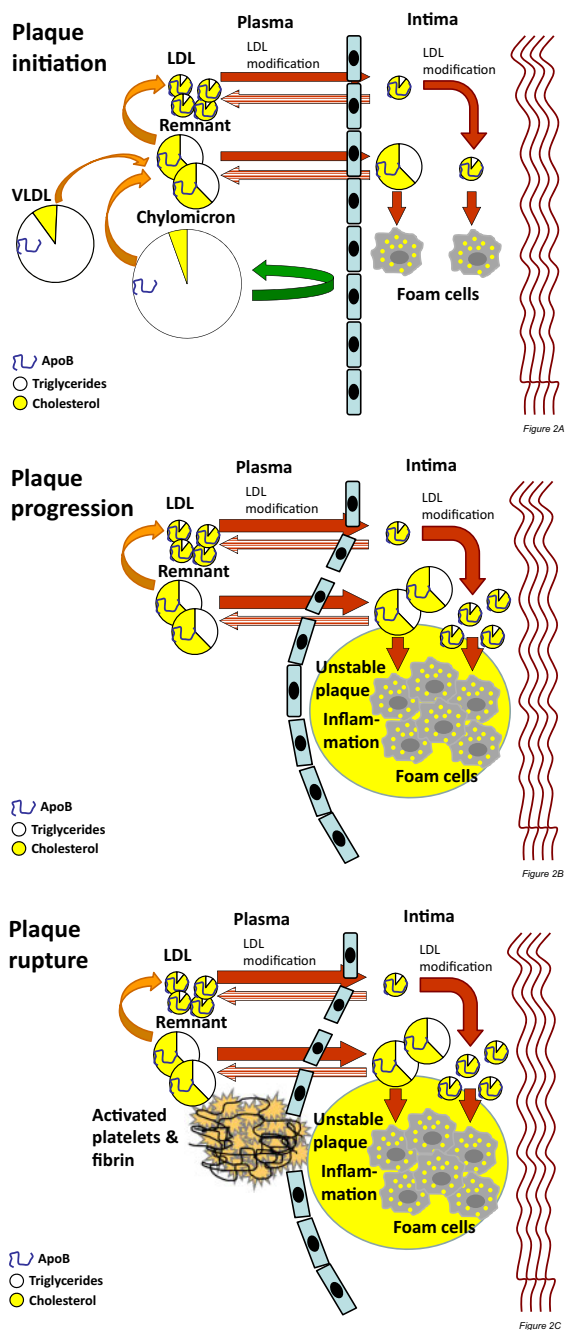
Figure 2 From elevated triglyceride-rich lipoproteins to atherosclerotic plaque initiation, plaque progression, and finally plaque rupture causing myocardial infarction or ischaemic stroke. This mechanistic cartoon depicts the situation in the non-fasting or postprandial state with lipoprotein in plasma both of intestinal (chylomicrons and chylomicron remnants) and hepatic origin [very low-density lipoproteins, very low-density lipoprotein remnants (= intermediate-density lipoproteins), and low-density lipoproteins]. Low-density lipoproteins and remnants cross the endothelial layer of intima in a process dependent on blood pressure, lipoprotein size, and concentration, possibly involving transcytosis. Figure produced by Professor B. G. Nordestgaard. apoB, apolipoprotein B; LDL, low-density lipoproteins; VLDL, very low-density lipoproteins.

where due to their larger size than that of LDL and HDL, they are trapped selectively.[30] Here, TG hydrolysis leads to liberation of tissue-toxic free fatty acids and consequent

local inflammation, while the entire particles are taken up directly by macrophages to produce foam cells and atherosclerosis.[13]

Vulnerable atherosclerotic plaques, possibly due to inflammation from liberated free fatty acids during TG hydrolysis, then lead to plaque rupture and subsequent MI or ischaemic stroke (*Figure 2*).[13,14] In accordance with this idea, elevated TGs and remnant cholesterol are observationally and causally related to whole-body low-grade inflammation while elevated LDL cholesterol is not.[18,31]

Current treatment

Reflections from current guideline recommendations for management of hyperlipidaemia

As outlined above, hypertriglyceridaemia and combined hyperlipidaemia are causally linked to cardiovascular risk.[13,15] Such risk is in large part mediated by a number of metabolic and genetic alterations which result in an increased number of apoB-containing particles. Therefore, it is not surprising that LDL-lowering (and thus apoB lowering) approaches can also decrease cardiovascular morbidity and mortality in subjects with hypertriglyceridaemia or combined hyperlipidaemia.[32] Indeed, LDL cholesterol reduction remains the primary therapeutic approach in patients with hypertriglyceridaemia or combined hyperlipidaemia, with LDL cholesterol targets dependent on the overall risk for ASCVD in any given individual.[2]

