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

JULY 2024

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]

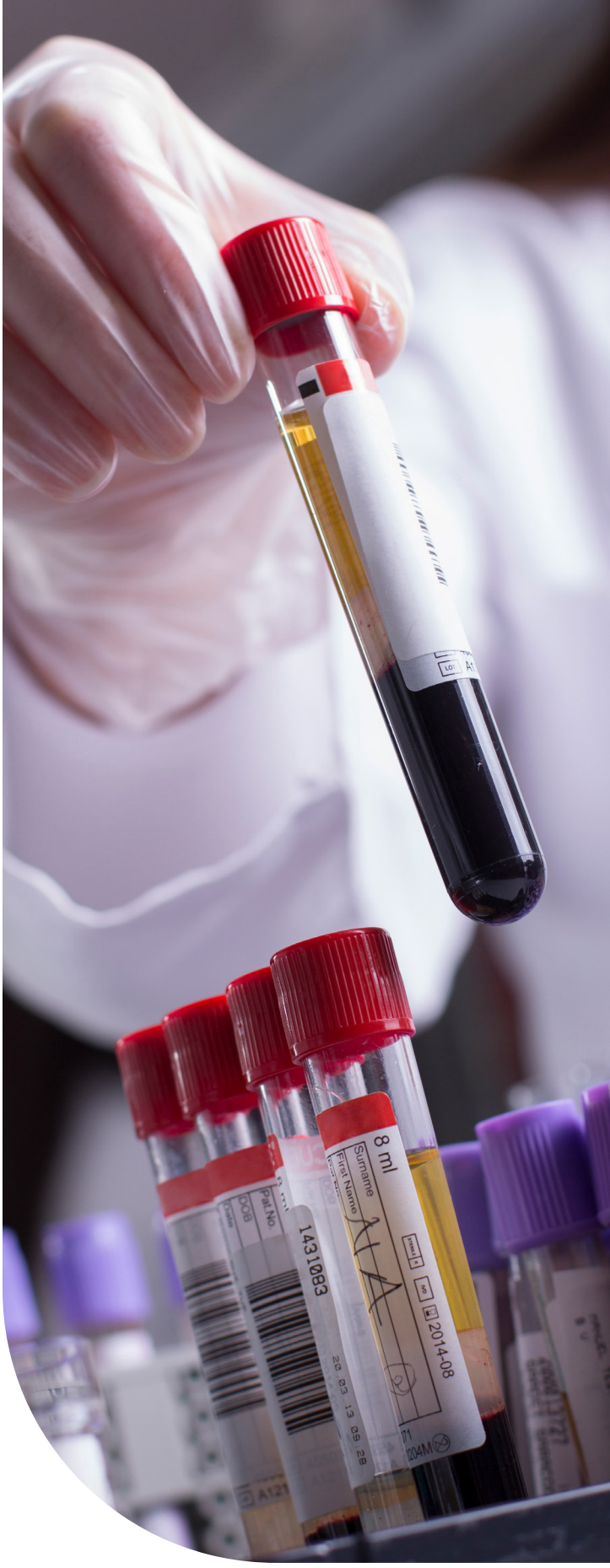
A full list of affiliations appears at the end of this document.

IAS INTERNATIONAL ATHEROSCLEROSIS SOCIETY

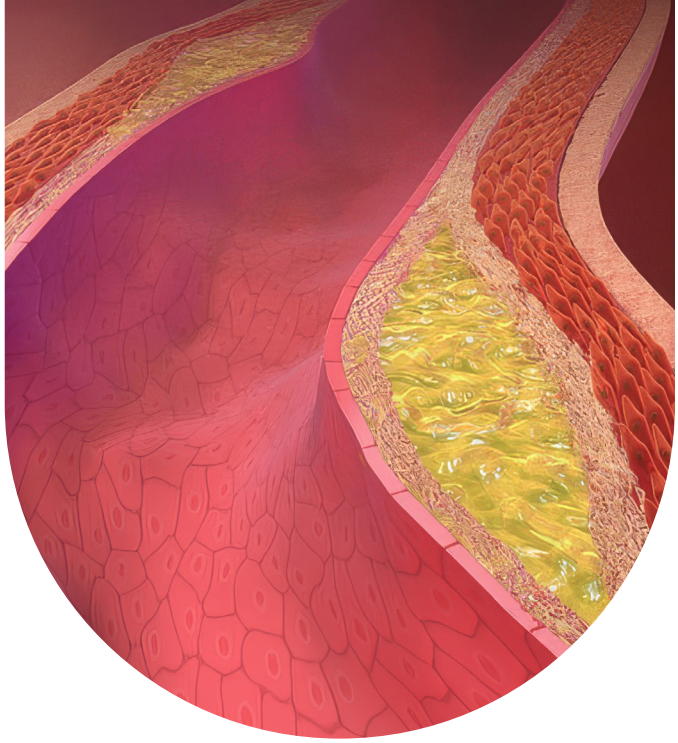
Table of Contents

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.



Background



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 endothelial 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]

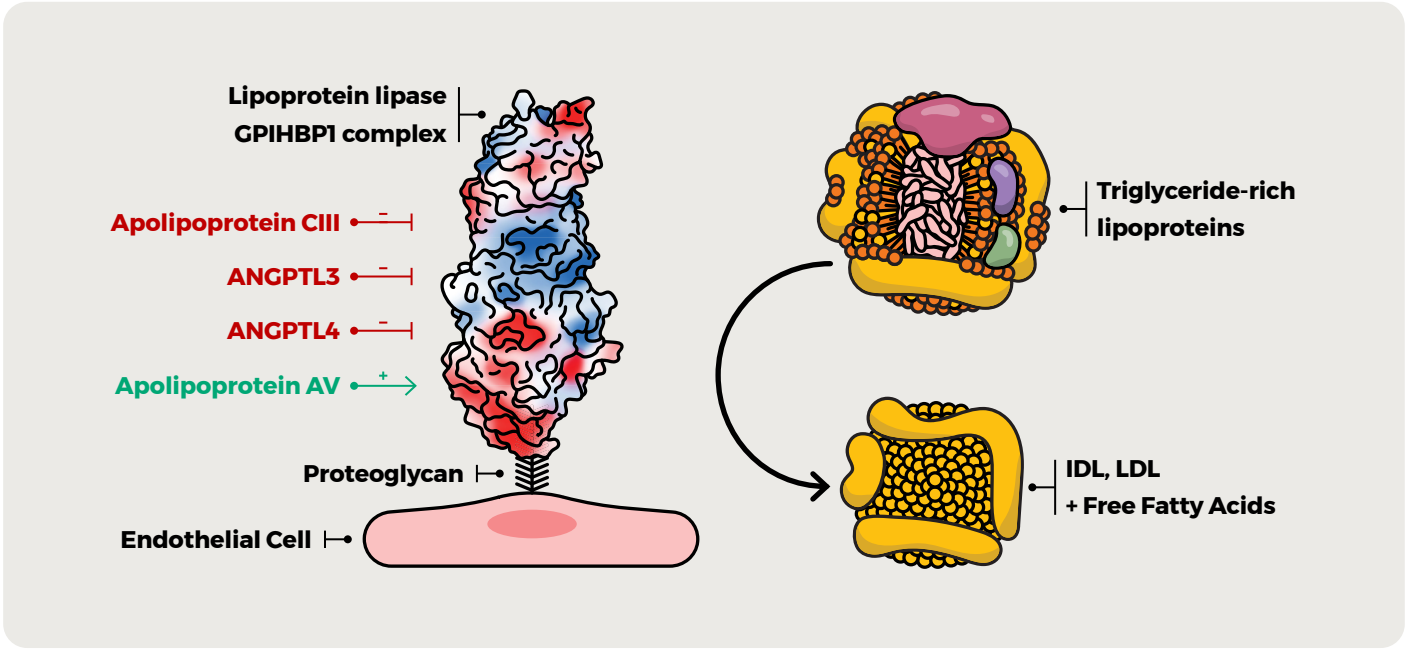


Figure 1: Lipoprotein lipase: a key to understanding triglyceride metabolism. The enzyme lipoprotein lipase (LPL) in a complex with GPIHBP1 (Glycosylphosphatidylinositol high density lipoprotein-binding protein-1) associates with the surface of endothelial cells by binding to proteoglycans. This enzyme trims fatty acids 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]

