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Concept and practice in the use of high-dose eicosapentaenoic acid for cardiovascular disease prevention in hypertriglyceridaemia

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ABSTRACT

Genetic and epidemiological evidence indicates that triglyceride-rich lipoproteins are causal risk factors for atherosclerotic cardiovascular disease (ASCVD). Elevated levels of plasma triglyceride are common in patients who are diabetic or obese and contribute substantially to residual, ongoing risk of an ASCVD event in individuals on low-density lipoprotein (LDL)-lowering treatment. Hypertriglyceridaemia, therefore, presents a target for further intervention. Clinical trials have demonstrated that high-dose eicosapentaenoic acid (EPA) is effective in reducing ASCVD risk in patients on statin therapy, and it is now being incorporated into strategies using combination lipid-regulating treatment to manage aggressively those at highest risk. This review summarises the concepts underpinning the use of high-dose EPA alongside intensive LDL-lowering therapy, especially in the context of post-acute coronary syndrome. A practical implementation algorithm is presented setting out treatment options for combination therapy, and the place of high-dose EPA in ASCVD prevention in hypertriglyceridaemia.

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INTRODUCTION

Ischaemic heart disease remains the main cause of death worldwide.[1] Within its multifactorial aetiology low-density lipoprotein (LDL) and other apolipoprotein (apo) B-containing lipoproteins play a central, causal role, promoting the development of the underlying process of atherosclerosis. The use of statins and other drugs—ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, bempedoic acid—to lower LDL is a central strategy in the prevention of atherosclerotic cardiovascular disease (ASCVD) in both primary and secondary settings.[2] However, in many individuals, a substantial ASCVD risk remains after LDL-cholesterol (LDL-C) goal achievement, and elevated plasma triglyceride (TG) is recognised as an important component of this residual risk.[3] Plasma TG, or more specifically TG-rich lipoproteins (TRL), is therefore an additional target for lipid-lowering therapy. Outcome studies of TG lowering using classical drugs such as fibrates and high-dose niacin when added to statins failed to demonstrate further ASCVD risk reduction, although retrospective analyses suggest that subgroups characterised by high TG and low high-density lipoprotein (HDL) may have positive results.[4–7] An alternative approach, treatment with high-dose eicosapentaenoic acid (EPA), has been shown to reduce cardiovascular risk in patients with (and without) hypertriglyceridaemia who are on statins.[8–10]

This review explores the concepts behind, and practical implementation of, an evidence-based therapeutic strategy that tailors further intervention according to the plasma lipid profile in patients on standard statin therapy who are often undertreated.[11]

What is the relationship between plasma TGs, TRL and cardiovascular risk?

Genetic analyses provide robust evidence that elevated TG is a causal risk factor for ASCVD[12 13] and underpin the finding from epidemiological studies that raised TG levels are positively and linearly related to cardiovascular risk (figure 1A).[14 15] The importance of these observations is that they reveal an often unaddressed major risk factor that is of particular relevance in people with obesity or type 2 diabetes in whom TG levels are frequently elevated.[16] Further, outcome trials have shown that elevated TG levels (again especially in type 2 diabetics) are associated with high residual cardiovascular risk in statin-treated patients with established cardiovascular disease, even if they have well-controlled LDL-C.[17–19]

Plasma TG provides a measure of the total concentration of TRL (chylomicrons, very low-density lipoprotein (VLDL) and their remnants) in the circulation (figure 1B) and it is these apoB-containing TRL particles that promote the development of atherosclerosis. TG, itself, does not accumulate at sites of lesion formation. Rather, we now understand that TRL contribute to the process of atherogenesis through a number of pathogenic mechanisms including endothelial dysfunction, cholesterol deposition and foam cell formation and by stimulating inflammatory and pro-thrombotic pathways (figure 2).[16 20 21]

Plasma TG as measured routinely is an appropriate way to assess TRL abundance (figure 1B).[16] Non-fasting TG is at least equivalent to fasting TG in predicting ASCVD risk,[22] however, it is a fasting level that is used to classify individuals as hypertriglyceridemic. Alternatively, TRL cholesterol (TRL-C, also known as remnant cholesterol) (figure 1B) can be estimated or measured directly.[23] This biomarker is highly correlated with plasma TG and assessing the latter may be sufficient in most clinical settings.[24]

How can TRL-associated risk be decreased and what is the target population?

Hypertriglyceridaemia is present in approximately 10% of the adult population.[20] Moderate-to-severe