Despite the 'dominance' of LDL cholesterol in the recent ESC/EAS guideline recommendations, lipid targets are not restricted to LDL cholesterol, but also include non-HDL-cholesterol and apoB as secondary targets.[2] These parameters reflect the concentration of apoB-containing particles and thus global ASCVD risk to a greater degree than LDL cholesterol alone, a comment equally applicable to patients with hypertriglyceridaemia or combined hyperlipidaemia. If LDL cholesterol is at guideline-recommended goal but not at goal for apoB and/or non-HDL-cholesterol, then the latter goals can be achieved by either further LDL cholesterol reduction or by reduction of remnant cholesterol levels. While LDL cholesterol reduction has been shown to reduce cardiovascular events, data on remnant reduction (i.e. reduction of TG-rich lipoprotein concentrations) are more ambiguous (*Table 1*). Based on these observations, a number of algorithms have been developed to treat patients with hypertriglyceridaemia or combined hyperlipidaemia.[44]

Low-density lipoprotein cholesterol reduction

Low-density lipoprotein cholesterol reduction is established as the primary lipid approach for ASCVD risk reduction, independent of the underlying hyperlipidaemia. Low-density lipoprotein cholesterol treatment goals depend on the overall ASCVD risk and targets should be achieved with lifestyle modification initially and with drugs if required. Statins, frequently in combination with ezetimibe and/or PCSK9 inhibitors, should be used as the primary pharmacological approach. Although these agents have little effect on TG levels, this strategy is also successful in reducing

Table 1 Summary of randomized cardiovascular outcome studies involving triglyceride-lowering drugs

Trial	Treatment	Population	Statin	n	Primary endpoint	P < 0.05
Fibrates						
WHO[33]	Clofibrate	High cholesterol, no CHD	No	5331	Non-fatal MI + CHD death	Yes
CDP[34]	Clofibrate	CHD	No	3892	Non-fatal MI + CHD death	No
HHS[35]	Gemfibrozil	High cholesterol, no CHD	No	4081	MI + CHD death	Yes
VA-HIT[36]	Gemfibrozil	Low HDL, CHD	No	2531	Non-fatal MI + CHD death	Yes
BIP[37]	Bezafibrate	Previous MI or angina	No	3090	MI + sudden death	No
FIELD[38]	Fenofibrate	T2DM/CVD	No	9795	Non-fatal MI + CHD death	No
ACCORD[39]	Fenofibrate	T2DM/CVD	Yes	5518	MI + stroke + CV death	No
Niacin						
CDP[34]	IR-Niacin	CHD	No	3980	Non-fatal MI + CHD death	No
AIM-HIGH[40]	ER-Niacin	Dyslipidaemia + CHD	Yes	3414	MI + stroke + CAD death + revascularization	No
HPS2-THRIVE[41]	ER-Niacin + laropiprant	CHD, PAD, or DM	Yes	25 673	MI + stroke + CAD death + revascularization	No
High-dose omega-3-fatty acids						
JELIS (open label in Japan)[42]	Icosapent ethyl 1.8 g	High cholesterol	Yes	18 645	MI + stroke + sudden cardiac death + angina + revascularization + PCI + CABG	Yes
REDUCE-IT[43]	Icosapent ethyl 4 g	High TG + ASCVD or high-risk DM	Yes	8179	MI + stroke + CVD death + angina + revascularization	Yes

Randomized cardiovascular outcome studies that have evaluated triglyceride-lowering drugs are shown. The main inclusion criteria are listed under 'Population'. 'Statin' indicates whether the triglyceride-lowering drug was tested on a statin background medication or not. Table modified from Laufs *et al.*[44]

ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CAD, coronary artery disease, CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; TG, triglyceride.

cardiovascular morbidity–mortality in patients with hypertriglyceridaemia and combined hyperlipidaemia. While statins have minor effect on fasting TG levels, they can significantly decrease postprandial TG concentrations, and therefore may contribute to overall risk reduction.[45,46] Similarly, PCSK9 inhibitors beneficially affect postprandial lipid metabolism, while the data on ezetimibe are more ambiguous.[47-50]

Lifestyle

In patients with hypertriglyceridaemia or combined hyperlipidaemia, lifestyle modification (involving increase in physical activity, weight reduction, and dietary changes) can improve the lipid profile.[44] Concerning diet, reduction in the consumption of refined carbohydrate-rich foods, as well as sucrose and fructose, is important. Similarly, reduction of alcohol intake and the replacement of saturated fat with mono- or polyunsaturated fats translate into TG reduction. However, randomized, placebo-controlled trial evidence for these nutritional recommendations is lacking.