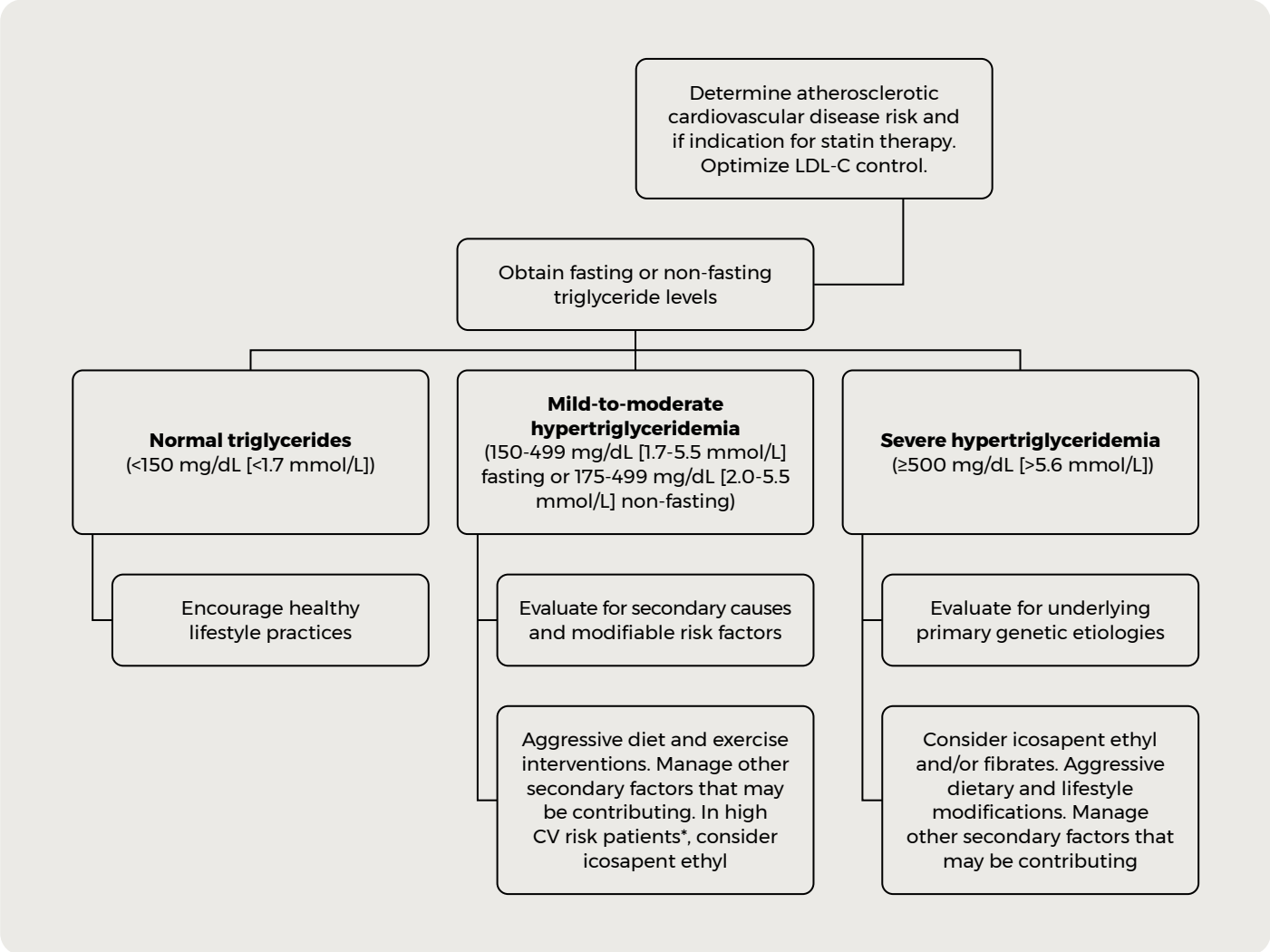


Figure 2: Treatment Algorithm for Patients with Hypertriglyceridemia. Presented is a clinical algorithm for managing patients based on triglyceride levels. High CV risk patients can be identified by applying REDUCE-IT enrollment criteria[143] (≥45 years with CV disease or ≥50 years with diabetes and 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 familial 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)

Disclosures

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.
2. Christina Bursill reported being involved in a research collaboration with CSL.
3. Gemma A. Figtree reports grants from National Health and Medical Research Council (Australia), grants from Abbott Diagnostic, Sanofi, Janssen Pharmaceuticals, and NSW Health. G.A.F reports honorarium from CSL, CPC Clinical Research, Sanofi, Boehringer-Ingelheim, Heart Foundation, and Abbott. G.A.F serves as Board Director for the Australian Cardiovascular Alliance (past President), Executive Committee Member for CPC Clinical Research, Founding Director and CMO for Prokardia and Kardiomics, and Executive Committee member for the CAD Frontiers A2D2 Consortium. In addition, G.A.F serves as CMO for the non-profit, CAD Frontiers, with industry partners including, Novartis, Amgen, Siemens Healthineers, ELUCID, Foresite Labs LLC, HeartFlow, Canon, Cleerly, Caristo, Genetech, Artyra, and Bitterroot Bio and Allelica.
4. Samantha L Hocking has received research grants from The Diabetes Australia Research Program and The National Health and Medical Research Council of Australia; received honoraria for lectures from Eli Lilly, Novo Nordisk, Sanofi Aventis, Astra Zeneca, Servier, Nestle Health Sciences and Amgen and has been or is on advisory boards for Novo Nordisk, Eli Lilly, Inova, Seqirus, Johnson & Johnson and Pfizer; and has been an investigator for industry-sponsored clinical trials run by Novo Nordisk, Eli Lilly, Rhythm pharmaceuticals, Millendo, Spruce Biosciences and Amgen.
5. Peter Libby is an unpaid consultant to, or involved in clinical trials for Amgen, Baim Institute, Beren Therapeutics, Esperion Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Novo Nordisk, Novartis, and Sanofi-Regeneron. Dr. Libby is a member of the scientific advisory board for Amgen, Caristo Diagnostics, CSL Behring, DalCor Pharmaceuticals, Dewpoint Therapeutics, Eulicid Bioimaging, Kancera, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, Novartis, PlaqueTec, Polygon Therapeutics, TenSixteen Bio, Soley Thereapeutics, and XBiotech, Inc. Dr. Libby's laboratory has received research funding in the last 2 years from Novartis, Novo Nordisk and Genentech. Dr. Libby is on the Board of Directors of XBiotech, Inc. Dr. Libby has a financial interest in Xbiotech, a company developing therapeutic human antibodies, in TenSixteen Bio, a company targeting somatic mosaicism and clonal hematopoiesis of indeterminate potential (CHIP) to discover and develop novel therapeutics to treat age-related diseases, and in Soley Therapeutics, a biotechnology company that is combining artificial intelligence with molecular and cellular response detection for discovering and developing new drugs, currently focusing on cancer therapeutics. Dr. Libby's interests were reviewed and are managed by Brigham and Women's Hospital and Mass General Brigham in accordance with their conflict-of-interest policies.
6. R. Preston Mason reported receiving grants from Amarin, Lexicon and Viatris and served as a consultant for Amarin, HLS and Viatris all outside this submitted work.
7. Erin D. Michos reports consulting for Amgen, Arrowhead, AstraZeneca, Boehringer Ingelheim, Edwards Life Science, Esperion, Ionis, Lilly, Medtronic, Merck, New Amsterdam, Novartis, Novo Nordisk, and Pfizer.
8. Michael Miller reported Amarin Corp, 89bio and Ionis: Scientific Consultant and Advisor.
9. Adam J. Nelson reported consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Novartis, Novo Nordisk and Sanofi.
10. Stephen J Nicholls has reported receiving research support from AstraZeneca, Amgen, Anthera, CSL Behring, Cerenis, Eli Lilly, Esperion, Resverlogix, Novartis, InfraReDx and Sanofi-Regeneron and is a consultant for Amgen, Akcea, AstraZeneca, Boehringer Ingelheim, CSL Behring, Daiichi Sankyo, Eli Lilly, Esperion, Kowa, Merck, Takeda, Pfizer, Sanofi-Regeneron, Novo Nordisk, CSL Sequiris and Vaxxinity.
11. Kerry-Anne Rye has received research funding from Secure Biomedical that is unrelated to the submitted work.
12. Ph. Gabriel Steg discloses receiving research grants from Amarin, AstraZeneca, Sanofi , having received funds for clinical trials, consulting or speaking from Amarin, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Idorsia, Novartis, Novo-Nordisk, PhaseBio, Pfizer, Sanofi. He is a Senior Associate Editor at Circulation and is Chief Medical Officer at Bioquantis.
13. Gerald F. Watts reports consulting fees and research grants from among Amgen, Arrowhead, Esperion, Novartis, Novo Nordisk.
14. Sophia Zoungas is employed by Monash University and receives funding from NHMRC, MRFF, and the Commonwealth Department of Health and Aged Care. She reports previous payments to institution (Monash University) from AstraZeneca, Boehringer Ingelheim, CSL Seqirus, Eli Lilly Australia, Moderna, MSD Australia, Sanofi and Novo Nordisk for participation in advisory and educational meetings.