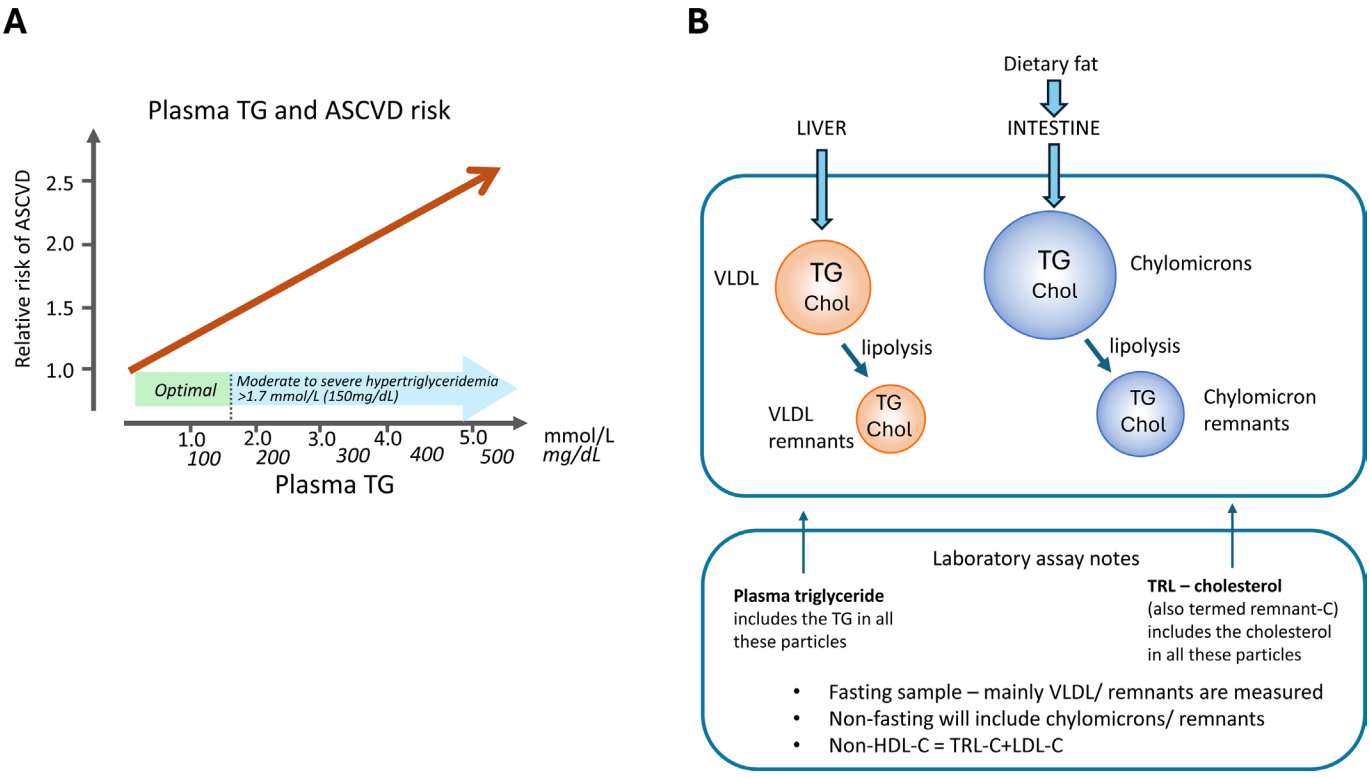

Figure 1 Relationship of plasma triglyceride to atherosclerosis. (A) Association of plasma TG with ASCVD event rate (based on data from [53]). Hypertriglyceridaemia is defined as TG above 1.7 mmol/L (150 mg/dL) (2,16). (B) Plasma TG is a biomarker for the abundance of TRL—chylomicrons, VLDL and their remnants. These apolipoprotein B-containing particles transport TG through the bloodstream. During dietary fat absorption, chylomicrons are made in the intestine to carry TG to tissues especially adipose tissue where it is stored. VLDL are secreted by the liver and supply TG to tissues, particularly muscle, in the fasted state. As TG contained in these particles is hydrolysed (lipolysis) smaller 'remnant' lipoproteins are formed. TRL also contains cholesterol (Chol) that is enriched in remnants. TRL cholesterol, also termed remnant cholesterol, is an alternative measure of TRL abundance. Plasma TG can be measured with the patient fasting or non-fasting, if non-fasting then TG levels are likely to be higher reflecting the presence of chylomicrons. ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; TRL, triglyceride-rich lipoproteins; VLDL, very low-density lipoprotein.

hypertriglyceridaemia is defined in the European (ESC-EAS) and guidelines[2 16] as a fasting plasma TG between 1.7 mmol/L (150 mg/dL) and 10 mmol/L (885 mg/dL) (figure 1A). In most cases, it is the result of polygenic susceptibility and contributing factors such as a diet rich in fat or with a high glycaemic index, excessive alcohol consumption, obesity, metabolic syndrome, type 2 diabetes, renal disease and certain medications (including corticosteroids, oestrogen, thiazides, antiretroviral drugs and second-generation antipsychotic agents).[16 20]

Accordingly, guidelines highlight the role of alcohol abstinence, weight reduction, regular physical exercise and dietary modification as a first step in reducing plasma TG.[2] Depending on the risk status of the individual, the next stage is to initiate pharmacological therapy with a defined LDL-C and/or non-HDL-C goal (non-HDL-C is easily measured and includes TRL-C and LDL-C) (figure 1B). The concept here is that high plasma TG identifies patients at increased risk who should be treated intensively, usually with combination lipid-lowering therapy.[25] Reduction in LDL-C is the primary intervention target, using statins first and then if needed by adding ezetimibe and PCSK9 inhibitors to achieve recommended goals. These agents, especially statins, can also have a clinically useful effect on TG/TRL levels, reducing them by up to 25% in hypertriglyceridemic patients.[20] This action of statins appears to be the result of stimulation of remnant lipoprotein clearance (figure 2) analogous to the way in which LDL-C is reduced.

