Triglycerides Revisited: A contemporary perspective on the assessment and management of cardiovascular risk due to elevated triglycerides

A Consensus Statement of the International Atherosclerosis Society

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Rahul Aggarwal, MD[1], Christina Bursill, BSc (Hons 1) PhD[2], Gemma A. Figtree, MBBS, DPhil[3], Samantha L. Hocking, MBBS, MMed (Clin Epi), PhD[4], R. Preston Mason, PhD[5], Erin D. Michos, MD, MHS[6], Michael Miller, MD[7], Adam J. Nelson, MBBS, MPH, MBA, PhD[8], Stephen J. Nicholls, MBBS, PhD[8], Kerry-Anne Rye, BSc (Hons), PhD[9], Ph. Gabriel Steg, MD[10], Gerald F. Watts, DSc, MD, PhD[11], Sophia Zoungas, MBBS (Hons) PhD[12], Peter Libby, MD[1]

A full list of affiliations appears at the end of this document.

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Abstract

Elevated triglycerides, or hypertriglyceridemia, is common globally and associated with increased cardiovascular (CV) risk. Despite this, hypertriglyceridemia remains underdiagnosed and undertreated. Hypertriglyceridemia can be caused by primary genetic etiologies or by secondary causes. Recognizing and managing secondary causes is critical. Lifestyle interventions are important to reduce triglyceride levels, including diet, weight loss, and physical activity interventions. Understanding the evidence behind the available medical therapies will inform clinical care, as reviewed in this statement, including fibrates and omega-3 fatty acids. Many novel therapies are currently in development for hypertriglyceridemia and show considerable promise.
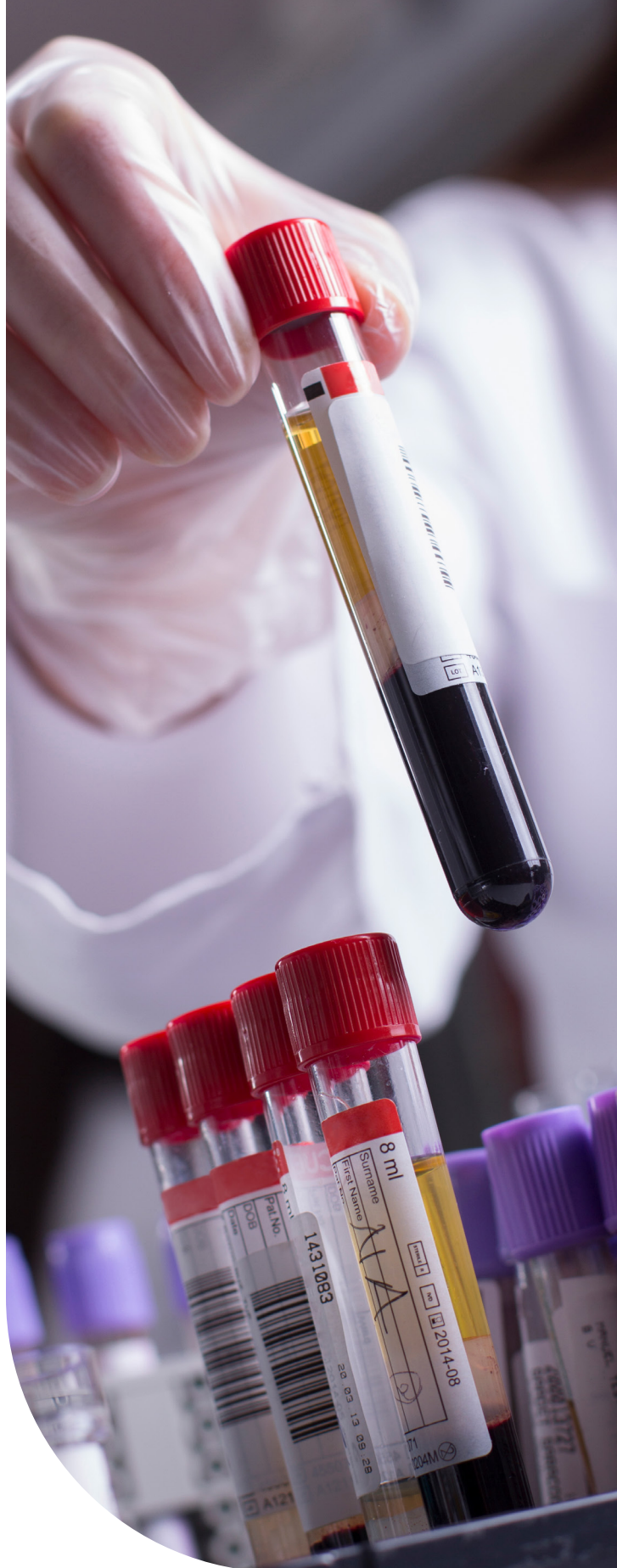
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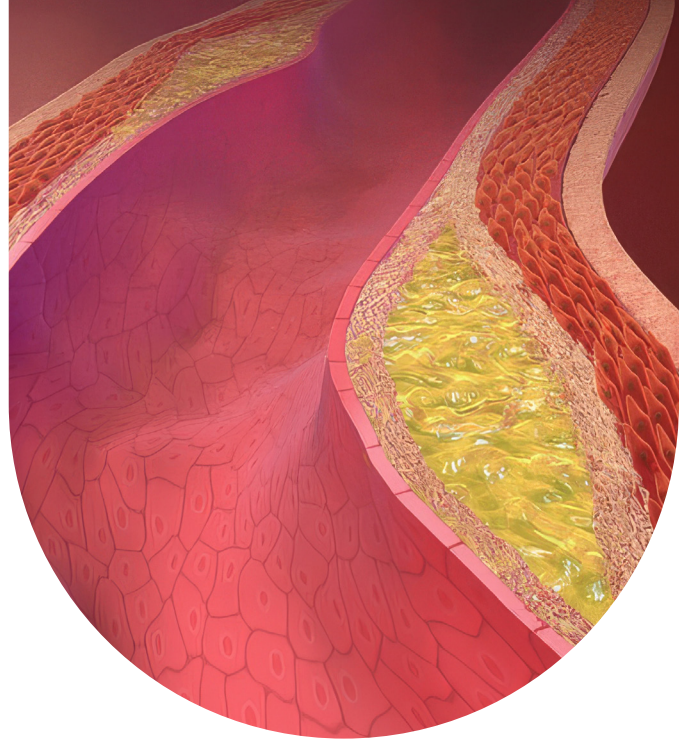
Introduction

While identifying and treating the now standard modifiable risk factors (SMuRFs: hypertension, diabetes mellitus, hypercholesterolemia, and smoking) have led to critical to reductions in cardiovascular disease (CVD) and death, there remains a substantial disease burden across the globe that these approaches do not address.[1,2]

Indeed, recent analysis of harmonized individual-level data from a global cohort of 1.5 million participants reported that five modifiable risk factors (SMuRFs and body-mass index) explain only 53% and 57% of the global population attributable fraction of 10-year CVD incidence for men and women, respectively.[3] Consistent with this, ~10-25% of first-time patients with myocardial infarction (MI) have no SMuRFs.[4–6] Appreciation has increased that dysregulated triglyceride metabolism is an independent and potentially modifiable risk factor, relevant to personal and population level therapeutic strategies.

Hypertriglyceridemia has a high prevalence worldwide as diabetes and attendant dysmetabolism sweeps the globe.[7–11] Epidemiological studies suggest that 10% to almost 25% of adults have elevated triglycerides.[7,12] The prevalence varies by race, ethnicity, and ancestry.[7,13]

Triglycerides levels associate inversely with high-density lipoprotein cholesterol (HDL-C) levels. Cardiovascular (CV) risk from hypertriglyceridemia was traditionally attributed to the reduction of the putative protective effects mediated by lower plasma HDL-C concentrations that generally accompany increased triglycerides. Studies evaluating CV risk with elevated triglycerides historically adjusted for HDL-C levels, which often decreased or nullified the association between triglycerides and CV risk.[14,15]

However, recent evidence highlights the importance of triglyceride-rich lipoproteins (TGRLs) in the causal pathway of CVD, demonstrating that patients with hypertriglyceridemia indeed have increased CV risk.[16–22] Nonetheless, hypertriglyceridemia remains underdiagnosed and undertreated.[16] Hypertriglyceridemia can lead to non-cardiac disease as well, such as hepatic steatosis and acute pancreatitis.[23] This review, however, focuses on the CV risk with elevated triglycerides, and provides practical information to aid clinicians in diagnosing and managing hypertriglyceridemia.