References

1. Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Barone Gibbs B, Beaton AZ, Boehme AK, Commodore-Mensah Y, Currie ME, Elkind MSV, Evenson KR, Generoso G, Heard DG, Hiremath S, Johansen MC, Kalani R, Kazi DS, Ko D, Liu J, Magnani JW, Michos ED, Mussolino ME, Navaneethan SD, Parikh NI, Perman SM, Poudel R, Rezk-Hanna M, Roth GA, Shah NS, St-Onge M-P, Thacker EL, Tsao CW, Urbut SM, Van Spall HGC, Voeks JH, Wang N-Y, Wong ND, Wong SS, Yaffe K, Palaniappan LP, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. *Circulation*. 2024;149:e347–e913.
2. Woodruff RC, Tong X, Khan SS, Shah NS, Jackson SL, Loustalot F, Vaughan AS. Trends in Cardiovascular Disease Mortality Rates and Excess Deaths, 2010-2022. *Am J Prev Med*. 2024;66:582–589.
3. Global Cardiovascular Risk Consortium, Magnussen C, Ojeda FM, Leong DP, Alegre-Diaz J, Amouyel P, Aviles-Santa L, De Bacquer D, Ballantyne CM, Bernabé-Ortiz A, Bobak M, Brenner H, Carrillo-Larco RM, de Lemos J, Dobson A, Dörr M, Donfrancesco C, Drygas W, Dullaart RP, Engström G, Ferrario MM, Ferrières J, de Gaetano G, Goldbourt U, Gonzalez C, Grassi G, Hodge AM, Hveem K, Iacoviello L, Ikram MK, Irazola V, Jobe M, Jousilahti P, Kaleebu P, Kavousi M, Kee F, Khalili D, Koenig W, Kontsevaya A, Kuulasmaa K, Lackner KJ, Leistner DM, Lind L, Linneberg A, Lorenz T, Lyngbakken MN, Malekzadeh R, Malyutina S, Mathiesen EB, Melander O, Metspalu A, Miranda JJ, Moitry M, Mugisha J, Nalini M, Nambi V, Ninomiya T, Oppermann K, d'Orsi E, Pająk A, Palmieri L, Panagiotakos D, Perianayagam A, Peters A, Poustchi H, Prentice AM, Prescott E, Risérus U, Salomaa V, Sans S, Sakata S, Schöttker B, Schutte AE, Sepanlou SG, Sharma SK, Shaw JE, Simons LA, Söderberg S, Tamosiunas A, Thorand B, Tunstall-Pedoe H, Twerenbold R, Vanuzzo D, Veronesi G, Waibel J, Wannamethee SG, Watanabe M, Wild PS, Yao Y, Zeng Y, Ziegler A, Blankenberg S. Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality. *N Engl J Med*. 2023;389:1273–1285.
4. Vernon ST, Coffey S, Bhindi R, Soo Hoo SY, Nelson GI, Ward MR, Hansen PS, Asrress KN, Chow CK, Celermajer DS, O'Sullivan JF, Figtree GA. Increasing proportion of ST elevation myocardial infarction patients with coronary atherosclerosis poorly explained by standard modifiable risk factors. *Eur J Prev Cardiol*. 2017;24:1824–1830.
5. Figtree GA, Vernon ST, Harmer JA, Gray MP, Arnott C, Bachour E, Barsha G, Brieger D, Brown A, Celermajer DS, Channon KM, Chew NWS, Chong JJH, Chow CK, Cistulli PA, Ellinor PT, Grieve SM, Guzik TJ, Hagström E, Jenkins A, Jennings G, Keech AC, Kott KA, Kritharides L, Mamas MA, Mehran R, Meikle PJ, Natarajan P, Negishi K, O'Sullivan J, Patel S, Psaltis PJ, Redfern J, Steg PG, Sullivan DR, Sundström J, Vogel B, Wilson A, Wong D, Bhatt DL, Kovacic JC, Nicholls SJ, CRE for CAD Collaborators. Clinical Pathway for Coronary Atherosclerosis in Patients Without Conventional Modifiable Risk Factors: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2023;82:1343–1359.
6. Figtree GA, Vernon ST, Hadziosmanovic N, Sundström J, Alfredsson J, Arnott C, Delatour V, Leósdóttir M, Hagström E. Mortality in STEMI patients without standard modifiable risk factors: a sex-disaggregated analysis of SWEDEHEART registry data. *Lancet Lond Engl*. 2021;397:1085–1094.
7. Aggarwal R, Bhatt DL, Rodriguez F, Yeh RW, Wadhera RK. Trends in Lipid Concentrations and Lipid Control Among US Adults, 2007-2018. *JAMA*. 2022;328:737–745.
8. Park K-Y, Hong S, Kim K-S, Han K, Park C-Y. Trends in Prevalence of Hypertriglyceridemia and Related Factors in Korean Adults: A Serial Cross-Sectional Study. *J Lipid Atheroscler*. 2023;12:201–212.
9. Ruiz-García A, Arranz-Martínez E, López-Uriarte B, Rivera-Teijido M, Palacios-Martínez D, Dávila-Blázquez GM, Rosillo-González A, González-Posada Delgado JA, Mariño-Suárez JE, Revilla-Pascual E, Quintana-Gómez JL, Íscar-Valenzuela I, Alonso-Roca R, Javierre-Miranda AP, Escrivá-Ferrairó RA, Tello-Meco I, Ibarra-Sánchez AM, Gutiérrez Sánchez MI, Iglesias Quintana JR, Hernández-Beltrán MI, Pérez Fernández M, Barrios-Rueda E, Pérez Muñoz R, Prieto Marcos M, Delgado Rodríguez S, Pleite Raposo R, Rodríguez-Cabanillas R, Morales-Chico MR, Fernández-Pacheco Vila D, Remón-Pérez B, Del Villar Redondo MJ, Reguillo-Díaz J, Aguilera Reija P, Rodríguez

Rodríguez AO, Gómez-Fernández O, Antón-Sanz MDC, Sánchez-Calso A, Doria-Carlin NA, Frías-Vargas MJ, en representación del Grupo de Investigación del Estudio SIMETAP. Prevalence of hypertriglyceridemia in adults and related cardiometabolic factors. SIMETAP-HTG study. *Clin E Investig En Arterioscler Publicacion Of Soc Espanola Arterioscler*. 2020;32:242–255.