Once lifestyle changes are implemented and patients stabilised on LDL-lowering therapy (as near to goal as possible), a further, critical step is to assess and treat TG-associated cardiovascular risk, especially in people with established cardiovascular disease and in high-risk patients who have not yet had an ASCVD event such as those with type 2 diabetes.[3 26] Guidelines no longer support the addition of fibrates or niacin to statin therapy in ASCVD prevention. Although these drugs decrease plasma TG by 25%–45%, they gave disappointing results in outcome trials.[4–7] What is now recommended is to consider the use of high-dose EPA (icosapent ethyl (IPE)—a highly purified formulation of EPA) to reduce ASCVD risk in patients with elevated plasma TG. This agent moderately reduces TG levels mainly by inhibiting chylomicron and VLDL production in the intestine and liver (figure 2). Other formulations of omega-3 fatty acids including lower dose EPA and combinations of EPA and docosahexaenoic acid (DHA) have similar TG-lowering actions but in major trials did not reduce ASCVD risk[27] for reasons that are not yet fully clear. Current thinking is that high-dose EPA monotherapy has a range of possible antiatherosclerotic actions beyond TG lowering including anti-inflammatory and antithrombotic effects, and stabilisation of cell membranes (figure 2).[28 29]

Broadly speaking, the target group for pharmacotherapy to reduce the risk associated with elevated TG is hypertriglyceridemic individuals with established ASCVD or at high risk of developing cardiovascular disease who are on optimal, tolerated

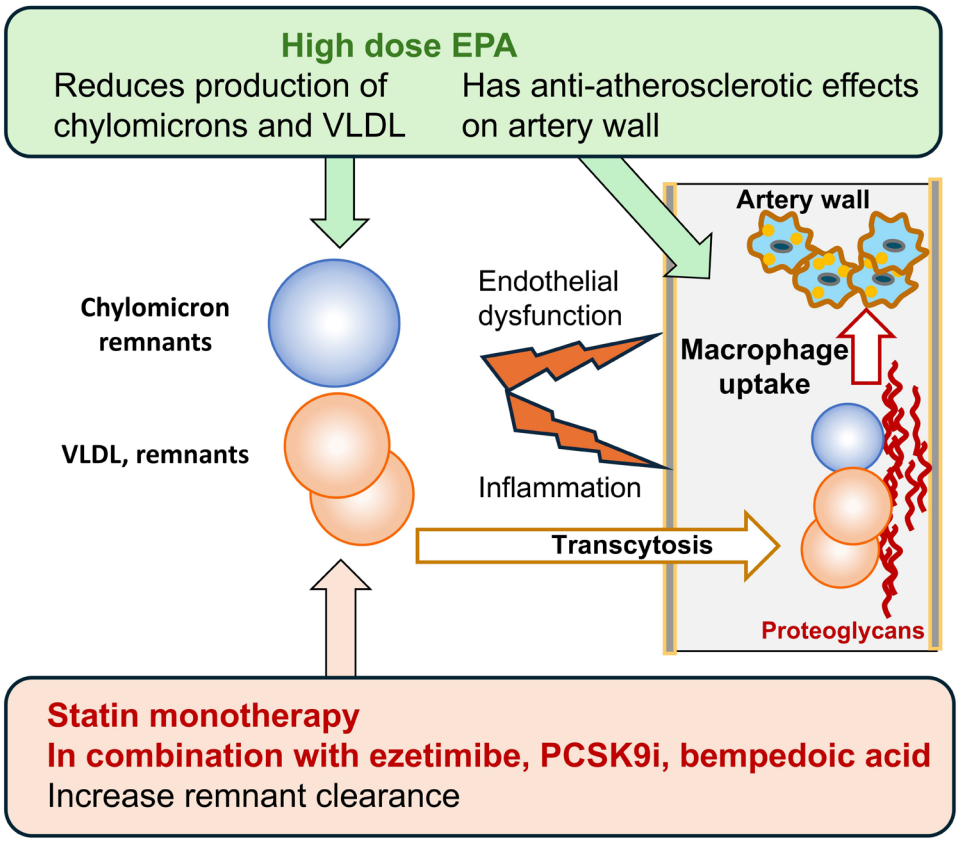

Figure 2 Role of triglyceride-rich lipoproteins in atherosclerosis. Chylomicron remnants and VLDL remnants can, like LDL, penetrate the artery wall. Once in the subendothelial space these particles can bind to extracellular proteoglycans and subsequently be ingested by macrophages leading to the formation of cholesterol-enriched 'foam' (lipid-filled) cells. In this way, cholesterol in TRL can contribute to atherosclerotic plaque progression (16). There is also emerging evidence that TRL and remnants may promote atherogenesis by causing inflammation, endothelial dysfunction, and by stimulating thrombosis. Drugs that increase lipoprotein receptor activity in the liver (statins, ezetimibe, PCSK9 inhibitors) can lower TRL by enhancing their clearance from the bloodstream. High dose EPA inhibits TRL synthesis and thereby lowers TRL levels in the circulation. EPA is also thought to have anti-inflammatory and anti-thrombotic effects. EPA, eicosapentaenoic acid; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; TRL, triglyceride-rich lipoproteins; VLDL, very low density lipoprotein.