Classification of Hypertriglyceridemia

Hypertriglyceridemia can be classified by degree of elevation of the plasma concentration of triglycerides (**Table 1**). Triglyceride levels <150 mg/dL (<1.7 mmol/L) are considered within the normal range.[24] Mild-to-moderate hypertriglyceridemia is defined as a fasting triglyceride concentration of 150-499 mg/dL (1.7-5.6 mmol/L) or non-fasting triglyceride concentration of 175-499 mg/dL (2.0-5.6 mmol/L).[24] Severe hypertriglyceridemia is a triglyceride level ≥500 mg/dL (>5.6 mmol/L).[24] However, it should be noted that triglyceride levels within the normal range have been associated with CV events.[25] Updated scientific and consensus statements from the American Heart Association and European Atherosclerosis Society include the designation of "optimal" for fasting triglyceride levels at <100 mg/dL (< 1.2 mmol/L).[26,27]

Pathophysiology

Triglycerides are composed of three fatty acid acyl chains attached to a glycerol backbone.[28] Triglycerides, as measured in the clinical laboratory, serve as a biomarker for a class of lipoproteins collectively known as TGRLs, which include chylomicron remnants and very low density lipoprotein remnants. These particles are spherical and have a central core of triglycerides and cholesterol esters surrounded by a layer of apolipoproteins, phospholipids, and unesterified cholesterol.[29]

TGRLs and their remnant particles mediate CV risk from their cholesterol content rather than triglycerides per se.[29] TGRL remnants are actually more atherogenic than low density lipoprotein (LDL) on a per particle basis.[30] TRGLs and their remnants also increase inflammation, especially vascular inflammation,[22,31] and promote atherosclerosis.[22] Indeed,

Updated scientific and consensus statements from the American Heart Association and European Atherosclerosis Society include the designation of "optimal" for fasting triglyceride levels at <100 mg/dL (< 1.2 mmol/L).[26,27]

the pro-inflammatory effects of TGRL exceeds that of LDL.[32] Triglyceride levels are associated with TGRL levels.[26,33-35]

Physiologically, triglycerides consumed in the diet are transported from the small intestine to other areas of the body (**Figure 1**). This process requires the incorporation of triglycerides into chylomicrons.[27] Chylomicrons subsequently travel to peripheral tissues where their triglycerides undergo hydrolysis by lipoprotein lipase (LPL). This hydrolysis releases free fatty acids for use by the peripheral tissues of the body.[27]

The liver synthesizes very low density lipoproteins (VLDLs), which transport triglycerides to peripheral tissues.[27] LPL is associated with the surface of microvascular endothe-

lial cells, and hydrolyzes triglycerides in TGRLs, releasing free fatty acids that can enter tissues to provide energy for storage or circulate bound to albumin. This process also converts VLDL to intermediate-density lipoproteins (IDLs), which are subsequently taken up by the liver via a receptor mediated process regulated by apoC3, apoE and endothelial lipase or undergo further hydrolysis by hepatic lipase to form LDL.[27]

Lipolysis of triglycerides in chylomicrons and VLDLs leads to formation of remnant particles.[36] These remnant particles, reflected by remnant-cholesterol concentration and included in the non-HDL-C metric, are independently predictive of increased CV risk.[22,26,37]
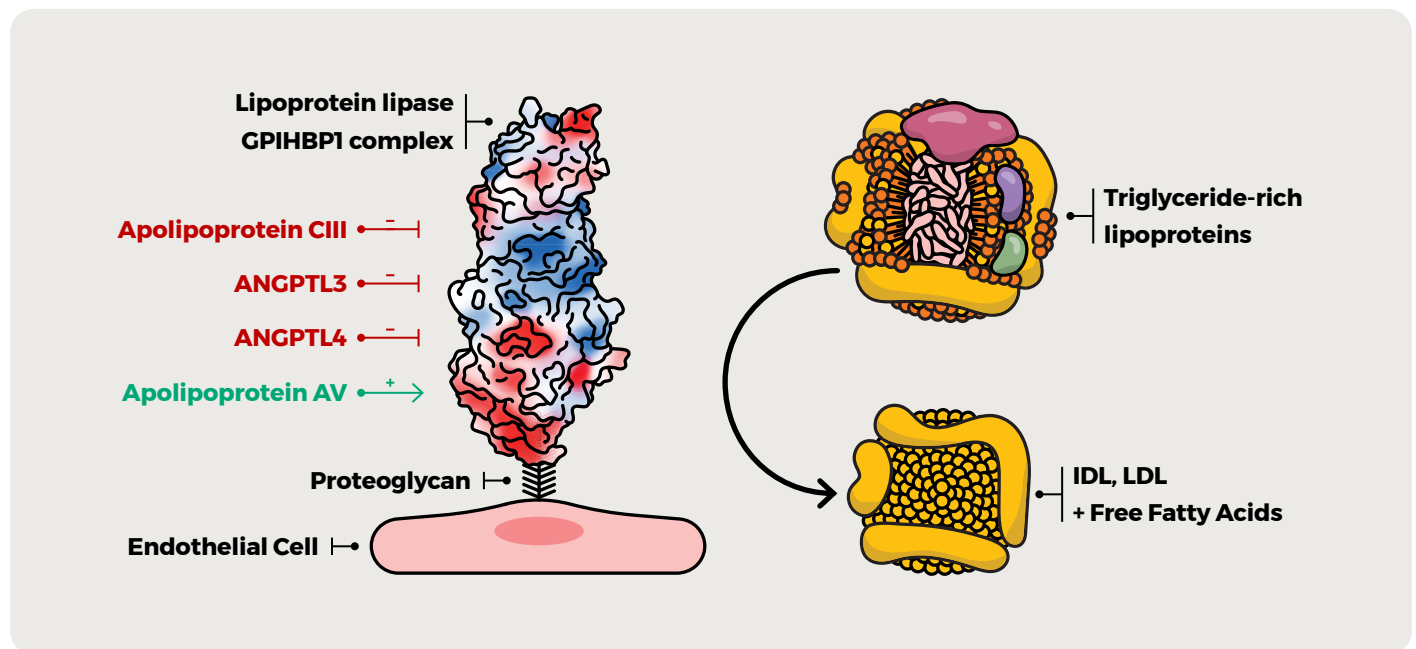
Figure 1: Lipoprotein lipase: a key to understanding triglyceride metabolism. The enzyme lipoprotein lipase (LPL) in a complex with GPIHBP1 (Glycosylphosphatidylinositol high density lipoprotein-binding protein-1) associates with the surface of endothelial cells by binding to proteoglycans. This enzyme trims triglyceride from triglyceride-rich lipoproteins (TGRL), which include remnants of chylomicrons produced by intestinal cells from dietary lipid and very low-density lipoproteins (LDL) synthesized endogenously by the liver. Lipoprotein lipase action yields the products free fatty acids and low-density lipoprotein and intermediate-density lipoproteins (IDL). The proteins named in red inhibit lipoprotein lipase, and thus raise blood triglyceride-rich lipoprotein concentrations by limiting triglyceride-rich lipoprotein catabolism. Novel therapeutic agents are targeting these LPL inhibitors and thus lower triglyceride-rich lipoprotein concentrations. Apolipoprotein AV activates lipoprotein lipase (shown in green). Strong human genetic evidence supports the causality of the modulators shown in regulating triglyceride-rich lipoproteins. **Adapted from:** *Eur Heart J*, September 2022; Volume 43, Issue 34: Pages 3198–3208.

Causes

Hypertriglyceridemia can be primary or secondary. Primary etiologies include genetic causes (described in the genetics section). The many secondary etiologies include different medical conditions, drugs, and metabolic dysfunctions.[24,27,38] Sedentary lifestyle, excess central adiposity, and diets high in simple carbohydrate or saturated fat can increase triglyceride levels, implicating the importance of diet and lifestyle factors on triglyceride levels. Suboptimal glucose management in type 2 diabetes frequently causes hypertriglyceridemia.[39] Excessive alcohol intake can increase triglyceride levels.[27] Hypothyroidism may elevate triglycerides. Many drugs also increase the risk of hypertriglyceridemia, including estrogens, retinoids, bile acid sequestrants, and cyclosporine.[24,27,38] Detailed secondary causes of hypertriglyceridemia are shown in **Table 2**.