10. Sakboonyarat B, Poovieng J, Jongcherdchootrakul K, Srisawat P, Hatthachote P, Mungthin M, Rangsin R. Prevalence of hypertriglyceridemia among Royal Thai Army personnel and its related cardiometabolic risk factors, from 2017 to 2021. *BMC Public Health*. 2022;22:1569.
11. Fang M, Wang D, Coresh J, Selvin E. Trends in Diabetes Treatment and Control in U.S. Adults, 1999–2018. *N Engl J Med*. 2021;384:2219–2228.
12. Fan W, Philip S, Granowitz C, Toth PP, Wong ND. Hypertriglyceridemia in statin-treated US adults: the National Health and Nutrition Examination Survey. *J Clin Lipidol*. 2019;13:100–108.
13. Gill PK, Dron JS, Dilliott AA, McIntyre AD, Cao H, Wang J, Movsesyan IG, Malloy MJ, Pullinger CR, Kane JP, Hegele RA. Ancestry-specific profiles of genetic determinants of severe hypertriglyceridemia. *J Clin Lipidol*. 2021;15:88–96.
14. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw K-T, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*. 2007;115:450–458.
15. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, Lawlor D, Reilly MP, Hingorani AD, Talmud PJ, Danesh J. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet Lond Engl*. 2010;375:1634–1639.
16. Saadatagah S, Pasha AK, Alhalabi L, Sandhyavenu H, Farwati M, Smith CY, Wood-Wentz CM, Bailey KR, Kullo IJ. Coronary Heart Disease Risk Associated with Primary Isolated Hypertriglyceridemia; a Population-Based Study. *J Am Heart Assoc*. 2021;10:e019343.
17. Toth PP, Granowitz C, Hull M, Liassou D, Anderson A, Philip S. High Triglycerides Are Associated With Increased Cardiovascular Events, Medical Costs, and Resource Use: A Real-World Administrative Claims Analysis of Statin-Treated Patients With High Residual Cardiovascular Risk. *J Am Heart Assoc*. 2018;7:e008740.
18. Klempfner R, Erez A, Sagit B-Z, Goldenberg I, Fisman E, Kopel E, Shlomo N, Israel A, Tenenbaum A. Elevated Triglyceride Level Is Independently Associated With Increased All-Cause Mortality in Patients With Established Coronary Heart Disease: Twenty-Two-Year Follow-Up of the Bezafibrate Infarction Prevention Study and Registry. *Circ Cardiovasc Qual Outcomes*. 2016;9:100–108.
19. Haim M, Benderly M, Brunner D, Behar S, Graff E, Reicher-Reiss H, Goldbourt U. Elevated serum triglyceride levels and long-term mortality in patients with coronary heart disease: the Bezafibrate Infarction Prevention (BIP) Registry. *Circulation*. 1999;100:475–482.
20. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298:299–308.
21. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E, PROVE IT-TIMI 22 Investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2008;51:724–730.
22. Raposeiras-Roubin S, Rosselló X, Oliva B, Fernández-Friera L, Mendiguren JM, Andrés V, Bueno H, Sanz J, Martínez de Vega V, Abu-Assi E, Iñiguez A, Fernández-Ortiz A, Ibáñez B, Fuster V. Triglycerides and Residual Atherosclerotic Risk. *J Am Coll Cardiol*. 2021;77:3031–3041.
23. Maruhama Y, Ohneda A, Tadaki H, Ohtsuki M, Yanbe A. Hepatic steatosis and the elevated plasma insulin level in patients with endogenous hypertriglyceridemia. *Metabolism*. 1975;24:653–664.
24. Virani SS, Morris PB, Agarwala A, Ballantyne CM, Birtcher KK, Kris-Etherton PM, Ladden-Stirling AB, Miller M, Orringer CE, Stone NJ. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;78:960–993.
25. Aberra T, Peterson ED, Pagidipati NJ, Mulder H, Wojdyla DM, Philip S, Granowitz C, Navar AM. The association between triglycerides and incident cardiovascular disease: What is "optimal"? *J Clin Lipidol*. 2020;14:438-447.e3.
26. Ginsberg HN, Packard CJ, Chapman MJ, Borén J, Aguilar-Salinas CA, Averna M, Ference BA, Gaudet D, Hegele RA, Kersten S, Lewis GF, Lichtenstein AH, Moulin P, Nordestgaard BG, Remaley AT, Staels B, Stroes ESG, Taskinen M-R, Tokgözoğlu LS, Tybjaerg-Hansen A, Stock JK, Catapano AL. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society. *Eur Heart J*. 2021;42:4791–4806.

27. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S, American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Nursing, Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2011;123:2292–2333.
28. Tada H, Takamura M, Kawashiri M. Chapter Five - Genomics of hypertriglyceridemia [Internet]. In: Makowski GS, editor. Advances in Clinical Chemistry. Elsevier; 2020 [cited 2024 Apr 18]. p. 141–169.Available from: https://www.sciencedirect.com/science/article/pii/S0065242319301076
29. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. *Eur Heart J*. 2020;41:99–109c.
30. Tybjærg-Hansen A, Nordestgaard BG, Christoffersen M. Triglyceride-rich remnant lipoproteins are more atherogenic than LDL per particle: is this important? *Eur Heart J*. 2023;44:4196–4198.
31. Hansen SEJ, Madsen CM, Varbo A, Nordestgaard BG. Low-Grade Inflammation in the Association between Mild-to-Moderate Hypertriglyceridemia and Risk of Acute Pancreatitis: A Study of More Than 115000 Individuals from the General Population. *Clin Chem*. 2019;65:321–332.
32. Peng X, Wu H. Inflammatory Links Between Hypertriglyceridemia and Atherogenesis. *Curr Atheroscler Rep*. 2022;24:297–306.
33. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Nordestgaard BG, Ray KK, Reiner Z, Taskinen M-R, Tokgözoglu L, Tybjærg-Hansen A, Watts GF, European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*. 2011;32:1345–1361.
34. Nordestgaard BG. Triglyceride-Rich Lipoproteins and Atherosclerotic Cardiovascular Disease: New Insights From Epidemiology, Genetics, and Biology. *Circ Res*. 2016;118:547–563.
35. Chan DC, Kritharides L, Watts GF. The remnant-cholesterol/CRP nexus: Trouble and strife when the fat hits the fire. *Atherosclerosis*. 2023;379:117169.
36. Chait A, Ginsberg HN, Vaisar T, Heinecke JW, Goldberg IJ, Bornfeldt KE. Remnants of the Triglyceride-Rich Lipoproteins, Diabetes, and Cardiovascular Disease. *Diabetes*. 2020;69:508–516.
37. Saeed A, Feofanova EV, Yu B, Sun W, Virani SS, Nambi V, Coresh J, Guild CS, Boerwinkle E, Ballantyne CM, Hoogeveen RC. Remnant-Like Particle Cholesterol, Low-Density Lipoprotein Triglycerides, and Incident Cardiovascular Disease. *J Am Coll Cardiol*. 2018;72:156–169.
38. Oh RC, Trivette ET, Westerfield KL. Management of Hypertriglyceridemia: Common Questions and Answers. *Am Fam Physician*. 2020;102:347–354.
39. Goldberg IJ. Clinical review 124: Diabetic dyslipidemia: causes and consequences. *J Clin Endocrinol Metab*. 2001;86:965–971.
40. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, Borén J, Bruckert E, Catapano AL, Descamps OS, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AFH, Stroes E, Taskinen M-R, Tybjærg-Hansen A, Watts GF, Wiklund O. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol*. 2014;2:655–666.
41. Retterstøl K, Narverud I, Selmer R, Berge KE, Osnes IV, Ulven SM, Halvorsen B, Aukrust P, Holven KB, Iversen PO. Severe hypertriglyceridemia in Norway: prevalence, clinical and genetic characteristics. *Lipids Health Dis*. 2017;16:115.
42. Watts GF, Ooi EMM, Chan DC. Demystifying the management of hypertriglyceridaemia. *Nat Rev Cardiol*. 2013;10:648–661.
43. Pollin TI, Damcott CM, Shen H, Ott SH, Shelton J, Horenstein RB, Post W, McLenithan JC, Bielak LF, Peyser PA, Mitchell BD, Miller M, O'Connell JR, Shuldiner AR. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. *Science*. 2008;322:1702–1705.
44. Qamar A, Khetarpal SA, Khera AV, Qasim A, Rader DJ, Reilly MP. Plasma apolipoprotein C-III levels, triglycerides, and coronary artery calcification in type 2 diabetics. *Arterioscler Thromb Vasc Biol*. 2015;35:1880–1888.
45. Coding Variation in ANGPTL4, LPL, and SVEP1 and the Risk of Coronary Disease. *N Engl J Med*. 2016;374:1898.
46. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, Laufs U, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, Danesh J, Nicholls SJ, Bhatt DL, Sabatine MS, Catapano AL. Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease. *JAMA*. 2019;321:364–373.
47. Richardson TG, Wang Q, Sanderson E, Mahajan A, McCarthy MI, Frayling TM, Ala-Korpela M, Sniderman A, Smith GD, Holmes MV. Effects of apolipoprotein B on lifespan and risks of major diseases including type