Fibrates

Fibrates can reduce TG plasma concentrations by up to 70% with considerable inter-individual variation.[51] In monotherapy, fibrates have been shown to reduce cardiovascular risk, but no additional benefit was observed when used in combination with statins in individuals without elevated TGs.[35,36,39] It remains unclear as to whether the lack of additional benefit relates to methodological issues (study design, enrolment criteria), or true failure. This question is of some importance as *post hoc* subgroup analyses indicate that patients with hypertriglyceridaemia associated with low HDL may benefit from statin-fibrate combination therapy.[14,52] The results of an ongoing outcome trial (PROMINENT) using a new fibrate (pemafibrate) will probably clarify the value of fibrate therapy.[53,54]

Niacin

In a similar manner to fibrates, niacin therapy has been shown to translate into benefit when used without statins but did not show benefit in combination with statins.[40,41,55] Niacin is therefore no longer available in most countries and should not be used to treat patients with hypertriglyceridaemia or combined hyperlipidaemia.

Volanesorsen

Volanesorsen is a second-generation chimeric antisense inhibitor, which impairs the translation of apolipoprotein C-III mRNA.[56,57] It is approved in Europe for the treatment of patients with genetically proven familial chylomicronemia syndrome and therefore with elevated risk for pancreatitis.

Due to the rarity of the disease, it is unclear whether this drug can equally reduce cardiovascular events.

Omega-3 fatty acids

Based on epidemiological data, a number of studies have evaluated the effect of low-dose omega-3-fatty acids (1 g/day) on cardiovascular events. With the exception of one early Italian study, none of the trials (and especially those involving adequate background therapy including statins, aspirin, and beta-blockers) showed any benefit with respect to ASCVD risk reduction.[58,59] Therefore, low-dose omega-3 fatty acids should not be used for cardiovascular risk reduction.

A higher dose of eicosapentaenoic acid (EPA, 1.8 g/day) was evaluated in Japan in an open-label study in 18 645 men and women with hypercholesterolaemia in primary prevention.[42] Patients were randomized to receive 1800 mg of EPA daily on a statin background (EPA group) or statin only. After a mean follow-up of 4.6 years, there was a significant 19% relative risk reduction (RRR) in major coronary events (2.8% vs. 3.5%; $P = 0.011$). Both groups had a similar reduction in LDL cholesterol, but the EPA group had a significantly more pronounced TG reduction (9% vs. 4%). Interestingly, an equal benefit of EPA was seen in patients with TG levels above the mean and those below the mean.

A higher dose (4 g/day) of icosapent ethyl, a precursor of EPA, was used in the REDUCE-IT trial, which will be discussed in the following section.[43]

The REDUCE-IT trial

The preceding text has highlighted the increasing interest in therapeutic strategies which are targeted to lower circulating levels of TG-rich lipoproteins, thereby reflecting emerging data which indicate that TG-rich lipoproteins play a causal role in the pathophysiology of ASCVD. Long-chain n-3 polyunsaturated fatty acids (PUFAs) exert multiple effects on the cardiovascular system, one of which is to lower TG levels.[60,61] Triglyceride lowering induced by n-3 PUFAs is linearly dose-dependent, but with large inter-individual variation in response (*Figure 3*). However, as typical daily dietary consumption of n-3 PUFAs (predominantly in the form of fish) is low in many countries and typically <200 mg/day, only modest lowering of plasma TG occurs (<10%).[61] Thus it is unlikely that such low consumption might contribute significantly to the reduced cardiovascular risk noted in several observational studies.[61]

A key question arises: if substantial lowering of TG-rich lipoproteins could be obtained with high doses of n-3 PUFAs (*Figure 3*), such as doses >3 g/day, then would this effect translate into marked TG reduction with associated cardiovascular benefit? It is in this context that the REDUCE-IT trial (Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial; REDUCE-IT; NCT01492361) is of immediate relevance.[43,62–65]