Genetics

Many genetic loci variants have been implicated in hypertriglyceridemia, including mutations in *LPL, APOC2, APOA5, LMF1, GPIHBP1,* and *GPD1.*[29,40] Genetic studies have shown that certain genetic alterations related to hypertriglyceridemia can lead to increased CV risk,[15,41,42] such as defects of *APOA5, APOC3, ANGPTL3* and *ANGPTL4.*[15,43–45] Mendelian randomization studies have shown association with genetic variants and CV risk, particularly among modulators of LPL activity.[46,47] Certain genetic variants can increase apolipoprotein B (ApoB) levels, which are associated with CV risk.[46,48] Genetic causes of hypertriglyceridemia can also be monogenic or polygenic,[49] and each of these genetic risks can combine with lifestyle factors to increase triglyceride levels. Monogenic disorders are generally inherited in an autosomal recessive pattern[40] and their overall prevalence is low.[49]

Familial chylomicronemia syndrome is a monogenic disorder caused by decreased clearance of chylomicrons leading to markedly elevated levels of these lipoproteins in the circulation.[49,50] Patients with familial chylomicronemia syndrome have severe hypertriglyceridemia, with the majority of patients exceeding levels of 1,770 mg/dL (20 mmol/L).[51] These patients may have recurrent episodes of pancreatitis that may be the presenting feature, and can be life-threatening, or other signs of severe hypertriglyceridemia such as eruptive xanthomas, hepatosplenomegaly, or lipemia retinalis. These patients often present in childhood or adolescence.[49,50]

Other causes of monogenic hypertriglyceridemia include transient infantile hypertriglyceridemia, congenital lipodystrophies, and familial dysbetalipoproteinemia.[49] Transient infantile hypertriglyceridemia is secondary to over-secretion of triglycerides by the liver.[49] Familial dysbetalipoproteinemia is caused by decreased remnant lipoprotein clearance.[52,53] In congenital lipodystrophies, the reduced ability of fat tissues to store triglycerides leads to hypertriglyceridemia and deposition of triglycerides in ectopic sites.[54,55]

Polygenic predispositions to hypertriglyceridemia are more common than monogenic conditions.[40,56] In many of these patients, multiple different gene loci have modifications causing small effects which cumulatively contribute to increased risk. Genome-wide association studies have implicated over 300 loci influencing triglyceride levels.[49] Patients with polygenic risk and predisposing secondary causes of hypertriglyceridemia can have substantially higher CVD.

A severe example is multifactorial chylomicronemia syndrome.[57,58] Patients with this condition can have severely elevated triglycerides due to a combination of genetic predisposition and the addition of secondary causes of hypertriglyceridemia.[57,58] However, many patients with genetic predisposition to hypertriglyceridemia with secondary risk factors will not develop elevated triglycerides as severe as that found in multifactorial chylomicronemia syndrome, but nevertheless exhibit a moderate hypertriglyceridemia that increases the risk of CVD.

Specific Populations

A high proportion of the Australian population is of European ancestry, including English and Irish.[59] Aboriginal and Torres Strait Islander individuals makes up about 4%, while Asian ethnicity about 8% of the total population.[59-61] New Zealand also has a majority of individuals of European descent,[62] and also includes individuals of Māori, Pacific Island, and Asian ethnicity.[62] In Australia and New Zealand, triglyceride levels differ significantly by ethnicity and ancestry.[63]

Aboriginal and Torres Strait Islanders are at high-risk of developing diabetes, dyslipidemias, including hypertriglyceridemia, and other cardiometabolic risk factors.[64,65] These diseases develop at younger adult ages than other populations.[65] In fact, 25% of Aboriginal and Torres Strait Islanders have hypertriglyceridemia, a rate significantly higher than other Australian populations.[66] Higher rates of excess abdominal adiposity and type 2 diabetes likely contribute to the increased risk of hypertriglyceridemia,[66,67] as well as social determinants of health such as poor education, unemployment, and racial discrimination.[68] Limited data on genetic risk factors exist in this population. Lipid lowering therapy use in this population is low, despite their high CV risk.[69] Guidelines recommend early age screening for CV risk factors in this Aboriginal and Torres Strait Islanders.[68]

Māori and Pacific Islanders in New Zealand also have high prevalence of CVD.[70-72] Type 2 diabetes is especially prevalent.[73] Triglyceride levels are higher in the Māori population, though not in the Pacific Islander population, compared to the overall population of New Zealand.[70,73] The burden of CV risk factors and disease leads to significant mortality among Māori and Pacific individuals, with a large proportion of CVD being avoidable.[70,74] Social determinants of health significantly influence disparities in these population, including access to health care and racism. Strategies to mitigate risk factors are essential.[75,76] Optimal triglyceride control may comprise one important strategy to reduce CV risk in these high CV risk populations.

Among Asian ethnicity adults in Australia and New Zealand, including Chinese and South Asian adults, cardiometabolic risk factors are common and these individuals have high CV risk.[77-80] South Asians have a propensity towards central adiposity, which can increase CV risk, and rates of metabolic risk factors at lower body mass indices.[81-84] Hypertriglyceridemia is common among Asian adults,[7,85,86] likely influenced by both environmental and genetic factors. For instance, apolipoprotein A5 polymorphisms associate with elevated triglyceride levels in the Chinese population.[87,88] Overall, factors to mitigate disparities among Australian and New Zealand ethnicity and ancestry groups will be important for CVD prevention.

25% of Aboriginal and Torres Strait Islanders have hypertriglyceridemia, a rate significantly higher than other Australian populations.[66]

Diagnosis

Clinical Assessment

When evaluating patients for hypertriglyceridemia, clinicians should obtain a comprehensive history, as this can provide important information for making a diagnosis.[24] Evaluation should assess lifestyle factors, past medical history, medication use, alcohol use, and family history. A focus on identifying secondary causes of hypertriglyceridemia is important (**Table 2**), especially as hypertriglyceridemia clusters with other CV risk factors in the cardio-kidney metabolic syndrome.[89,90] Patients with increased central adiposity (i.e. increased waist circumference) or metabolic risk factors such as diabetes or kidney disease are at particularly high risk. Physical examination findings such as eruptive xanthomas, hepatosplenomegaly, right upper quadrant pain, and lipemia retinalis are rare.[24]

Many patients with severe hypertriglyceridemia are identified during an episode of acute pancreatitis.[91–93] Hypertriglyceridemia leads to about 10% of acute pancreatitis cases, ranking third behind alcohol or gallstone-induced.[27] Though there is a substantial increase in risk of acute pancreatitis with triglyceride levels >900 mg/dL (>10 mmol/L),[91,94] patients with mild-to-moderate hypertriglyceridemia may also have elevated risk.[95] All patients presenting with acute pancreatitis should have triglyceride levels evaluated.