2 diabetes: a mendelian randomisation analysis using outcomes in first-degree relatives. *Lancet Healthy Longev*. 2021;2:e317–e326.
48. Johannesen CDL, Langsted A, Nordestgaard BG, Mortensen MB. Excess Apolipoprotein B and Cardiovascular Risk in Women and Men. *J Am Coll Cardiol*. 2024;83:2262–2273.
49. Carrasquilla GD, Christiansen MR, Kilpeläinen TO. The Genetic Basis of Hypertriglyceridemia. *Curr Atheroscler Rep*. 2021;23:39.
50. Alves M, Laranjeira F, Correia-da-Silva G. Understanding Hypertriglyceridemia: Integrating Genetic Insights. *Genes*. 2024;15:190.
51. Baass A, Paquette M, Bernard S, Hegele RA. Familial chylomicronemia syndrome: an under-recognized cause of severe hypertriglyceridaemia. *J Intern Med*. 2020;287:340–348.
52. Koopal C, Marais AD, Visseren FLJ. Familial dysbetalipoproteinemia: an underdiagnosed lipid disorder. *Curr Opin Endocrinol Diabetes Obes*. 2017;24:133–139.
53. Heidemann BE, Koopal C, Baass A, Defesche JC, Zuurbier L, Mulder MT, Roeters van Lennep JE, Riksen NP, Boot C, Marais AD, Visseren FLJ. Establishing the relationship between familial dysbetalipoproteinemia and genetic variants in the APOE gene. *Clin Genet*. 2022;102:253–261.
54. Brown RJ, Araujo-Vilar D, Cheung PT, Dunger D, Garg A, Jack M, Mungai L, Oral EA, Patni N, Rother KI, von Schnurbein J, Sorkina E, Stanley T, Vigouroux C, Wabitsch M, Williams R, Yorifuji T. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. *J Clin Endocrinol Metab*. 2016;101:4500–4511.
55. Patni N, Garg A. Congenital generalized lipodystrophies--new insights into metabolic dysfunction. *Nat Rev Endocrinol*. 2015;11:522–534.
56. Dron JS, Wang J, Cao H, McIntyre AD, Iacocca MA, Menard JR, Movsesyan I, Malloy MJ, Pullinger CR, Kane JP, Hegele RA. Severe hypertriglyceridemia is primarily polygenic. *J Clin Lipidol*. 2019;13:80–88.
57. Chait A. Multifactorial chylomicronemia syndrome. *Curr Opin Endocrinol Diabetes Obes*. 2024;31:78–83.
58. Chait A, Eckel RH. The Chylomicronemia Syndrome Is Most Often Multifactorial: A Narrative Review of Causes and Treatment. *Ann Intern Med*. 2019;170:626–634.
59. Powell JM, Lange RT. People of Australia [Internet]. Britannica. [cited 2024 May 21];Available from: https://www.britannica.com/place/Australia/People
60. Australian Bureau of Statistics. Estimates of Aboriginal and Torres Strait Islander Australians [Internet]. Aust. Bur. Stat. 2023 [cited 2024 Jul 8];Available from: https://www.abs.gov.au/statistics/people/aboriginal-and-torres-strait-islander-peoples/estimates-aboriginal-and-torres-strait-islander-australians/latest-release
61. CIA.Gov. Australia - Country Summary [Internet]. World Factb. [cited 2024 Jul 8];Available from: https://www.cia.gov/the-world-factbook/countries/australia/summaries/
62. Vowles J, Blyth AB. People of New Zealand [Internet]. 2024 [cited 2024 Jul 8];Available from: https://www.britannica.com/place/New-Zealand/People
63. Meshkini M, Alaei-Shahmiri F, Mamotte C, Earnest J. Ethnic Variation in Lipid Profile and Its Associations with Body Composition and Diet: Differences Between Iranians, Indians and Caucasians Living in Australia. *J Immigr Minor Health*. 2017;19:67–73.
64. O'Dea K, Traianedes K, Hopper JL, Larkins RG. Impaired glucose tolerance, hyperinsulinemia, and hypertriglyceridemia in Australian aborigines from the desert. *Diabetes Care*. 1988;11:23–29.
65. O'Dea K, Patel M, Kubisch D, Hopper J, Traianedes K. Obesity, diabetes, and hyperlipidemia in a central Australian aboriginal community with a long history of acculturation. *Diabetes Care*. 1993;16:1004–1010.
66. Australian Bureau of Statistics. Australian Aboriginal and Torres Strait Islander Health Survey: Biomedical Results, 2012-13 [Internet]. Aust. Bur. Stat. 2014 [cited 2024 Jul 8];Available from: https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4727.0.55.003~2012-13~Main%20Features~Triglycerides~122
67. Australian Bureau of Statistics. 4722.0.55.006 - Overweight and Obesity - Aboriginal and Torres Strait Islander people: A snapshot, 2004-05 [Internet]. 2008 [cited 2024 Jul 22];Available from: https://www.abs.gov.au/ausstats/abs@.nsf/mf/4722.0.55.006
68. Agostino JW, Wong D, Paige E, Wade V, Connell C, Davey ME, Peiris DP, Fitzsimmons D, Burgess CP, Mahoney R, Lonsdale E, Fernando P, Malamoo L, Eades S, Brown A, Jennings G, Lovett RW, Banks E. Cardiovascular disease risk assessment for Aboriginal and Torres Strait Islander adults aged under 35 years: a consensus statement. *Med J Aust*. 2020;212:422–427.
69. Calabria B, Korda RJ, Lovett RW, Fernando P, Martin T, Malamoo L, Welsh J, Banks E. Absolute cardiovascular disease risk and lipid-lowering therapy among Aboriginal and Torres Strait Islander Australians. *Med J Aust*. 2018;209:35–41.
70. Cameron VA, Faatoese AF, Gillies MW, Robertson PJ, Huria TM, Doughty RN, Whalley GA, Richards MA, Troughton RW, Tikao-Mason KN, Wells EJ, Sheerin IG, Pitama SG. A cohort study comparing cardiovascular risk factors in rural Māori, urban Māori and non-Māori communities in New Zealand. *BMJ Open*. 2012;2:e000799.
71. Heart Research Institute NZ. Heart Disease and Maori • Heart Research Institute NZ [Internet]. Heart Res. Inst. NZ.