LDL-lowering therapy (usually statin or statin plus ezetimibe) and have a persistently (after lifestyle modification and attention to underlying disorders) raised TG. More specifically, in line with the inclusion criteria for Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), high-dose EPA therapy is appropriate for those with TG between 1.7 mmol/L (150 mg/dL) and 5.64 mmol/L (500 mg/dL) who have established ASCVD, or type 2 diabetes plus another ASCVD risk factor.[9] About 12%–25% of subjects with established ASCVD on statin therapy are in this TG range.[30 31] Above the TG upper limit, there is a lack of evidence as to the benefits of high-dose EPA, and it is the increasing risk of acute pancreatitis that becomes a major concern (even more so when TG >10.0 mmol/L (885 mg/dL)) for which alternate or additional interventions are likely to be needed.[20]

What clinical trial evidence supports interventions to lower LDL-C and TG-associated CVD risk?

LDL lowering using statins is recommended first-line therapy to reduce ASCVD risk. In a meta-analysis of 26 trials, a 1.0 mmol/L reduction in LDL-C was associated with a 22% risk reduction of major atherosclerotic cardiovascular events (MACE).[32] Further LDL-C reduction accompanied by decreases in ASCVD risk can be achieved using ezetimibe, and/or PCSK9 inhibitors (alirocumab, evolocumab) in combination with statins, while bempedoic acid is of use in statin-intolerant patients.[25] Table 1 summarises outcome studies of multiple therapeutic modalities in terms of relative risk reduction and treatment effectiveness (number needed to treat to prevent one event (NNT)), while figure 3 focusses specifically on post-acute coronary syndrome (ACS) a common condition for which outcomes can be usefully compared across studies. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial study[33] in post-ACS patients, addition of ezetimibe to statin yielded a further small but significant 6.4% risk reduction (table 1, figure 3). The efficacy of PCSK9 inhibition in post-ACS patients was tested in ODYSSEY OUTCOMES[34] where treatment with alirocumab on top of statin resulted in 15% fewer MACE. Likewise, in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk trial,[35] patients had a 15% lower rate of MACE on evolocumab plus statin versus statin alone (table 1). Finally, in a trial in high-cardiovascular risk patients unable or unwilling to take a moderate or high dose of statins (22% were on low-dose statins), bempedoic acid therapy reduced LDL-C by 21% and gave a significant 13% reduction in cardiovascular outcomes.[36]

In large trials, niacin,[6 7] fibrates[4 5] and low-dose fish oil supplements[37] lowered plasma TG but showed no associated cardiovascular risk reduction when added to statins. It was the landmark REDUCE-IT trial[9] that established high-dose EPA

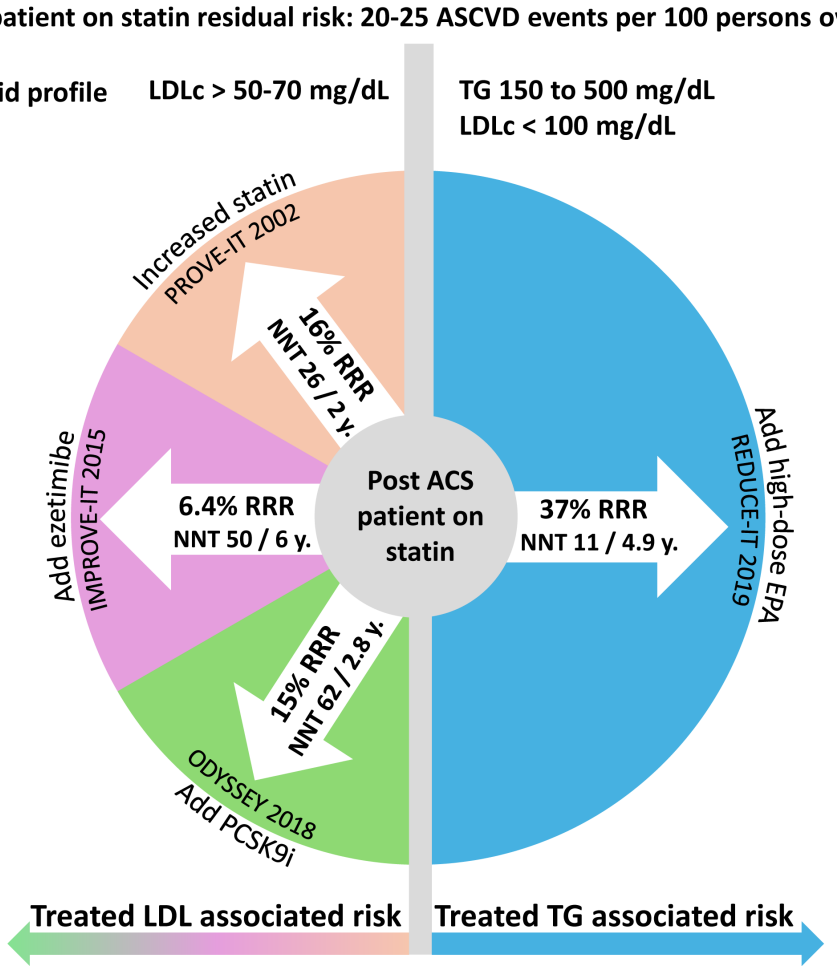

Figure 3 Comparison of trials of therapies addressing lipid-associated risk in acute coronary syndrome. Recent ACS cohorts comprised all subjects recruited to PROVE-IT, IMPROVE-IT and ODYSSEY OUTCOMES and 10.3% of subjects recruited to REDUCE-IT. For each trial, the per cent relative risk reduction (RRR for active drug vs placebo) is given along with the number needed to treat (NNT). Note the length of follow-up has to be taken into account when comparing NNTs in different studies. ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; EPA, eicosapentaenoic acid; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL, low-density lipoprotein; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PCSK9i, Proprotein convertase subtilisin/kexin type 9 inhibitor; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; TG, triglyceride.