REDUCE-IT was a multinational phase 3b randomized, double-blind, placebo-controlled trial (RCT) of high-dose icosapent ethyl [4 g/day; 2 g twice daily (BID)], a highly purified ethyl ester of an n-3 PUFA, EPA, vs. placebo. The study was designed to evaluate the effect of this agent on
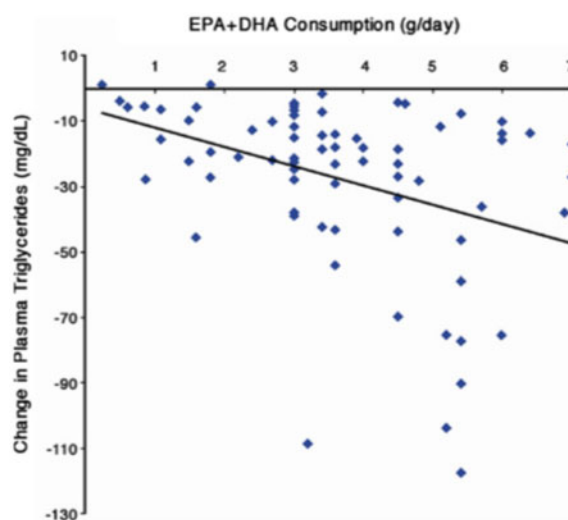
Figure 3 Dose-response effects of n-3 PUFA consumption on fasting plasma triglycerides in RCTs. Based on 55 placebo-controlled trials of n-3 PUFA consumption for two or more weeks as extracted from a prior systematic review[276] as well as two additional RCTs of fish or n-3 PUFA consumption[169,277,278] to provide additional dose-response information at doses of <1 g/day eicosapentaenoic acid + docosahexaenoic acid (DHA). Each point represents the change in plasma triglycerides from baseline for each individual study arm, as compared with control. The solid line represents the line of best fit calculated from linear regression. Overall, each 1 g/day increase of eicosapentaenoic acid + DHA reduced triglycerides by −5.9 mg/dL (95% confidence interval −2.5 to −9.3 mg/dL). This effect was significantly greater in trials of individuals with higher starting triglyceride levels (*P* interaction < 0.001). Among trials of individuals with mean baseline triglycerides below the median (<83 mg/dL), each 1 g/day eicosapentaenoic acid + DHA decreased triglycerides by −1.7 mg/dL (95% confidence interval −3.1 to −0.2 mg/dL). Among trials of individuals with mean baseline triglycerides above the median (>83 mg/dL), each 1 g/day eicosapentaenoic acid + DHA decreased triglycerides by −8.4 mg/dL (95% confidence interval −13.7 to −3.2 mg/dL). See Figure 4, ref.[61] with permission.

prevention of cardiovascular events in high-risk statin-treated patients ($n = 8179$), with or without ezetimibe, with controlled LDL-C (40-100 mg/dL; 1.0-2.6 mmol/L), moderately elevated TG levels ($\geq$135 mg/dL; 1.5 mmol/L), and other cardiovascular risk factors.[62] REDUCE-IT enrolled men or women $\geq$45 years of age with established cardiovascular disease, or age $\geq$50 years with diabetes mellitus and one additional cardiovascular risk factor. All patients were maintained on statin therapy throughout the trial. Importantly, enrolment targeted some 70% of secondary prevention patients with established ASCVD, and some 30% of primary prevention patients at high risk of premature ASCVD (notably diabetes requiring medication and one risk factor). The main objective was to evaluate whether such treatment might reduce ischaemic events in statin-treated patients with elevated plasma TG levels at high or very high cardiovascular risk. The primary endpoint was a composite of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina, while the key secondary endpoint represented a composite of cardiovascular death, non-fatal MI , or non-fatal stroke; as such, REDUCE-IT was an event-driven study.[43]

The baseline phenotype of patients in REDUCE-IT is of special interest; they were middle-aged (mean age 64 years), predominantly male (70.2%), obese (body mass
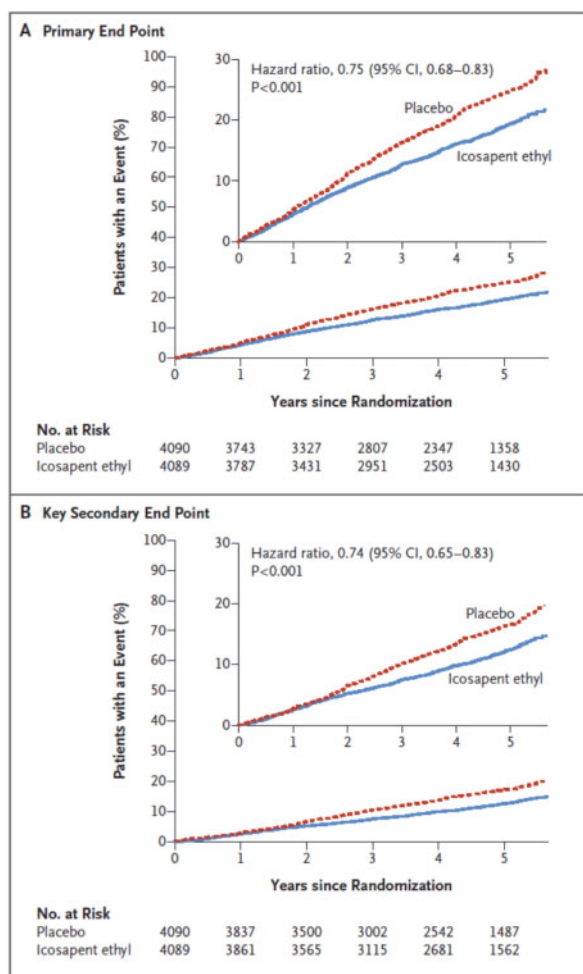
Figure 4 Cumulative incidence of cardiovascular events. (*A*) The Kaplan-Meier event curves for the primary efficacy composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina in the icosapent ethyl group and the placebo group, in a time-to-event analysis. (*B*) The Kaplan-Meier event curves for the key secondary efficacy composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in the two trial groups, in a time-to-event analysis. In each panel, the inset shows the same data on an expanded *y*-axis. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses. See Figure 1A, ref.[43] with permission. CI, confidence interval.