[cited 2024 Jul 8];Available from: https://www.hri.org.nz/health/learn/cardiovascular-disease/heart-disease-in-the-māori-community
72. Grey C, Wells S, Riddell T, Kerr A, Gentles D, Pylypchuk R, Marshall R, Ameratunga S, Drury P, Elley CR, Kyle C, Exeter D, Jackson R. A comparative analysis of the cardiovascular disease risk factor profiles of Pacific peoples and Europeans living in New Zealand assessed in routine primary care: PREDICT CVD-11. *N Z Med J*. 2010;123:62–75.
73. Yu D, Cai Y, Osuagwu UL, Pickering K, Baker J, Cutfield R, Jansen RM, Orr-Walker BJ, Sundborn G, Zhao Z, Simmons D. Metabolic Profiles of Maori, Pacific, and European New Zealanders With Type 2 Diabetes Over 25 Years. *Diabetes Care*. 2021;dc211255.
74. Devlin G, Tukuitonga C, Grey C, Richards M, Rolleston A, Doughty R, Legget M, Mann J. Call to action-the urgent need for a heart health plan in New Zealand. *N Z Med J*. 2023;136:103–108.
75. Mason K, Toohey F, Gott M, Moeke-Maxwell T. Māori: living and dying with cardiovascular disease in Aotearoa New Zealand. *Curr Opin Support Palliat Care*. 2019;13:3–8.
76. Tane T, Selak V, Eggleton K, Harwood M. Drivers of access to cardiovascular health care for rural Indigenous Peoples: a scoping review. *Rural Remote Health*. 2024;24:8674.
77. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, Watanabe M, Kadota A, Okuda N, Kadowaki T, Nakamura Y, Okamura T. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation*. 2008;118:2702–2709.
78. Gupta M, Singh N, Verma S. South Asians and cardiovascular risk: what clinicians should know. *Circulation*. 2006;113:e924-929.
79. Li X, Wu C, Lu J, Chen B, Li Y, Yang Y, Hu S, Li J. Cardiovascular risk factors in China: a nationwide population-based cohort study. *Lancet Public Health*. 2020;5:e672–e681.
80. Guo S, Lucas RM, Joshy G, Banks E. Cardiovascular disease risk factor profiles of 263,356 older Australians according to region of birth and acculturation, with a focus on migrants born in Asia. *PloS One*. 2015;10:e0115627.
81. Misra A, Khurana L. The metabolic syndrome in South Asians: epidemiology, determinants, and prevention. *Metab Syndr Relat Disord*. 2009;7:497–514.
82. Misra A, Vikram NK. Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. *Nutr Burbank Los Angel Cty Calif*. 2004;20:482–491.
83. Georgoulis M, Damigou E, Chrysohoou C, Barkas F, Kravvariti E, Tsioufis C, Pitsavos C, Liberopoulos E, Sfikakis PP, Panagiotakos DB, ATTICA study group. Increased body weight and central adiposity markers are positively associated with the 20-year incidence of cardiovascular disease: The ATTICA epidemiological study (2002-2022). *Nutr Res N Y N*. 2024;121:1–15.
84. Aggarwal R, Bibbins-Domingo K, Yeh RW, Song Y, Chiu N, Wadhera RK, Shen C, Kazi DS. Diabetes Screening by Race and Ethnicity in the United States: Equivalent Body Mass Index and Age Thresholds. *Ann Intern Med* [Internet]. 2022 [cited 2022 May 22];Available from: https://www.acpjournals.org/doi/10.7326/M20-8079
85. Bilen O, Kamal A, Virani SS. Lipoprotein abnormalities in South Asians and its association with cardiovascular disease: Current state and future directions. *World J Cardiol*. 2016;8:247–257.
86. Li J, Wang L, Li Y, Bi Y, Jiang Y, Mi S, Dai M, Xu Y, Ning G, Zhao W. [Epidemiologic characteristics of dyslipidemia in Chinese adults 2010]. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2012;46:414–418.
87. Jiang CQ, Liu B, Cheung BM, Lam TH, Lin JM, Li Jin Y, Yue XJ, Ong KL, Tam S, Wong KS, Tomlinson B, Lam KS, Thomas GN. A single nucleotide polymorphism in APOA5 determines triglyceride levels in Hong Kong and Guangzhou Chinese. *Eur J Hum Genet*. 2010;18:1255–1260.
88. Liu Y, Dai S, Qin S, Zhou J, Wang Z, Yin G. The pathogenic mutations of APOA5 in Chinese patients with hyperlipidemic acute pancreatitis. *Lipids Health Dis*. 2024;23:44.
89. Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, Coresh J, Baker-Smith CM, Carnethon MR, Després J-P, Ho JE, Joseph JJ, Kernan WN, Khera A, Kosiborod MN, Lekavich CL, Lewis EF, Lo KB, Ozkan B, Palaniappan LP, Patel SS, Pencina MJ, Powell-Wiley TM, Sperling LS, Virani SS, Wright JT, Rajgopal Singh R, Elkind MSV, Rangaswami J, American Heart Association. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. *Circulation*. 2023;148:1636–1664.
90. Aggarwal R, Ostrominski JW, Vaduganathan M. Prevalence of Cardiovascular-Kidney-Metabolic Syndrome Stages in US Adults, 2011-2020. *JAMA*. 2024;e246892.
91. Karalis DG. A Review of Clinical Practice Guidelines for the Management of Hypertriglyceridemia: A Focus on High Dose Omega-3 Fatty Acids. *Adv Ther*. 2017;34:300–323.
92. Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. *J Clin Gastroenterol*. 2014;48:195–203.
93. Toskes PP. Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am*. 1990;19:783–791.

94. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Angelantonio ED, Franco OH, Halvorsen S, Richard Hobbs FD, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B, ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur Heart J*. 2021;42:3227–3337.
95. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting Mild-to-Moderate Hypertriglyceridemia and Risk of Acute Pancreatitis. *JAMA Intern Med*. 2016;176:1834–1842.
96. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143.
97. Driver SL, Martin SS, Gluckman TJ, Clary JM, Blumenthal RS, Stone NJ. Fasting or Nonfasting Lipid Measurements: It Depends on the Question. *J Am Coll Cardiol*. 2016;67:1227–1234.
98. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. 2008;300:2142–2152.
99. Langsted A, Freiberg JJ, Nordestgaard BG. Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. *Circulation*. 2008;118:2047–2056.
100. Cartier L-J, Collins C, Lagacé M, Douville P. Comparison of fasting and non-fasting lipid profiles in a large cohort of patients presenting at a community hospital. *Clin Biochem*. 2018;52:61–66.
101. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
102. Martin SS, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, Jones SR. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA*. 2013;310:2061–2068.
103. Sampson M, Wolska A, Warnick R, Lucero D, Remaley AT. A New Equation Based on the Standard Lipid Panel for Calculating Small Dense Low-Density Lipoprotein-Cholesterol and Its Use as a Risk-Enhancer Test. *Clin Chem*. 2021;67:987–997.
104. Tirosh A, Rudich A, Shochat T, Tekes-Manova D, Israeli E, Henkin Y, Kochba I, Shai I. Changes in triglyceride levels and risk for coronary heart disease in young men. *Ann Intern Med*. 2007;147:377–385.
105. Patel J, Sharma T, Allan C, Curnew G. Use of Lifestyle Modifications for Management of a Patient with Severely High Total Cholesterol (> 14 mmol/L) and Triglycerides (> 40 mmol/L). *J Lifestyle Med*. 2021;11:43–46.
106. Artinian NT, Fletcher GF, Mozaffarian D, Kris-Etherton P, Van Horn L, Lichtenstein AH, Kumanyika S, Kraus WE, Fleg JL, Redeker NS, Meininger JC, Banks J, Stuart-Shor EM, Fletcher BJ, Miller TD, Hughes S, Braun LT, Kopin LA, Berra K, Hayman LL, Ewing LJ, Ades PA, Durstine JL, Houston-Miller N, Burke LE, American Heart Association Prevention Committee of the Council on Cardiovascular Nursing. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122:406–441.
107. Goldfarb MJ, Saylor MA, Bozkurt B, Code J, Di Palo KE, Durante A, Flanary K, Masterson Creber R, Ogunniyi MO, Rodriguez F, Gulati M, American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Hypertension; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Council on Quality of Care and Outcomes Research. Patient-Centered Adult Cardiovascular Care: A Scientific Statement From the American Heart Association. *Circulation*. 2024;149:e1176–e1188.
108. Chan DC, Watts GF, Ng TWK, Yamashita S, Barrett PHR. Effect of weight loss on markers of triglyceride-rich lipoprotein metabolism in the metabolic syndrome. *Eur J Clin Invest*. 2008;38:743–751.
109. Byrne A, Makadia S, Sutherland A, Miller M. Optimizing Non-Pharmacologic Management of Hypertriglyceridemia. *Arch Med Res*. 2017;48:483–487.
110. Kushner PA, Cobble ME. Hypertriglyceridemia: the importance of identifying patients at risk. *Postgrad Med*. 2016;128:848–858.
111. Rhodes KS, Weintraub M, Marchlewicz EH, Rubenfire M, Brook RD. Medical nutrition therapy is the essential cornerstone for effective treatment of “refractory” severe