Laboratory Testing

Blood triglyceride concentrations are measured in either fasting or non-fasting states, as both fasting and non-fasting samples correlate with cardiovascular risk.[20,96–98] While triglycerides can increase after fatty meal consumption, the extent of increase depends on the amount of fat consumed.[27,99,100]

Patients with triglycerides ≥400 mg/dL (≥4.5 mmol/L) should have repeat fasting measurements. Similarly, clinicians should use fasting measurements to reduce variability in measurements when monitoring response to therapies.[24] High triglycerides can cause inaccuracies in estimation of low-density lipoprotein cholesterol (LDL-C) derived from formulas. For instance, the Friedewald equation cannot be used for LDL-C determination if triglyceride levels are ≥400 (≥4.5 mmol/L) mg/dL.[101] Direct measurements of LDL-C can be used in this situation, though other equations show promise in patients with elevated triglycerides.[102,103]

Management

Lifestyle Modifications

All patients with hypertriglyceridemia should adopt lifestyle measures that may decrease triglyceride levels.[104,105] Interventions include weight loss, dietary changes, reduction of alcohol intake, and regular exercise. Counselling strategies such as motivational interviewing and regular feedback are important to obtain these goals.[106] Patient-centered care which accounts for patients' values and shared-decision making merit special focus.[107] Weight loss can significantly reduce triglyceride levels.[108] A 5-10% weight reduction can lead to an approximate 20% decrease in triglyceride levels.[109,110] Diet and exercise modifications can help to achieve weight loss. Dietary modifications can lead to 10-20% reduction in triglyceride levels, and depending on the degree of caloric restriction, even higher reductions in triglycerides.[24,109,111] When selecting a diet plan, restriction of calories, saturated fats, refined sugars, and simple carbohydrates are essential.[24,112,113] A focus should be on caloric restriction to decrease weight, which improves triglyceride levels. Simple carbohydrates cause more triglyceride increase than complex carbohydrates and should be limited.[24] High protein diets can also improve triglyceride levels.[24] Lean meats, poultry, and plant-based proteins are preferred to red meat.[24]

As described above, alcohol may increase triglyceride levels, especially when accompanied by high fat intake.[114,115]

Patients with mild-to-moderate hypertriglyceridemia should restrict their alcohol consumption.[24] Those with severe hypertriglyceridemia should avoid alcohol completely. Beverages with sugar should be limited. Legumes, vegetables, and lean fish should be emphasized in diet plans. Patients with severe hypertriglyceridemia who remain at very high risk for pancreatitis should have aggressive lifestyle modifications.[24] Referral to a dietician can help improve nutritional practices with personalized recommendations that are likely to be more sustainable over time.

Aerobic and endurance exercise can decrease triglyceride levels by as much as 30%.[24,116] Exercise increases fatty acid use, reduces post prandial triglyceride concentrations, and reduces fat stores.[24,117] Daily routines should incorporate an exercise plan, with guidelines recommending moderate-intensity exercise for at least 150 minutes per week or vigorous-intensity exercise for at least 75 minutes per week.[118,119]

Statins

Statins are inhibitors of HMG-CoA reductase[120] and first-line therapy for use in patients with elevated LDL-C or high CV risk[96,121] Statins can reduce triglyceride levels by 10-30%, with greater effects observed with higher baseline concentrations.[27] However, in clinical trials evaluating statin

therapy, these agents have not demonstrated consistent CV event reduction across varying triglyceride levels.[122,123] These agents should be used among patients indicated for non-hypertriglyceridemia indications, as limited evidence supports benefit in isolated hypertriglyceridemia without associated cardiovascular risk factors. However, among patients taking statins, lowering triglyceride levels, to below 150 mg/dL (<1.7 mmol/L), has been associated with decreased CV risk, irrespective of LDL-C levels.[21]

Fibrates

Fibrates can substantially reduce triglyceride levels by 25-50%.[27,38] Fibrates function by increasing the activity of peroxisome proliferator-activated receptor-α (PPAR α).[124] Patients with severe hypertriglyceridemia (≥500 mg/dL [>5.6 mmol/L]) can be considered for fibrate therapy to minimize the risk of acute pancreatitis (**Figure 2**).[24,38]
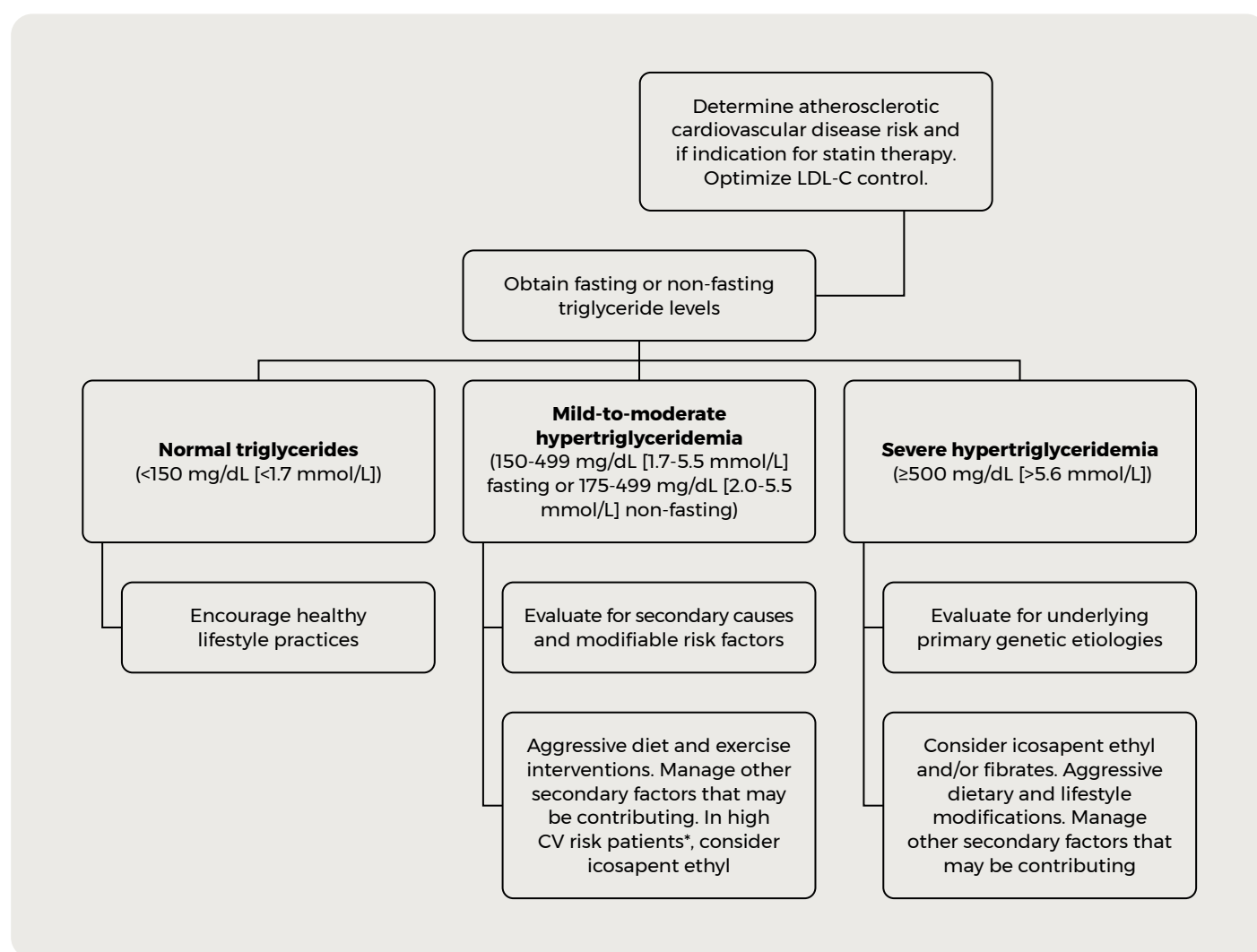
Figure 2: Treatment Algorithm for Patients with Hypertriglyceridemia. Presented is a clinical algorithm for managing patients based on triglyceride levels. High CV risk patients can be identified by applying REDUCE-IT enrollment criteria[143] (≥45 years with CV disease or ≥50 years with diabetes and one additional CV risk factor).

These agents have been studied in multiple randomized trials and those tested in the statin era have not shown reduction macrovascular CV risk among patients with mild-to-moderate hypertriglyceridemia.[125,126] Therefore they are not recommended in these patients.[24]

Unwanted effects of fibrates include gastrointestinal symptoms such as diarrhea or abdominal pain, myopathies, venous thromboembolisms, cholelithiasis, increases in creatinine, and liver enzyme elevation.[127–129] These agents are contraindicated in patients with acute liver disease, gall bladder disease, or severe renal impairment (estimated glomerular filtration rate [eGFR] ≤30 mL/min/1.73m^2).[127,129]

Fibrates include fenofibrate, gemfibrozil, bezafibrate, ciprofibrate, and pemafibrate. Bezafibrate, ciprofibrate, and pemafibrate are not approved in many countries such as the US. Gemfibrozil has higher rates of muscle toxicity, especially among patients on statins. Gemfibrozil, in particular, can inhibit the glucuronidation of statins, impairing their metabolism, and increase their blood concentrations increasing the liability of the combination to cause rhabdomyolysis. Fenofibrate is preferred to gemfibrozil for this reason.