index > 30; 57%), and diabetic (59%, of which <1% were type 1), with median levels of LDL cholesterol, HDL cholesterol, and TGs of 75, 40, and 216 mg/dL (1.9, 1.0, and 2.5 mmol/L), respectively (*Table 2*). The majority of patients (61%) presented TG levels >200 mg/dL, 10% presented TG levels within the guideline-recommended limits (<150 mg/dL).[2,66] One-fifth of patients presented the high TG/low HDL-C phenotype (TG > 200 and HDL-C ≤ 40 mg/dL), a phenotype typically associated with high cardiovascular risk.[67]

Principle findings
Over a median duration of follow-up of 4.9 years (maximum 6.2 years), a total of 1606 adjudicated primary endpoint

events occurred. Of these events, 17.2% presented in patients in the icosapent ethyl group, and 22.0% in individuals in the placebo group, a highly significant difference [hazard ratio 0.75, 95% confidence interval (CI) 0.68-0.83; *P* = 0.00000001]; the RRR was 25%. The number needed to treat to avoid one primary endpoint event was 21 (95% CI 15-33). The event curves based on a Kaplan-Meier analysis of the primary endpoint are shown in *Figure 4* (see Figure 1A, ref.[43] with permission), and revealed an early trend to curve separation between the treatment and placebo groups commencing in the period from 1 to 2 years of study duration. A key secondary endpoint event occurred in 11.2% of patients in the icosapent ethyl group, as compared with 14.8% in the placebo group (hazard ratio 0.74, 95% CI 0.65-0.83; *P* = 0.0000006); the RRR was 26%. In turn, the number needed to treat to avoid one key secondary endpoint event was 28 (95% CI 20-47).

Subsequently, the impact of icosapent ethyl on the totality of ischaemic events over the duration of the trial was evaluated in a prespecified analysis using several statistical models; such analyses concurred to show that major, significant reductions in total events occurred in the intervention arm relative to placebo, with marked diminution in both relative and absolute risk.[63-65] Thus, icosapent ethyl treatment resulted in a 30% reduction in total (i.e., first and subsequent events) ischaemic events for the primary composite endpoint; similar, highly significant findings were seen for the secondary composite endpoint. Remarkably, not only first and second, but also equally third and fourth events were significantly reduced in both the composite primary and secondary endpoints, these events occurring while patients were receiving randomized study drug in the icosapent ethyl and placebo arms, respectively (*Figure 5*).

Impact of icosapent ethyl on plasma lipid levels and an inflammatory marker
Icosapent ethyl mediated a reduction of 18% in median plasma TG levels from baseline to 1 year; concomitantly, TG levels increased nominally by 2% in the placebo group, resulting in a median reduction which was 20% greater in the intervention arm as compared to placebo (*P* < 0.001). Correspondingly, LDL cholesterol was 7% lower in the intervention arm (median increase 3%) as compared to placebo (*P* < 0.001), while the corresponding median % difference in apoB was 10% at 2 years of follow-up (*P* < 0.001). Levels of a systemic marker of inflammation, high-sensitivity C-reactive protein (CRP), were 38% lower in the intervention vs. placebo arm at 2 years of follow-up; however, this was partly driven by an increase in CRP in the placebo arm. Finally, plasma concentrations of EPA rose from a median baseline level of 26.1 to 144.0 μg/mL at year 1 of follow-up; after correction for change in the placebo level (−2.9%), a net increment of 3.6-fold occurred in EPA levels (*P* < 0.001).[43]

When the relationship of baseline TG tertiles [medians of 163, 217, and 304 mg/dL (1.9, 2.5, and 3.5 mmol/L), respectively] was evaluated in relation to the primary endpoint of first events and to total events in a prespecified analysis, icosapent ethyl significantly reduced

Table 2 Characteristics of patients included in the REDUCE-IT trial (with permission from[43])[a]