hypertriglyceridemia regardless of pharmaceutical treatment: Evidence from a Lipid Management Program. *J Clin Lipidol*. 2015;9:559–567.
112. Fechner E, Smeets ETHC, Schrauwen P, Mensink RP. The Effects of Different Degrees of Carbohydrate Restriction and Carbohydrate Replacement on Cardiometabolic Risk Markers in Humans-A Systematic Review and Meta-Analysis. *Nutrients*. 2020;12:991.
113. Stoernell CK, Tangney CC, Rockway SW. Short-term changes in lipoprotein subclasses and C-reactive protein levels of hypertriglyceridemic adults on low-carbohydrate and low-fat diets. *Nutr Res N Y N*. 2008;28:443–449.
114. Pownall HJ, Ballantyne CM, Kimball KT, Simpson SL, Yeshurun D, Gotto AM. Effect of moderate alcohol consumption on hypertriglyceridemia: a study in the fasting state. *Arch Intern Med*. 1999;159:981–987.
115. Klop B, do Rego AT, Cabezas MC. Alcohol and plasma triglycerides. *Curr Opin Lipidol*. 2013;24:321–326.
116. Martin WH. Effects of acute and chronic exercise on fat metabolism. *Exerc Sport Sci Rev*. 1996;24:203–231.
117. Koutsari C, Karpe F, Humphreys SM, Frayn KN, Hardman AE. Exercise prevents the accumulation of triglyceride-rich lipoproteins and their remnants seen when changing to a high-carbohydrate diet. *Arterioscler Thromb Vasc Biol*. 2001;21:1520–1525.
118. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD. The Physical Activity Guidelines for Americans. *JAMA*. 2018;320:2020–2028.
119. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC, Virani SS, Williams KA, Yeboah J, Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74:e177–e232.
120. Stancu C, Sima A. Statins: mechanism of action and effects. *J Cell Mol Med*. 2001;5:378–387.
121. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O, ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J*. 2020;41:111–188.
122. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
123. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet Lond Engl*. 2002;360:7–22.
124. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation*. 1998;98:2088–2093.
125. Das Pradhan A, Glynn RJ, Fruchart J-C, MacFadyen JG, Zaharris ES, Everett BM, Campbell SE, Oshima R, Amarenco P, Blom DJ, Brinton EA, Eckel RH, Elam MB, Felicio JS, Ginsberg HN, Goudev A, Ishibashi S, Joseph J, Kodama T, Koenig W, Leiter LA, Lorenzatti AJ, Mankovsky B, Marx N, Nordestgaard BG, Páll D, Ray KK, Santos RD, Soran H, Susekov A, Tendera M, Yokote K, Paynter NP, Buring JE, Libby P, Ridker PM, PROMINENT Investigators. Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. *N Engl J Med*. 2022;387:1923–1934.
126. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1563–1574.
127. Davidson MH, Armani A, McKenney JM, Jacobson TA. Safety considerations with fibrate therapy. *Am J Cardiol*. 2007;99:3C-18C.
128. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. *Am J Med*. 1987;83:26–36.
129. Ting R-D, Keech AC, Drury PL, Donoghoe MW, Hedley J, Jenkins AJ, Davis TME, Lehto S, Celermajer D, Simes RJ, Rajamani K, Stanton K. Benefits and Safety of Long-Term Fenofibrate Therapy in People With Type 2 Diabetes and Renal Impairment. *Diabetes Care*. 2012;35:218–225.
130. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237–1245.
131. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-

density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341:410–418.
132. Bloomfield Rubins H, Davenport J, Babikian V, Brass LM, Collins D, Wexler L, Wagner S, Papademetriou V, Rutan G, Robins SJ, VA-HIT Study Group. Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: The Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation*. 2001;103:2828–2833.
133. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M, FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet Lond Engl*. 2005;366:1849–1861.
134. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, Grobbee DE, Cass A, Chalmers J, Perkovic V. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet Lond Engl*. 2010;375:1875–1884.
135. Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TME, Moffitt MS, Taskinen M-R, Simes RJ, Tse D, Williamson E, Merrifield A, Laatikainen LT, d'Emden MC, Crimet DC, O'Connell RL, Colman PG, FIELD study investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet Lond Engl*. 2007;370:1687–1697.
136. Chew EY, Davis MD, Danis RP, Lovato JF, Perdue LH, Greven C, Genuth S, Goff DC, Leiter LA, Ismail-Beigi F, Ambrosius WT. The Effects of Medical Management on the Progression of Diabetic Retinopathy in Persons with Type 2 Diabetes: The ACCORD Eye Study. *Ophthalmology*. 2014;121:2443–2451.
137. Ong J, Newman D, Sharma N, Ooi J-L. The use of fenofibrate in the management of patients with diabetic retinopathy: an evidence-based review. *Aust Fam Physician*. 2015;44:367–370.
138. Gille A, Bodor ET, Ahmed K, Offermanns S. Nicotinic acid: pharmacological effects and mechanisms of action. *Annu Rev Pharmacol Toxicol*. 2008;48:79–106.
139. McKenney J. New perspectives on the use of niacin in the treatment of lipid disorders. *Arch Intern Med*. 2004;164:697–705.
140. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013;34:1279–1291.
141. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255–2267.
142. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, Davidson MH, Kastelein JJP, Koenig W, McGuire DK, Mozaffarian D, Ridker PM, Ray KK, Katona BG, Himmelmann A, Loss LE, Rensfeldt M, Lundström T, Agrawal R, Menon V, Wolski K, Nissen SE. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. *JAMA*. 2020;324:2268–2280.
143. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Juliano RA, Jiao L, Granowitz C, Tardif J-C, Ballantyne CM, REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22.
144. Albert BB, Derraik JGB, Cameron-Smith D, Hofman PL, Tumanov S, Villas-Boas SG, Garg ML, Cutfield WS. Fish oil supplements in New Zealand are highly oxidised and do not meet label content of n-3 PUFA. *Sci Rep*. 2015;5:7928.
145. Sherratt SCR, Lero M, Mason RP. Are dietary fish oil supplements appropriate for dyslipidemia management? A review of the evidence. *Curr Opin Lipidol*. 2020;31:94–100.
146. Brinton EA, Mason RP. Prescription omega-3 fatty acid products containing highly purified eicosapentaenoic acid (EPA). *Lipids Health Dis*. 2017;16:23.
147. Fialkow J. Omega-3 Fatty Acid Formulations in Cardiovascular Disease: Dietary Supplements are Not Substitutes for Prescription Products. *Am J Cardiovasc Drugs Drugs Devices Interv*. 2016;16:229–239.
148. ORIGIN Trial Investigators, Bosch J, Gerstein HC, Dagenais GR, Díaz R, Dyal L, Jung H, Maggiono AP, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367:309–318.
149. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, Murawska A, Young A, Lay M, Chen F, Sammons E, Waters E, Adler A, Bodansky J, Farmer A, McPherson R, Neil A, Simpson D, Peto R, Baigent C, Collins R, Parish S, Armitage J. Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus. *N Engl J Med*. 2018;379:1540–1550.
150. Manson JE, Bassuk SS, Buring JE, VITAL Research Group. Principal results of the VITamin D and OmegA-3 TriaL (VITAL) and updated meta-analyses of relevant vitamin D trials. *J Steroid Biochem Mol Biol*. 2020;198:105522.
151. Kalstad AA, Myhre PL, Laake K, Tveit SH, Schmidt EB, Smith