Fibrates have been extensively studied in clinical trials (**Table 3**). Early studies that evaluated fibrates were the Helsinki Heart Study (HHS) and the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT).[130–132] Both of these clinicals trials included patients not on statins and showed improvements in composite CV outcomes with fibrates (34% in HHS and 22% in VA-HIT), though in an era without statin use, limiting their extension to current practice. The Fenofibrate Intervention and Event Lowering in Diabetes Study (FIELD) had directly conflicting results with HHS and VA-HIT. FIELD randomized 9,795 non-statin taking patients with type 2 diabetes and found no significant reduction in CV outcomes with fenofibrate (HR: 0.89; 95% CI: 0.75, 1.05, P=0.16). The trial had a 29% reduction in triglycerides with fenofibrate compared with placebo. However, there was a higher rate of statin use after randomization among the placebo group than the fenofibrate group (17% vs 8%), which may have mitigated the outcome differences between the placebo and fenofibrate group.[133]

Clinical trials among patients on statins included the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trials. ACCORD randomized 5518 patients with type 2 diabetes, high CV risk, and LDL-C of 60-180 mg/dL (1.6-4.7 mmol/L) to fenofibrate or placebo.[126] After 4.7 years of follow-up, the fenofibrate group had a larger reduction in triglyceride levels compared with the placebo group (42 mg/dL [0.5 mmol/L] vs 16 mg/dL [0.2 mmol/L]). However, there was no significant difference in the primary CV outcome (HR: 0.92; 95% CI: 0.79, 1.08, P=0.32).[126]

Subgroup analyses of ACCORD suggested possible benefit in patients with high triglycerides and low HDL-C.[126] Furthermore, meta-analyses of major trials such as FIELD and ACCORD suggested CV benefit.[134] This led to design of the PROMINENT trial.[125] PROMINENT randomized individuals with type 2 diabetes, mild-to-moderate hypertriglyceridemia (200-499 mg/dL [2.3-5.6 mmol/L]), and low HDL-C (≤ 40 mg/dL [≤1.0 mmol/L]) to pemafibrate compared with placebo. The potent, selective PPAR-alpha modulator pemafibrate was chosen due to fewer drug-drug interaction liabilities and creatinine increases than other marketed fibrates. Median triglyceride levels in the study were 271 mg/dL [3.1 mmol/L]. The pemafibrate group had a 26.2% greater reduction in triglyceride concentrations than the placebo group. Despite this triglyceride improvement, pemafibrate did not reduce the primary CV outcome (HR: 1.03; 95% CI: 0.91, 1.15).[125] ApoB levels did increase in the pemafibrate group, which could have mitigated any CV benefit.[125] However, ACCORD and FIELD yielded signals for microvascular benefit.[135,136]

Overall, these clinical trials suggest that fibrates are unlikely to reduce macrovascular CV risk among patients with mild-to-moderate hypertriglyceridemia receiving statins.[24] However, they are a reasonable therapy choice for lowering triglycerides, primarily among patients with severe hypertriglyceridemia who have high risk for pancreatitis from elevated triglycerides. Patients with severe hypertriglyceridemia should be targeted to a triglyceride level of <500 mg/dL (≤5.6 mmol/L).[125] Potential microvascular benefit,

though, may exist with fibrates, with Australia approving it for this diabetic retinopathy treatment.[137]

Niacin

Niacin is a water soluble B complex vitamin that stimulates the nicotinic acid receptor.[138] Niacin can reduce triglyceride levels by 20-50%.[27,139] Despite impressive triglyceride lowering, niacin is not recommended for clinical use in patients with hypertriglyceridemia for two reasons. First, niacin has numerous unwanted actions, including worsening hyperglycemia, flushing, and hepatotoxicity.[38] Side effects lead to a high rate of treatment discontinuation.[139] This was shown in the Heart Protection Study 2-Treatment of HDL-C to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial.[140] HPS2-THRIVE randomized 25,673 patients with occlusive arterial disease on simvastatin to niacin and laropiprant compared with placebo. The niacin/laropiprant group had higher rates of myopathies (risk ratio 4.4, 95% CI: 2.6, 7.5, P<0.0001).[140] Second, niacin has not demonstrated CV outcomes benefit. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL-C/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial enrolled 3414 patients with low HDL-C (<40 mg/dL [<1.0 mmol/L] for men, <50 mg/dL [>1.3 mmol/L] for women) and elevated triglycerides (15-500 mg/dL [1.7-4.5 mmol/L]), to niacin compared with placebo.[141] Patients were statin-treated, with established CVD, and well-controlled LDL-C. Despite lowering triglyceride levels, no significant reduction in the composite CV endpoint was observed (HR: 1.02; 95% CI: 0.87, 1.21; P=0.79).[141]

Omega-3 Fatty Acids

Omega-3 fatty acids have undergone extensive study for the management of patients with hypertriglyceridemia. These preparations can contain various proportions of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Numerous clinical trials have studied EPA and DHA combination

omega-3 fatty acids as well as purified EPA omega-3 fatty acids. Various doses have also been tested. Regardless of EPA and DHA composition, these medications have shown consistent triglyceride reductions of 20-50%.[27,142,143]

It merits emphasis that the pharmaceutical grade omega-3 fatty acid preparations used in recent trials differ markedly and importantly from products marketed as fish oil supplements. A study from the University of Auckland found that <10% of 32 common fish oil supplement products in New Zealand had omega-3 fatty acid levels that matched the stated label amounts while more than 80% had lipid oxidation levels that exceeded industry standards.[144] These supplements do not undergo regulatory approval, or rigorous quality control, and often contain oxidized lipids, saturated fats, and other contaminants.[145] Their use is not evidence-based and should be discouraged.[146,147]

Combination EPA and DHA Omega-3 Fatty Acids

Clinical trials of combination formulations of EPA and DHA have not demonstrated CV reduction benefit. These agents are not recommended for prevention of CVD as a result. Major trials that studied EPA and DHA combinations were the Outcome Reduction with an Initial Glargine Intervention (ORIGIN), A Study of Cardiovascular Events in Diabetes (ASCEND), Vitamin D and Omega-3 Trial (VITAL), OMega-3 fatty acids in Elderly patients with Myocardial Infarction (OMEMI), and Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) (**Table 4**).[142,148-151]

ORIGIN enrolled 12,536 patients with high CV risk and impaired fasting glucose or diabetes.[148] Patients were randomized to 1g EPA and DHA combination omega-3 fatty acid vs olive oil placebo. The omega-3 fatty acids did not significantly reduce CV mortality (HR: 0.98; 95% CI: 0.87, 1.10, P=0.72).[148] ASCEND studied patients with diabetes but without CVD.[149] 15,480 patients were similarly randomized to 1g EPA and DHA combination omega-3 fatty acid compared with olive oil. The primary CV outcome was similar to ORIGIN showing no significant difference between treatment groups (HR: 1.00; 95% CI: 0.91, 1.09).[149] VITAL confirmed

these findings by enrolling 25,871 patients with no known CVD and randomizing them to a 1g EPA/DHA combination omega-3 fatty acid compared with olive oil.[150] Similarly, this omega-3 fatty acid treatment showed no major reduction in CV outcomes (HR: 0.92; 95% CI: 0.80, 1.06).[150]

Other studies of EPA and DHA combination included OMEMI and STRENGTH.[142,151] OMEMI randomized 1,027 elderly patients (ages 70-82 years) with recent MI to a 1.8g combination marine n-3 polyunsaturated fatty acid or corn oil.[151] No major reduction in CV outcomes were observed with the intervention (HR: 1.08; 95% CI: 0.82, 1.41). STRENGTH enrolled 13,078 patients with high CV risk on statin therapy. Patients were required to have elevated triglyceride levels (180-499 mg/dL [2.0-5.6 mmol/L] and low HDL-C (<42 mg/dL [<1.1 mmol/L] for men, <47 mg/dL [<1.2 mmol/L] women). STRENGTH randomized these patients to 4g combination EPA and DHA omega-3 fatty acid compared with corn oil placebo. This study used a higher dose omega-3 fatty acid compared to prior studies. After a median follow up of 3.5 years, there was no significant reduction in the primary composite CV endpoint (HR: 0.99; 95% CI: 0.90, 1.09).[142]

The combination of ORIGIN, ASCEND, VITAL, OMEMI, and STRENGTH demonstrated lack of efficacy in EPA-DHA combination omega-3 fatty acids for reducing CV events in patients, indicating limited clinical benefit of using these agents. Lower or higher dose regimens did not influence these outcomes.