Characteristics	Icosapent ethyl (N = 4089)	Placebo (N = 4090)
Age		
Median (IQR) (years)	64.0 (57.0-69.0)	64.0 (57.0-69.0)
≥65 years, *n* (%)	1857 (45.4)	1906 (46.6)
Male gender, *n* (%)	2927 (71.6)	2895 (70.8)
White race,[b] *n* (%)	3691 (90.3)	3688 (90.2)
Body mass index[c]		
Median (IQR)	30.8 (27.8-34.5)	30.8 (27.9-34.7)
≥30, *n* (%)	2331 (57.0)	2362 (57.8)
Geographic region,[d] *n* (%)		
USA, Canada, the Netherlands, Australia, New Zealand, and South Africa	2906 (71.1)	2905 (71.0)
Eastern European	1053 (25.8)	1053 (25.7)
Asia-Pacific	130 (3.2)	132 (3.2)
Cardiovascular risk stratum, *n* (%)		
Secondary prevention cohort	2892 (70.7)	2893 (70.7)
Primary prevention cohort	1197 (29.3)	1197 (29.3)
Ezetimibe use, *n* (%)	262 (6.4)	262 (6.4)
Statin intensity, *n* (%)		
Low	254 (6.2)	267 (6.5)
Moderate	2533 (61.9)	2575 (63.0)
High	1290 (31.5)	1226 (30.0)
Data missing	12 (0.3)	22 (0.5)
Diabetes, *n* (%)		
Type 1	27 (0.7)	30 (0.7)
Type 2	2367 (57.9)	2363 (57.8)
No diabetes at baseline	1695 (41.5)	1694 (41.4)
Data missing	0	3 (0.1)
Median high-sensitivity CRP level (IQR) (mg/L)	2.2 (1.1-4.5)	2.1 (1.1-4.5)
Median triglyceride level (IQR) (mg/dL)	216.5 (176.5-272.0)	216.0 (175.5-274.0)
Median HDL cholesterol level (IQR) (mg/dL)	40.0 (34.5-46.0)	40.0 (35.0-46.0)
Median LDL cholesterol level (IQR) (mg/dL)	74.5 (62.0-88.0)	76.0 (63.0-89.0)
Distribution of triglyceride levels, *n*/total *n* (%)		
<150 mg/dL	412/4086 (10.1)	429/4089 (10.5)
≥150 to <200 mg/dL	1193/4086 (29.2)	1191/4089 (29.1)
≥200 mg/dL	2481/4086 (60.7)	2469/4089 (60.4)
Triglyceride level ≥200 mg/dL and HDL cholesterol level ≤35 mg/dL, *n* (%)	823 (20.1)	794 (19.4)
Median eicosapentaenoic acid level (IQR) (μg/mL)	26.1 (17.1-40.1)	26.1 (17.1-39.9)

CRP, C-reactive protein; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

[a]Median LDL cholesterol level at baseline differed significantly between the trial groups ($P = 0.03$); there were no other significant between-group differences in baseline characteristics. To convert the values for triglycerides to millimoles per litre, multiply by 0.01129. To convert the values for cholesterol to millimoles per litre, multiply by 0.02586. In general, the baseline value was defined as the last non-missing measurement obtained before randomization. The baseline LDL cholesterol value as measured by means of preparative ultracentrifugation was used in our analyses; however, if the preparative ultracentrifugation value was missing, the LDL cholesterol value measured by another method was used in the following order of priority: the value obtained by means of direct measurement of LDL cholesterol, the value derived with the use of the Friedewald equation (only for patients with a triglyceride level <400 mg/dL), and the value derived with the use of the calculation published by Johns Hopkins University investigators. At the first and second screening visits, the LDL cholesterol value obtained by direct measurement was used if at the same visit the triglyceride level was higher than 400 mg/dL. At all remaining visits, the LDL cholesterol value was obtained by means of direct measurement or preparative ultracentrifugation if at the same visit the triglyceride level was higher than 400 mg/dL. For all other measures of lipid and lipoprotein markers, whenever possible, the baseline value was derived as the arithmetic mean of the value obtained at visit 2 (Day 0) and the value obtained at the preceding screening visit. If only one of these values was available, that single value was used as the baseline value. Percentages may not total 100 because of rounding.

[b]Race was reported by the investigators.

[c]Body mass index is the weight in kilograms divided by the square of the height in metres.