(IPE 4 g/day) as an effective agent for reducing ASCVD risk in statin-treated individuals with hypertriglyceridaemia (tables 1 and 2). The 25% risk reduction was consistent across subgroups including those post-ACS[38] (figure 3), those with chronic renal failure[39] and those with metabolic syndrome without diabetes.[40] The results from REDUCE-IT were echoed in the smaller but informative Japan EPA Lipid Intervention Study (JELIS) and RESPECT trials (table 2). JELIS reported a risk reduction of 19% on EPA monotherapy,[8] while the recent Randomised Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy Statin and Eicosapentaenoic Acid trial demonstrated a numerically 21% lower risk of the primary endpoint that did not reach statistical significance, although the secondary composite endpoint of coronary events did (table 2).[10]

When considering the REDUCE-IT trial, it should be noted that small but statistically significant increases in biomarkers such as LDL-C and hs-CRP occurred in the placebo arm (where mineral oil was given). These changes which may have led to a slightly worse outcome in that arm[41] could in large part be accounted for by discontinuation or reduction of background statin therapy. Whatever the reason, a 'worst case scenario' analysis by the FDA indicated that these changes could not account for more than 3% of the 25% relative risk reduction seen on high-dose EPA.[42]

A large trial of EPA plus DHA therapy—Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia study—did not show a clinical benefit in terms of MACE risk reduction in subjects comparable to those recruited to REDUCE-IT (table 2).[27] There has been a great deal of speculation as to why these two trials of similar design produced such markedly different results. It is postulated that EPA and DHA while both lowering TG and TRL may have differing effects on other antiatherosclerotic mechanisms.[28 29] Along these lines, a recent meta-analysis of randomised, controlled coronary revascularisation trials comparing EPA monotherapy with EPA plus DHA (18 trials, 132 144 participants) reported greater benefit when patients received EPA alone versus the combination[43] (see reference 44 for a critique of this study).[44]

Figure 3 presents outcome results for key lipid-lowering trials in statin-treated post-ACS subjects. Patients with this condition require aggressive management due to the very high risk of a recurrent cardiovascular event (approximately 4% to

Table 1 Comparative clinical benefits of treating elevated plasma lipids, chronic inflammation and thrombosis risk in subjects with or at high risk for ASCVD

TG-associated risk	LDL-associated risk			Inflammation-associated risk	Thrombosis-associated risk
DESIGN—study drug, trial name, enrolment period, median follow-up length and % with prior ASCVD					
IPE (EPA) REDUCE-IT* 2011–16 4.9 years 71%	Ezetimibe IMPROVE-IT 2005–10 6 years 100%	Evolocumab FOURIER 2013–15 2.2 years 100%	Alirocumab ODYSSEY OUTCOMES 2012–17 2.8 years 100%	Colchicine COLCOT 2015–18 1.9 years 100%	Rivaroxaban ATLAS ACS TIMI 51 2008–2011 1.1 years 100%
RESULTS—risk reduction (HR), event rates, and effectiveness (number needed to treat—NNT)					
HR 0.75 17.2% vs 22.0% NNT 21	HR 0.94 32.7% vs 34.7% NNT 50	HR 0.85 9.8% vs 11.3% NNT 67	HR 0.85 9.5% vs 11.1% NNT 62	HR 0.77 5.5% vs 7.1% NNT 62	HR 0.84 8.9% vs 10.7% NNT 56
NNT is calculated from the absolute risk reduction and depends on study length, so caution must be exercised when comparing across trials					
Major safety findings—event rates, number needed to harm (NNH)					
Bleeding 2.7% vs 2.1% NNH 166 Atrial fibrillation 5.3% vs 3.9% NNH 71	None	Local injection site reaction	Local injection site reaction	Pneumonia 0.9% vs 0.4% NNH 200	Bleeding 2.1% vs 0.6% NNH 66
NNH for specific adverse outcomes					

REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, unstable angina)).
IMPROVE-IT: Improved Reduction of Outcomes: Vytorin Efficacy International Trial (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, unstable angina).
FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, unstable angina).
ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (death from coronary heart disease, non-fatal MI, ischemic stroke, unstable angina).
COLCOT: Colchicine Cardiovascular Outcome Trial (CV death, non-fatal MI, non-fatal stroke, hospitalisation for angina leading to coronary revascularisation, resuscitated cardiac arrest)
ATLAS ACS: Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS (CV death, non-fatal MI, non-fatal stroke)
*Study acronyms and endpoints used for HR calculation.
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; EPA, eicosapentaenoic acid; IPE, icosapent ethyl; LDL, low-density lipoprotein; MI, myocardial infarction; TG, triglyceride.