Pure EPA Omega-3 Fatty Acids/Icosapent Ethyl: Overview

The evidence for pure EPA based omega-3 fatty acids have contrasted that of EPA and DHA combination drugs, with trials suggesting CV outcome benefits. Based on clinical trials, and that elevated triglycerides continue to associate with CVD risk despite effective LDL-C lowering therapy,[21] patients with high CV risk and mild-to-moderate hypertriglyceridemia are reasonable candidates for therapy, as are patients with severe hypertriglyceridemia.[24,143] Icosapent ethyl can be the considered agent as it is approved in many countries;[143] a highly purified EPA omega-3 fatty acid that is dosed at 2g twice per day (4g/day). Like other omega-3 derived fatty

acids, icosapent ethyl increases the risk of atrial fibrillation or flutter, and potentially the risk of bleeding. While these unwanted actions should be considered prior to prescribing therapy, it was reassuring that thromboembolic stroke risk fell in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT).[143]

EPA Omega-3 Fatty Acids/Icosapent Ethyl: Evidence

The Japan EPA Lipid Intervention Study (JELIS) studied pure EPA that enrolled 18,645 Japanese patients with total cholesterol ≥251 mg/dL (≥6.5 mmol/L) who were randomized to 1.8 mg/day EPA and statin compared with statin only (pravastatin 10mg or simvastatin 5mg).[152] After a mean follow-up of 4.6 years, the EPA group had significantly lower rates of the composite CV endpoint of major adverse cardiovascular events (MACE) (2.8% vs 3.5%, P=0.01) (**Table 4**).[152] Reduction in triglycerides were modest, suggesting that triglyceride lowering did not drive the benefit of therapy.[152]

The Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography (CHERRY) and Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy (EVAPORATE) evaluated coronary plaque burden with pure EPA omega-3 fatty acids.[153,154] In CHERRY, 193 Japanese patients with coronary heart disease who underwent percutaneous coronary intervention were randomized to pitavastatin and 1.8 g/day of EPA compared with pitavastatin. CHERRY demonstrated a significant decrease in coronary plaque volume in the EPA group.[153] EVAPORATE randomized 80 patients with triglycerides of 135-499 mg/dL [1.5-5.6 mmol/L] and LDL-C >40 mg/dL [>1.0 mmol/L] and ≤115 mg/dL (≤3.0 mmol/L, on statin, and with mild or greater obstruction on coronary computed tomography angiography (CCTA) to icosapent ethyl (4g/day) vs placebo. EVAPORATE also showed significant reduction in coronary plaque at 18 months.[154]

The Randomized trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy – Statin and EPA (RESPECT-EPA) enrolled 2,506 patients with chronic coro-

nary artery disease, on statin therapy, and with low EPA/arachidonic acid ratio.[155] Patients were randomized to icosapent ethyl 1.8 g/day compared with standard of care. After 5 years of follow-up, there was a trend towards improvement in the composite outcome of CV death, MI, stroke, unstable angina, and revascularization (9.1% vs 10.6%, P=0.055). A secondary CV endpoint of sudden cardiac death, MI, unstable angina requiring hospitalization or revascularization, or coronary revascularization showed a statistically significant reduction in the icosapent ethyl group.[156]

The strongest evidence for icosapent ethyl derives from Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT).[143] This trial enrolled 8,179 patients from 11 different countries with high CV risk on statin therapy who had triglyceride levels of 135 to 499 mg/dL [1.5-5.6 mmol/L]and LDL-C of 41-100 mg/dL [1.1-2.6 mmol/L]. These patients were randomized to 4g/day of iscosapent ethyl or mineral oil placebo. The icosapent ethyl group had a 20% greater reduction in triglyceride levels. After a median of 4.9 years, there was a significant reduction in the primary composite outcome of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina (HR: 0.75; 95% CI: 0.68, 0.83; P<0.001). There were higher rates of atrial fibrillation or atrial flutter hospitalizations (3.1% vs 2.1%, P=0.004) and a trend towards higher rates of serious bleeding events (2.7% vs 2.1%, P=0.06) in the icosapent ethyl compared with placebo group.[143]

Icosapent Ethyl: Efficacy Debate

Since the results of REDUCE-IT, controversy emerged regarding the efficacy of icosapent ethyl.[157] The basis for the controversy stems from the mineral oil comparator used. Some have raised concern that mineral oil may not be inert, and inadvertently reduce statin absorption among patients on the placebo group. A secondary study of REDUCE-IT suggested increases in LDL-C and high sensitivity C-reactive protein (hsCRP) with mineral oil.[158] REDUCE-IT showed LDL-C increases were higher in the placebo group than the icosapent ethyl group (10.2% vs 3.1% respectively).[159] Similar patterns were observed with increases in hsCRP in the placebo group.

A few key considerations pertain when evaluating the controversy in REDUCE-IT. In secondary studies of REDUCE-IT, there were no significant differences in CVD event rates in placebo-treated patients with or without LDL-C elevation or with or without hsCRP elevation.[159] The efficacy of icosapent ethyl was also similar irrespective of statin type, arguing against statin absorption issues, as differential response would be expected among different statin intensities and lipophilicity.[160] JELIS and RESPECT-EPA did not use mineral oil as a comparator but both suggested directionally similar efficacy with icosapent ethyl as in REDUCE-IT.[152,156] Potential limitations include that JELIS enrolled patients with high LDL-C levels and that the trend towards improvement in outcomes in RESPECT-EPA was not statistically significant (P=0.055). A modelling study suggests that the biomarker changes, such as LDL-C or triglycerides do not explain the benefit observed in REDUCE-IT, though it was unclear if these benefits were due to possible EPA specific benefit in the icosapent group or harm from mineral oil in the placebo group.[161,162] The degree of LDL-C change between the two comparator groups, though, does not likely explain the entire 25% reduction in the primary outcome observed in REDUCE-IT. The degree of CV benefit relative to the modest LDL-C increases contributed to the US Food and Drug Administration (FDA) approval of icosapent ethyl for REDUCE-IT eligible patients in the US.

Trials of purified EPA formulations, icosapent ethyl, and combination EPA and DHA have demonstrated consistent and similar triglyceride lowering effects. However, only purified EPA resulted in CV reduction. Thus, icosapent ethyl may reduce CV events by a mechanism independent of triglyceride lowering. One possibility relates to higher on-treatment EPA and/or EPA/arachidonic acid (AA) ratio levels that may have contributed to these benefits.[163–166] A mediation analysis, however, suggests potential contribution of EPA increases, arachidonic acid (AA) decreases, and triglyceride lowering.[167] While the exact mechanism(s) of benefit remain incompletely elucidated, another potential avenue for further exploration includes evaluating differences in anti-inflammatory properties and other cardioprotective actions between EPA and DHA.[146,165,168]

Future Directions

Novel Therapies Under Investigation – APOC3 and ANGPTL3 targeted therapy

Many novel therapies are currently in development for patients with elevated triglycerides. These include targets of apolipoprotein C3 (APOC3) and angiopoietin-like protein 3 (ANGPTL3).[169,170] ANGPTL3 is primarily found in the liver and inhibits LPL and endothelial lipase.[169,170] Loss of function of the *ANGPTL3* gene leads to lower levels of triglycerides, chylomicrons, VLDL cholesterol, HDL-C, and LDL-C.[170,171] APOC3 is also found in the liver, as well as the intestines, and inhibits LPL and non-LPL mediated clearance of TGRLs via hepatic receptors.[170] Loss-of-function variants of *APOC3* is associated with decreased triglyceride levels and increased HDL-C.[169,172] Mendelian randomization genetic studies have shown that both *ANGPTL3* and *APOC3* loss-of-function is associated with decreased CV risk.[171–173] Because of the triglyceride lowering effects of genetic deficiency in ANGPTL3 and ApoC3, these two pathways are now subjects of targeted therapies for reduction in plasma triglycerides (i.e., ANGPLT3 and ApoC3 inhibitors).