[d]Eastern European region includes Poland, Romania, Russia, and Ukraine, and Asia-Pacific region includes India.
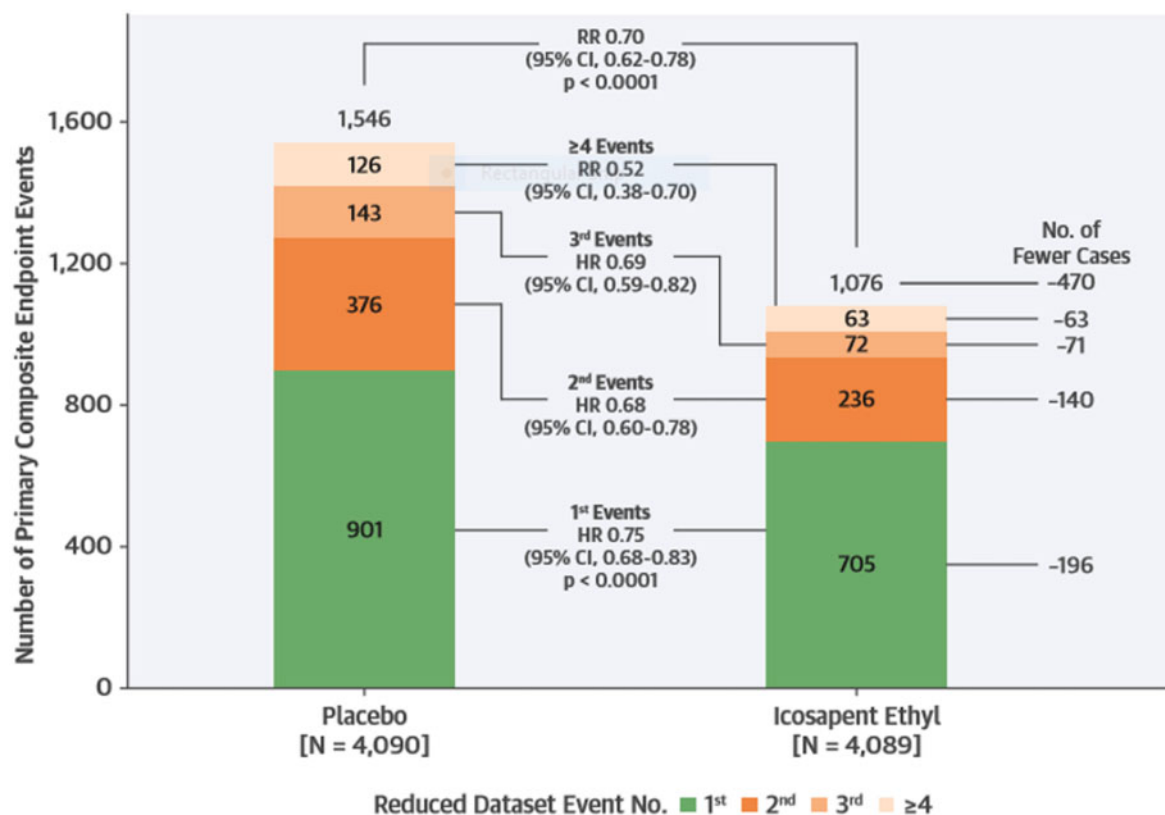
Figure 5 Distribution of first and subsequent primary composite endpoint events in the reduced dataset for patients randomized 1:1 to icosapent ethyl versus placebo. Hazard rations and 95% confidence intervals for between treatment group comparisons were generated using Li-Lagakos modified Wei-Lin-Weissfeld method for the first, second, and third event categories. Rage ratio and 95% confidence interval for between group comparisons used a negative binomial model for additional events beyond first, second, and third occurrences, i.e. fourth event or more and overall treatment comparison. Analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day by counting as a single event. See Central Illustration, ref.[64] with permission. CI, confidence interval; HR, hazard ration; RR, rage ratio.

both first and total ischaemic cardiovascular events across all TG tertiles.[63] The greatest reduction in risk was seen at the highest TG tertile [TG 250-1400 mg/dL (2.8-15.9 mmol/L); hazard ratio 0.68, CI 0.57-0.80; $P < 0.0001$]. Moreover, participants presenting the high TG/low HDL cholesterol phenotype at baseline displayed markedly superior RRR to those without (RRR, 38% vs. 21% in those lacking this lipid phenotype). These findings have several potential implications (i) that elevated TG levels at baseline conferred incremental cardiovascular risk; (ii) that the clinical benefit of high-dose icosapent ethyl was further potentiated by metabolic features present in participants in the highest TG tertile, (iii) that even those with the lowest tertile TG levels had much above normal levels, and (iv) that the manifestation of clinical benefit in all TG tertiles might reflect attenuation of atherogenic mechanisms associated with TG-rich lipoproteins which are integral properties of these particles. Icosapent ethyl intervention in REDUCE-IT conferred significant and consistent clinical benefit across all subgroups.[43] Notable among them was the absence of any effect of baseline LDL cholesterol (as tertiles) on such benefit. Both diabetic and non-diabetic individuals exhibited reduction of both primary and secondary composite endpoints upon icosapent ethyl intervention.

Adherence to study drug, safety, and tolerability

First, data for adherence to study drug showed that the majority of all events occurred while patients in both arms were on randomized drug treatment. Overall, the safety and tolerability of high-dose icosapent ethyl (4 g/day) in the REDUCE-IT trial was entirely satisfactory over the duration of the study.