5% annually). LDL-C and plasma TG are commonly elevated or above goal even on optimal tolerated statin treatment, and therefore both are targets for further intervention. The figure summarises the benefits of further LDL-C reduction (using a high statin dose or adding ezetimibe or a PCSK9 inhibitor) and the use of high-dose EPA to address TG-associated ASCVD risk. In hypertriglyceridaemic post-ACS patients, addition of high-dose EPA to statin therapy provided a benefit that was of the same magnitude in terms of relative risk reduction and effectiveness (NNT) as further LDL-C lowering.

Table 2 Key recent clinical outcome trials of omega-3 fatty acids (EPA and EPA+DHA) in ASCVD prevention

Study (year)	REDUCE-IT* (2019)[9]	JELIS (2007)[8]	RESPECT-EPA (2024)[10]	STRENGTH (2020)[27]
Design	Randomised, double-blind, placebo-controlled	Randomised, open-label, blinded endpoint	Randomised, open-label, blinded end-point	Randomised, double-blind, placebo-controlled
No. subjects	8179	18645	2506	13078
Patient population	Established ASCVD (71%) or diabetes and ≥1 other risk factor (29%)	Mixed population with and without ASCVD	Established ASCVD (stable CAD)	Established ASCVD or high-risk primary prevention
Baseline lipid profile	TG 150–500 mg/dL LDL-C 41–100 mg/dL	Total cholesterol>251 mg/dL	No thresholds for TG and LDL-C levels EPA/arachidonic acid ratio<0.4	TG 180–500 mg/dL LDL-C<100 mg/dL
Study drug	EPA (IPE) 4 g/day	EPA 1.8 g/day	EPA (IPE) 1.8 g/ day	EPA+DHA 4 g/day
Follow-up	4.9 years	4.6 years	5 years	3.5 years
Primary endpoint	Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, unstable angina	Sudden cardiac death, myocardial infarction, coronary revascularisation, unstable angina	Cardiovascular death, nonfatal myocardial infarction, nonfatal ischaemic stroke, coronary revascularisation, unstable angina	Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, unstable angina
Relative risk reduction (HR)	0.75 (95% CI, 0.68 to 0.83)	0.81 (95% CI, 0.69 to 0.95)	0.79 (95% CI, 0.62 to 1.00)	0.99 (95% CI, 0.90 to 1.09)

*Study acronyms.
ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HR, hazard ratio; JELIS, Japan EPA Lipid Intervention Study; LDL, low-density lipoprotein; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; RESPECT-EPA, Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy Statin and Eicosapentaenoic Acid; STRENGTH, Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia; TG, triglyceride.

Finally, in the wider clinical context, physicians treating patients with established ASCVD (especially in the post-ACS situation) are required to address an individual's global cardiovascular risk including elevated plasma lipids, chronic inflammation and risk of thrombosis. In formulating therapeutic strategies, it is worth noting that (as summarised in table 1) in terms of relative risk reduction and effectiveness (NNT) attention to lipid targets (with intensive LDL lowering and high dose EPA) ranked well alongside other commonly employed interventions such as anti-inflammatory and anti-platelet treatment. Furthermore, in tailoring therapy to the lipid profile of the post-ACS patient, it may be appropriate to consider a combined approach of aggressively lowering LDL-C and using high-dose EPA.

It should also be noted that an increased risk of atrial fibrillation was a consistent finding in omega-3 outcome trials with a higher incidence seen on EPA or EPA+DHA (table 1[45]). While this side effect is a consideration in selecting patients for treatment especially post-ACS, it has been reported that the overall risk of stroke in subjects with prior or incident atrial fibrillation was reduced by high-dose EPA therapy.[46]

In summary, outcome trials have demonstrated the value of LDL lowering using a range of drugs, especially in combination, and an apparent continuous relationship between the degree of LDL reduction and decrease in risk. Trials of TG lowering present a different picture. Clinical benefit has been shown with high-dose EPA, but not with other agents. While TG reduction likely contributes in part to the ASCVD risk reduction on high-dose EPA, other mechanisms also appear to be involved and may actually be predominant. In individual trials conducted to date, there was no clear association between the degree of TG lowering and ASCVD risk reduction. Accordingly, while guidelines recommend a threshold level at which to consider initiating therapy (as described above),[2] no treatment goal has been set for TG reduction.

What kind of patients benefit most from high-dose eicosapentaenoic acid therapy?

Based primarily on the evidence from the REDUCE-IT study, international and national bodies have incorporated the targeted use of high-dose, pharmaceutical grade EPA into guidelines for the treatment of raised plasma TG in at-risk individuals. It can be useful to crystallise the practical implementation of this therapeutic approach by considering patient cases as set out in figure 4. In each case, the patient has received LDL-lowering therapy, and the on-treatment LDL-C would be considered within the range achieved in routine practice.[47] However, clinical trial evidence indicates that due to the background medical and cardiometabolic status, the patient in each case is still at high risk.