Olezarsen is an antisense oligonucleotide that inhibits ApoC3 messenger RNA (mRNA).[173–175] In patients with famil-ial chylomicronemia syndrome, this agent showed significant reduction in triglyceride levels and in frequency of acute pancreatitis.[173,174] Similar decreases in triglyceride levels were observed in a trial of patients with moderate hypertriglyceridemia and elevated CV risk with olezarsen. Plozasiran is a small interfering-RNA (siRNA) therapy that targets the mRNA of ApoC3. This agent also showed reduction in triglyceride levels in patients with severe hypertriglyceridemia and patients with mixed hyperlipidemia.[176,177]

Evinacumab, zodasiran, and solbinsiran all inhibit the ANGPTL3 pathway.[169,171,178,179] The monoclonal antibody evinacumab inhibits ANGPTL3.[178] In patients with homozygous familial hypercholesterolemia, evinacumab reduced triglyceride levels, and reduced LDL-C independently of LDL receptor dependent mechanisms.[178] This therapy is now FDA-approved in the US for homozygous familial hypercholesterolemia.[178,180] Zodasiran is a siRNA inhibitor therapy for ANGPTL3 and showed decreases in triglyceride levels among patients with mixed hyperlipidemia.[171] Solbinsiran is an siRNA inhibitor of therapy of ANGPTL3 in early-stage investigation.[169,179]

While this review focuses on the beneficial effects of these agents under investigation for triglyceride lowering, many also improve other lipid related biomarkers such as LDL-C or ApoB.[171,178] There is currently an unmet need for management of severe hypertriglyceridemia which can lead to life-threatening bouts of recurrent acute pancreatitis. These drugs may fill that gap. Whether these agents can reduce CV events in patients with hypertriglyceridemia requires future trials.

Conclusion

Summary

In summary, all patients with hypertriglyceridemia should receive advice on intensive lifestyle measures. Clinicians should focus on dietary modifications, exercise regimens, and weight reduction. Limiting refined carbohydrates and saturated fats is critical. Among patients with mild-to-moderate hypertriglyceridemia, lifestyle modifications should be trialed initially. If triglycerides remain elevated after lifestyle changes (≥150 mg/dL [≥1.7 mmol/L]), and the patient is at high CV risk, icosapent ethyl can be considered. Criteria for high CV risk include those similar to REDUCE-IT enrollment criteria—patients with either CVD or diabetes and at least one additional CV risk factor, alongside elevated triglycerides. In patients with severe hypertriglyceridemia, reducing triglycerides to <500 mg/dL (1.7 mmol/L) is a reasonable consideration to avert the potential risk of pancreatitis. Intensive dietary and other lifestyle measures to reduce triglyceride levels in the 30-60% range, provide the core therapeutic foundation. This may be supplemented with fibrates, as newer therapies are investigated (e.g., FGF21 analogs, APOC3 and ANGPTL3 targeted therapies), as well as icosapent ethyl to improve CV and cardiometabolic risk associated with hypertriglyceridemia. Identification and management of elevated triglyceride-containing lipoproteins offers a neglected approach to reduce residual cardiovascular risk of considerable import to public health and individual patients.

Table 1: Comparison of Guidelines for the Management of Hypertriglyceridemia

The table is based on recommendations by the 2021 ACC Expert Consensus Decision Pathway on Hypertriglyceridemia,[24] 2018 AHA/ACC Cholesterol Clinical Practice Guidelines,[96] and 2021 ESC Guidelines on Cardiovascular Disease Prevention.[94] 2021 ESC guidelines state that non-fasting triglyceride measurements are reasonable to obtain but do not specify different cutoffs for fasting vs non-fasting levels. Similarly, the 2021 ESC guidelines do not list a cutoff for severe hypertriglyceridemia, but it would be reasonable to extend classification from other guidelines (i.e., ≥ 500 mg/dL [>5.6 mmol/L]). All guidelines emphasize cardiovascular risk stratification and consideration of statins for LDL-C management as important primary goals. 2023 ESC Guidelines on Acute Coronary Syndromes was not included due to limited discussion regarding triglyceride levels. However, the guidelines state that icosapent ethyl can be considered for patients with ACS and triglyceride levels of 135-499 mg/dL (1.5-5.6 mmol/L) in addition to statin therapy.[181] Abbreviations: ACC: American College of Cardiology, ACS: acute coronary syndrome, ASCVD: atherosclerotic cardiovascular disease, AHA: American Heart Association, CV: cardiovascular, ESC: European Society of Cardiology, IPE: icosapent ethyl.

	2021 ACC Expert Consensus on Hypertriglyceridemia	2021 ESC Primary Prevention Guidelines	2018 AHA/ ACC Cholesterol Guidelines
Hypertriglyceridemia Definition	Mild-to-moderate hypertriglyceridemia: ≥150 mg/dL (≥1.7 mmol/L) fasting or ≥175 (≥2.0 mmol/L) non-fasting triglycerides Severe hypertriglyceridemia: ≥500 mg/dL (>5.6 mmol/L)	Mild-to-moderate hypertriglyceridemia: >150 mg/dL (≥1.7 mmol/L) Severe hypertriglyceridemia: Not stated	Mild-to-moderate hypertriglyceridemia: ≥175 mg/dL (≥2.0 mmol/L) fasting or non-fasting Severe hypertriglyceridemia: ≥500 mg/dL (>5.6 mmol/L)
Statin Use	Very important to risk assess for statin initiation	Very important to risk assess for statin initiation	Very important to risk assess for statin initiation

Table 1 Continued

Are aggressive lifestyle modifications recommended for all patients?	Yes	Yes	Yes
Management of Mild-to-Moderate Hypertriglyceridemia	Adults with ASCVD: Maximize statin therapy for LDL-C goals. Optimize lifestyle measures. If triglycerides still elevated, consider IPE. Adults with diabetes mellitus but without ASCVD: Maximize statin therapy for LDL-C goals. Optimize lifestyle measures. If ≥50 years and at least one other CV risk factor, consider IPE. Otherwise continue lifestyle modifications. Adults without ASCVD or diabetes mellitus: Optimize lifestyle measures. No add on therapy for triglycerides.	High CV Risk: Consider IPE if triglycerides elevated despite statin and lifestyle measures (>200 mg/dL [>2.3 mmol/L]). Non-High CV risk: Consider fibrates (fenofibrate or bezafibrate) if persistently elevated triglycerides despite statin and lifestyle measures (>200 mg/dL [>2.3 mmol/L]).	Optimize statin therapy and lifestyle measures.
Management of Severe Hypertriglyceridemia	Optimize diet, including low fat diet and abstinence from alcohol. Optimize statin therapy. Evaluate for secondary causes. Consider fibrates or omega-3 fatty acids (IPE or omega-3 acid ethyl esters).	No detailed guidance. Avoid alcohol and manage secondary causes. Refer to lipid specialist.	Emphasize diet, including low-fat diet. Avoid alcohol. Optimize statin therapy. Consider fibrates or omega-3 fatty acids. If fibrate selected, prefer fenofibrate over gemfibrozil.

Table 2: Secondary Causes of Hypertriglyceridemia

Presented are secondary causes of hypertriglyceridemia.[24,27,38]

Diseases

Diabetes Mellitus
Hypothyroidism
Cushing's Syndrome
Obesity
Metabolic Syndrome
Chronic Kidney Disease
Nephrotic Syndrome
Glycogen Storage Diseases
Autoimmune Diseases
Multiple Myeloma
Liver Disease
HIV

Drugs

Beta Blockers
Propofol
Thiazide Diuretics
Glucocorticoids
Oral Estrogens
Isotretinoins
HIV Protease Inhibitors
Cyclophosphamide
Tacrolimus/Sirolimus
Cyclosporine
Bile-acid sequestrants
Antipsychotic Medications

Lifestyle Factors

Alcohol Use
High Carbohydrate or High Saturated Fat Diets
Excessive Caloric Intake
Smoking

Other

Pregnancy

Table 3: Clinical Trials Evaluating Fibrates

Presented are randomized clinical trials assessing fibrates. Abbreviations: CAD: coronary artery disease, CV: cardiovascular, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, MI: myocardial infarction.