The physiological effects of n-3 PUFAs on cardiac function are well documented, and include attenuated heart rate and arrhythmias.[61] In REDUCE-IT, it was observed that atrial fibrillation/flutter occurred more frequently in the intervention arm (5.8% vs. 4.5%, respectively; $P = 0.0079$).[43] As an adjudicated endpoint, atrial fibrillation/flutter requiring hospitalization ≥24 h presented at a higher incidence with icosapent ethyl than placebo (3.1% vs. 2.1%; $P = 0.004$). Atrial arrhythmias may contribute to heart failure (HF), but no harmful effect on newly emergent HF was found. While stroke, MI, cardiac arrest, and sudden cardiac death are potential clinical outcomes related to atrial fibrillation and/or flutter, it is relevant that a substantially lower risk of these events was observed in the intervention arm as compared to placebo.

In line with the documented anti-thrombotic effects of n-3 PUFAs, total adverse bleeding events presented more frequently in the intervention arm as compared to placebo

(11.8% vs. 9.9%, respectively; $P = 0.0055$).[43,61] The incidence of serious adverse bleeding events was low and trended towards statistical significance in the icosapent ethyl vs. the placebo group [2.7% (111/4089) vs. 2.1% (85/4090), respectively; $P = 0.06$]; no fatal bleeding events occurred in either group.[43] By comparison with low-dose aspirin in high-risk patients, bleeding rates seen with icosapent ethyl were generally lower.[68] Importantly, when positively adjudicated atrial fibrillation or flutter and serious bleeding events were integrated into the primary and key secondary endpoint data in *post hoc* analyses, the overall study benefit/risk findings were unchanged.

Limitations

REDUCE-IT was a large RCT performed with state-of-the-art methodology, and has therefore provided robust data. As such, limitations in its design are restricted. Median LDL cholesterol levels at baseline 75 mg/dL were close to ESC/EAS recommended guideline goals of ~70 mg/dL at the inception of the trial in 2011, thereby reflecting a high proportion of patients receiving moderate or high-intensity statins (>90%).[43,69] It could also be argued that use of another oil as placebo, in this case mineral oil, is a limitation; however, when the active medication is in the form of an oil it is not possible to use a 'true' placebo in the placebo arm. That said, as the JELIS trial not using mineral oil in the control group observed similar beneficial effect as icosapent ethyl 4 g/day, it is unlikely that mineral oil as the placebo should explain the findings of the REDUCE-IT trial.

Benefit-risk implications of the REDUCE-IT trial

Considered together, the robust clinical evidence obtained in the REDUCE-IT trial fully substantiates the notion that icosapent ethyl, a prodrug of EPA, significantly reduces cardiovascular morbidity and mortality in dyslipidaemic patients treated efficaciously with statins in both primary and secondary prevention. Indeed, icosapent ethyl treatment resulted in highly statistically significant reductions in both the primary and secondary composite endpoints in the trial, in individual components of both endpoints, and additionally, in the prespecified testing hierarchy. In general, findings were consistent across patient subgroups. This ethyl ester of EPA was well tolerated overall, with two safety signals at low rates of frequency: serious bleeding events and atrial fibrillation/flutter. Both of these adverse event represent a feature of the mechanisms of action of n-3 PUFAs.[61] We conclude therefore that consideration of all facets of the REDUCE-It trial indicates that the benefit-risk ratio strongly favours cardiovascular risk reduction by icosapent ethyl.[63-65]

Clearly then, treatment with icosapent ethyl at high dose (4 g/day) constitutes a validated therapeutic agent for reduction of residual risk in statin-treated, dyslipidaemic patients at high cardiovascular risk, providing reductions in first and total ischaemic events by 25% and 30%, respectively, relative to placebo. Such clinical benefit could not, however, be explained by TG reduction alone.[43] REDUCE-IT was not designed to define the mechanisms of action of icosapent ethyl/EPA. Indeed, earlier reviews have discussed the pleiotropic actions of n-3 PUFAs at length, which include not only their direct effects but also those of their bioactive metabolites.[61] It is therefore of considerable pertinence that on-treatment circulating levels of icosapent ethyl-derived EPA were recently reported to correlate strongly with the primary endpoint, the key secondary endpoint, cardiovascular death, MI, stroke, coronary revascularization, unstable angina, sudden cardiac death, cardiac arrest, new-onset HF, and all-cause mortality.[70] The molecular actions of EPA are therefore at the heart of the substantial cardiovascular benefit unequivocally observed in the intervention arm of the REDUCE-IT trial.

Data Availability

No new data were generated or analysed in support of this review article.

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