Case 1 is typical of many post-ACS patients in whom it is essential to control the lipid profile as effectively as possible. Given that LDL-C was above goal on statin plus ezetimibe (figure 4), she was put on a PCSK9 inhibitor and achieved an LDL-C in line with ESC/EAS recommendations. However, concern remained over persistent hypertriglyceridaemia and so IPE 2 g two times per day was added. The absolute benefit of high-dose EPA is substantial in ACS (figure 3); it is necessary on average to treat only 11 patients to avoid one major cardiovascular event.[38]

Case 2 has a cardiometabolic disorder that is common in individuals at high risk of ASCVD. His 10-year SCORE2-DIABETES risk was 20.6%. The patient is frankly hypercholesterolaemic in addition to having diabetes and hypertension and requires aggressive therapy to lower LDL-C as the first lipid-lowering target. Lifestyle changes were instituted, and he was put on triple

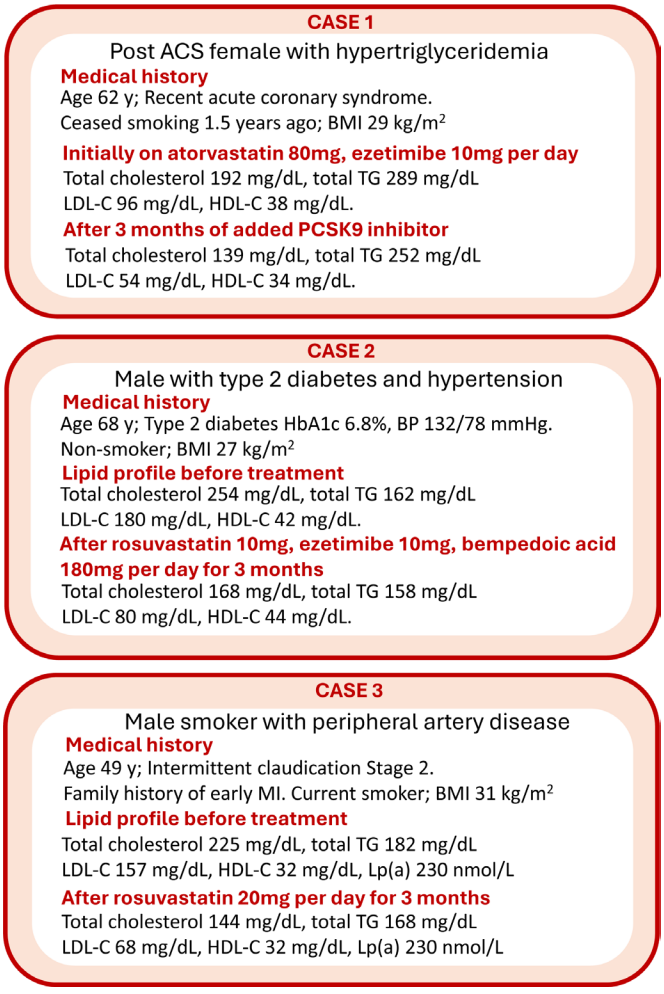

Figure 4 Case histories of typical candidates for high-dose EPA treatment. ACS, acute coronary syndrome; BMI, body mass index; BP, blood pressure; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); MI, myocardial infarction; PCSK9, Proprotein convertase subtilisin/kexin type 9; TG, triglyceride.

LDL-lowering therapy with the results shown in figure 4. As is the case in many countries, PCSK9 inhibitor is not reimbursed in this clinical setting (primary prevention, LDL-C <2.6 mmol/L (<100 mg/dL)) and in light of his risk status, IPE 2 g two times per day was added. Patients with diabetes at high or very high cardiovascular risk despite not having overt cardiovascular disease can benefit from high-dose EPA.[9]

Case 3 is a relatively young, obese smoker with a history of intermittent claudication (stage 2 Leriche-Fontaine) and a family history of early myocardial infarction. Having both a personal and family history of ASCVD places this patient at very high risk. Further, the incidence of myocardial infarction is greatly increased in people with peripheral artery disease.[48] Lipoprotein (a), an independent risk factor for ASCVD, was high and it is now recommended that Lp(a) is assessed routinely, especially in younger people at risk.[49] Lifestyle therapeutic changes, including an exercise plan and medically supported smoking cessation, were started. He was put on aspirin 100 mg, and statin therapy gave a substantial decrease in LDL-C (figure 4). On the basis of his persistently elevated TG and high Lp(a) IPE 2 g two times per day was added to the regimen. High-dose EPA has been shown to reduce MACE across a range of Lp(a) levels, including