Clinical Trial	Population	Intervention	Outcome	Result
Helsinki Heart Study	4,081 patients with hyperlipidemia (non-HDL-C ≥200 mg/dL [≥5.2 mmol/L]). Non statin treated patients.	Gemfibrozil vs Placebo	Composite of nonfatal MI or CV death	Gemfibrozil reduced relative risk of outcomes by 34% (95% CI:8.2, 52.6%, P<0.02)
VA-HIT	2,531 patients with established CAD, HDL-C <40 mg/dL (<1.0 mmol/L), and LDL-C <140 mg/dL (<3.6 mmol/L). Non statin treated patients.	Gemfibrozil vs Placebo	Composite of nonfatal MI or death from coronary causes	Gemfibrozil reduced relative risk of outcomes by 22% (95% CI: 7-35%, P=0.006) with gemfibrozil
FIELD	9,759 patients with type 2 diabetes not on statin therapy and total cholesterol of 116-251 mg/dL (3.0-6.5 mmol/L), total cholesterol/HDL-C ratio ≥4, or plasma triglyceride of 89 mg/dL-443 mg/dL (1.0-5.0 mmol/L)	Fenofibrate vs placebo	Composite of CV death, MI, stroke, and coronary or carotid revascularization	No significant reduction in outcomes (HR: 0.89; 95% CI: 0.75-1.05, P=0.16)
ACCORD	5,518 patients with type 2 diabetes, high CV risk, and LDL-C of 60-180 mg/dL [1.6-4.7 mmol/L]	Fenofibrate vs placebo	Composite of CV death, MI, or stroke	No significant reduction in outcomes (HR: 0.92; 95% CI: 0.79-1.08, P=0.32)
PROMINENT	10,497 patients with triglycerides of 200-499 [2.3-5.6 mmol/L] mg/dL and HDL-C ≥40 mg/dL [≥1.0 mmol/L]	Pemafibrate vs placebo	Composite of MI, stroke, coronary revascularization, or CV death	No significant reduction in outcomes (HR: 1.03; 95% CI: 0.91-1.15)

Table 4: Clinical Trials Evaluating Omega-3 Fatty Acids

Presented are randomized clinical trials assessing omega-3 fatty acids. Icosapent ethyl is purified EPA dosed at 2g twice per day (4g/day). Abbreviations: CVD: cardiovascular disease, DHA: Docosahexaenoic Acid, EPA: eicosapentaenoic acid, HDL-C: high-density lipoprotein cholesterol, LAP: low-attenuation plaque, IVUS: intravascular ultrasound, LDL-C: low-density lipoprotein cholesterol, MI: myocardial infarction, TAV: total atheroma volume.

Clinical Trial	Population	Intervention	Outcome	Result
EPA and DHA Combination				
ORIGIN	12,536 patients with high CV risk and impaired fasting glucose or diabetes.	1g EPA/DHA combination omega-3 vs olive oil placebo	CV mortality	No significant reduction in outcome (HR: 0.98; 95% CI: 0.87, 1.10, P=0.72).
ASCEND	15,480 patients with diabetes and no CVD history	1g EPA/DHA combination omega-3 vs olive oil placebo	Composite of MI, stroke, TIA, or vascular death	No significant reduction in outcome (HR: 1.00; 95% CI: 0.91, 1.09)
VITAL	25,871 with no CVD history	1g EPA/DHA combination vs olive oil placebo	Composite of MI, stroke, or CV death	No significant reduction in outcome (HR: 0.92; 95% CI: 0.80, 1.06, P=0.24)
OMEMI	1,027 elderly patients with recent MI	1.8g EPA/DHA combination vs corn oil	Composite of non-fatal MI, unscheduled revascularization, stroke, all-cause death, heart failure hospitalization	No significant reduction in outcome (HR: 1.08; 95% CI: 0.82, 1.41, P=0.60)

Table 4 Continued

STRENGTH	13,078 patients with high CV risk on statin therapy with triglycerides of 180-499 mg/dL [2.0-5.6 mmol/L] and low HDL-C (<42 mg/dL [<1.1 mmol/L] for men and <47 mg/dL [<1.2 mmol/L] for women)	4g EPA/DHA combination omega-3 carboxylic acid vs corn oil	Composite of CV death, MI, stroke, coronary revascularization or unstable angina requiring hospitalization	No significant reduction in outcome (HR: 0.99; 95% CI: 0.90, 1.09, P=0.84)
EPA Only			
CHERRY	193 Japanese patients with coronary heart disease who underwent percutaneous coronary intervention	Pitavastatin and 1.8g EPA vs pitavastatin	TAV using IVUS at 6-8 months.	Reduction in normalized TAV (-9.3 [95% CI: -14.3, -2.0] vs -1.7 [-10.3, 3.5], P<0.001)
EVAPORATE	80 patients with triglycerides of 135-499 mg/dL [1.5-5.6 mmol/L] and LDL-C of 41-115 mg/dL [1.1-3.0 mmol/L] on statin with mild or greater obstruction on coronary computed tomography angiography	Icosapent ethyl 4g per day vs mineral oil placebo	LAP volume using CT coronary angiography at 18 months.	Reduction in LAP: −0.3 ± 1.5 vs 0.9 ± 1.7 mm3, P=0.006
JELIS	18,645 patients with total cholesterol ≥251 mg/dL (≥6.5 mmol/L)	1.8g EPA and statin compared with statin (pravastatin or simvastatin)	Composite of major coronary events, which included sudden cardiac death, MI, unstable angina, angioplasty, stenting or coronary artery bypass grafting	Significant reduction in outcome with EPA (event rate: 2.8% vs 3.5%, P=0.01)

Table 4 Continued

REDUCE-IT	8,179 patients with high CV risk on statin therapy with triglyceride levels of 135-499 mg/dL [1.5-5.6 mmol/L] and LDL-C of 41-100 mg/dL [1.1-2.6 mmol/L]	Icosapent ethyl 4g per day vs mineral oil placebo	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina	Significant reduction in outcome with icosapent ethyl (HR: 0.75; 95% CI: 0.68, 0.83; P<0.001)
RESPECT-EPA	2,506 patients with chronic coronary artery disease on statins with low EPA: arachidonic acid ratio (<0.4)	1.8g of icosapent ethyl vs standard care	Composite of CV death, MI, stroke, unstable angina, and coronary revascularization	Trend towards reduction in outcome with EPA (9.1% vs 12.6%, P=0.055)

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1. Rahul Aggarwal reported receiving grants from Bristol Myers Squibb-Pfizer alliance; served as a consultant for Lexicon Pharmaceuticals; and being involved in research collaborations with Novartis, Lexicon, and Amarin all outside this submitted work.

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Affiliations

Rahul Aggarwal, MD[1], Christina Bursill, BSc (Hons 1) PhD[2], Gemma A. Figtree, MBBS, DPhil[3], Samantha L. Hocking, MBBS, MMed (Clin Epi), PhD[4], R. Preston Mason, PhD[5], Erin D. Michos, MD, MHS[6], Michael Miller, MD[7], Adam J. Nelson, MBBS, MPH, MBA, PhD[8], Stephen J. Nicholls, MBBS, PhD[8], Kerry-Anne Rye, BSc (Hons), PhD[9], Ph. Gabriel Steg, MD[10], Gerald F. Watts, DSc, MD, PhD[11], Sophia Zoungas, MBBS (Hons) PhD[12], Peter Libby, MD[1]

1. Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA, USA
2. South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, SA, Australia
3. Kolling Institute, University of Sydney, Sydney, NSW, Australia
4. Charles Perkins Centre, University of Sydney, Camperdown, NSW, Australia
5. Elucida Research, Beverly, MA, USA
6. Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
7. Corporal Michael J Crescenz Veterans Affairs Medical Center and University of Pennsylvania, Philadelphia, PA, USA
8. Victorian Heart Institute, Monash University, Clayton VIC, Australia
9. School of Biomedical Sciences, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia
10. Université Paris-Cité, AP-HP and INSERMU_1148, Paris, France
11. Departments of Cardiology and Internal Medicine, Royal Perth Hospital; School of Medicine, University of Western Australia, Perth, Australia
12. School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

Corresponding Author:
Peter Libby, MD
Division of Cardiovascular Medicine
Brigham and Women's Hospital
77 Ave Louis Pasteur, NRB 7, Boston, MA 02115
Email: plibby@bwh.harvard.edu

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