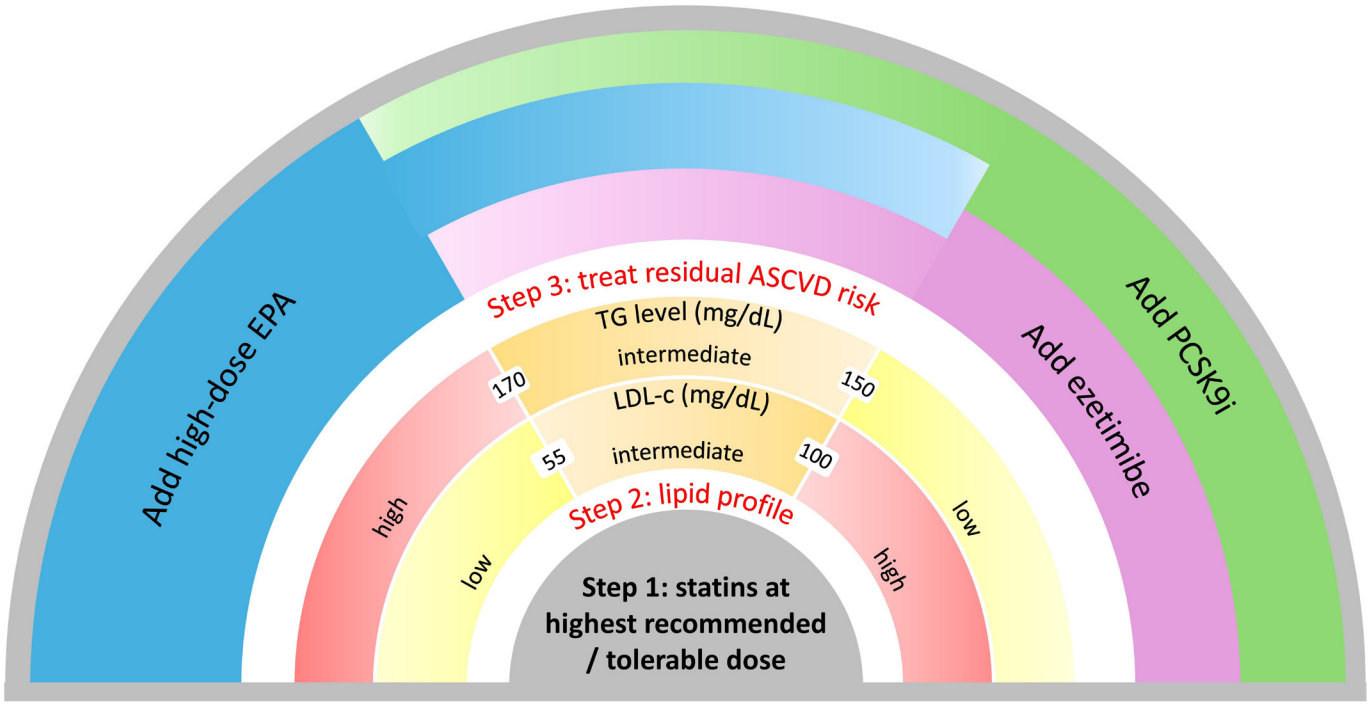

Figure 5 A 'desk-card' summary of combination therapeutic strategies in high-risk patients on optimal, tolerated statin therapy. Evaluation of the lipid profile of the individual once established on optimum tolerated statin treatment allows further therapeutic decisions to be made. Further LDL-C lowering is mandated when LDL-C is high. When TG is elevated, this risk can be addressed with high-dose EPA treatment. These are not mutually exclusive as seen in the Case Studies in figure 4; with mixed hyperlipidaemia a combination of approaches may be appropriate. A version with units in mmol/L is included in online supplemental figure 1. ASCVD, atherosclerotic cardiovascular disease; EPA, eicosapentaenoic acid; LDL, low-density lipoprotein; PCSK9i, Proprotein convertase subtilisin/kexin type 9 inhibitor; TG, triglyceride.

among those with clinically relevant elevations.[50] Parenthetically, at present, there are no marketed agents that specifically lower Lp(a) although PCSK9 inhibitors have been shown to reduce Lp(a) moderately.[51] Agents are in development, but in the meantime, the recommendation is to aggressively reduce the overall risk profile of individuals in whom this lipoprotein is increased.[49]

Concept into practice: a balanced lipid-lowering strategy for ASCVD prevention

There is now a clear imperative to move beyond the statin monotherapy era to centre future practice on a tailored approach that addresses more directly the individual lipid profile in the patient at risk. Once a patient is established on an optimal, tolerated statin dose, then there is a need to evaluate the residual risk and how much is due to LDL and what can be attributed to elevated TG. In many cases, combination therapy should be considered, and cogent schemes have been proposed for both high-risk primary prevention and the treatment of those with clinical cardiovascular disease.[25]

Figure 5 provides a 'desk-card' treatment scheme based on evidence from clinical trials. It sets out therapeutic options aligned to the LDL-C and TG levels in subjects on statins. First, a judgement has to be made as to the benefits of add-on LDL-lowering agents such as ezetimibe, PCSK9 inhibitors and bempedoic acid. The higher the LDL-C above goal, the greater the clinical benefit of more aggressive LDL reduction.[52] Second, the hypertriglyceridaemic status of the patient should be evaluated. If TG is elevated (>1.7 mmol/L, >150 mg/dL), the attendant risk can be ameliorated substantially by the addition of high-dose EPA to LDL-lowering therapy. It is only by addressing the totality of the risk associated with apoB-containing lipoproteins, as exemplified by the cases in figure 4, that further inroads will be made into preventing the growing issue of cardiovascular disease associated with hypertriglyceridaemia as the prevalence of obesity and diabetes increases worldwide.

In conclusion, this review highlights the central role that TRL and remnants play in atherosclerosis and the evidence that the risk associated with hypertriglyceridaemia can be reduced with appropriate therapy. It offers a practical guide as to when and in whom it is relevant to consider instituting high-dose EPA treatment in a comprehensive strategy addressing the totality of the ASCVD risk associated with TRL and LDL. The main challenges now lie in the implementation of the findings from clinical trials, access to the treatment, and the incorporation of effective strategies into everyday clinical practice.

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