P, Nilsen DWT, Tveit A, Fagerland MW, Solheim S, Seljeflot I, Arnesen H, OMEMI Investigators. Effects of n-3 Fatty Acid Supplements in Elderly Patients After Myocardial Infarction: A Randomized, Controlled Trial. *Circulation*. 2021;143:528–539.

152. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet Lond Engl*. 2007;369:1090–1098.
153. Watanabe T, Ando K, Daidoji H, Otaki Y, Sugawara S, Matsui M, Ikeno E, Hirono O, Miyawaki H, Yashiro Y, Nishiyama S, Arimoto T, Takahashi H, Shishido T, Miyashita T, Miyamoto T, Kubota I, CHERRY study investigators. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. *J Cardiol*. 2017;70:537–544.
154. Budoff MJ, Bhatt DL, Kinninger A, Lakshmanan S, Muhlestein JB, Le VT, May HT, Shaikh K, Shekar C, Roy SK, Tayek J, Nelson JR. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J*. 2020;41:3925–3932.
155. Miyauchi K, Iwata H, Nishizaki Y, Inoue T, Hirayama A, Kimura K, Ozaki Y, Murohara T, Ueshima K, Kuwabara Y, Tanaka-Mizuno S, Yanagisawa N, Sato T, Daida H, RESPECT-EPA Investigators. Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and Eicosapentaenoic Acid (RESPECT-EPA). *Circulation*. 2024;
156. Daida H, Nishizaki Y, Iwata H, Inoue T, Hirayama A, Kimura K, Ozaki Y, Murohara T, Ueshima K, Kuwabara Y, Tanaka-Mizuno S, Yanagisawa S, Sato T, Miyauchi K, RESPECT-EPA Investigators. Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid - RESPECT-EPA. 2022;
157. Curfman G, Shehada E. Icosapent ethyl: scientific and legal controversies. *Open Heart*. 2021;8:e001616.
158. Ridker PM, Rifai N, MacFadyen J, Glynn RJ, Jiao L, Steg PG, Miller M, Brinton EA, Jacobson TA, Tardif J-C, Ballantyne CM, Mason RP, Bhatt DL. Effects of Randomized Treatment With Icosapent Ethyl and a Mineral Oil Comparator on Interleukin-1β, Interleukin-6, C-Reactive Protein, Oxidized Low-Density Lipoprotein Cholesterol, Homocysteine, Lipoprotein(a), and Lipoprotein-Associated Phospholipase A2: A REDUCE-IT Biomarker Substudy. *Circulation*. 2022;146:372–379.
159. Olshansky B, Chung MK, Budoff MJ, Philip S, Jiao L, Doyle RT, Copland C, Giaquinto A, Juliano RA, Bhatt DL. Mineral oil: safety and use as placebo in REDUCE-IT and other clinical studies. *Eur Heart J Suppl J Eur Soc Cardiol*. 2020;22:J34–J48.
160. Singh N, Bhatt DL, Miller M, Steg PG, Brinton EA, Jacobson TA, Jiao L, Tardif J-C, Mason RP, Ballantyne CM, REDUCE-IT Investigators. Consistency of Benefit of Icosapent Ethyl by Background Statin Type in REDUCE-IT. *J Am Coll Cardiol*. 2022;79:220–222.
161. Doi T, Langsted A, Nordestgaard BG. A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: cohort study mimicking trial designs. *Eur Heart J*. 2021;42:4807–4817.
162. Doi T, Langsted A, Nordestgaard BG. Mineral oil and icosapent ethyl may jointly explain the between arm difference of cardiovascular risk in REDUCE-IT. *Eur Heart J*. 2021;42:4867–4868.
163. Myhre PL, Kalstad AA, Tveit SH, Laake K, Schmidt EB, Smith P, Nilsen DWT, Tveit A, Solheim S, Arnesen H, Seljeflot I. Changes in eicosapentaenoic acid and docosahexaenoic acid and risk of cardiovascular events and atrial fibrillation: A secondary analysis of the OMEMI trial. *J Intern Med*. 2022;291:637–647.
164. Toth PP, Chapman MJ, Parhofer KG, Nelson JR. Differentiating EPA from EPA/DHA in cardiovascular risk reduction. *Am Heart J Plus Cardiol Res Pract*. 2022;17:100148.
165. Mason RP, Libby P, Bhatt DL. Emerging Mechanisms of Cardiovascular Protection for the Omega-3 Fatty Acid Eicosapentaenoic Acid. *Arterioscler Thromb Vasc Biol*. 2020;40:1135–1147.
166. Miller M. Pemafibrate and other triglyceride-lowering therapies to reduce risk of cardiovascular and metabolic disease. *Curr Opin Cardiol*. 2024;39:286–291.
167. Szarek M, Bhatt D, Miller M, Steg PG, Brinton EA, Jacobson TA, Tardif JC, Ballantyne CM, Ketchum SB, Pineda AL, Dunbar RL, Siri-Tarino PW, Mason RP, REDUCE-IT Investigators. Eicosapentaenoic acid, arachidonic acid, and triglyceride levels mediate most of the benefit of icosapent ethyl in REDUCE-IT. *Eur Heart J*. 2023;44:ehad655.1309.
168. Sherratt SCR, Libby P, Bhatt DL, Mason RP. Comparative Effects of Mineral Oil, Corn Oil, Eicosapentaenoic Acid, and Docosahexaenoic Acid in an In Vitro Atherosclerosis Model. *J Am Heart Assoc*. 2023;12:e029109.
169. Tomlinson B, Wu Q, Zhong Y, Li Y. Advances in Dyslipidaemia Treatments: Focusing on ApoC3 and ANGPTL3 Inhibitors. *J Lipid Atheroscler*. 2024;13:2–20.
170. Hassan M. ANGPLT3: A novel modulator of lipid metabolism. *Glob Cardiol Sci Pract*. 2017:e201706.

171. Rosenson RS, Gaudet D, Hegele RA, Ballantyne CM, Nicholls SJ, Lucas KJ, San Martin J, Zhou R, Muhsin M, Chang T, Hellawell J, Watts GF, ARCHES-2 Trial Team. Zodasiran, an RNAi Therapeutic Targeting ANGPTL3, for Mixed Hyperlipidemia. *N Engl J Med*. 2024;
172. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute, Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitziel NO, Lange LA, Lu Y, Tang Z, Zhang H, Hindy G, Masca N, Stirrups K, Kanoni S, Do R, Jun G, Hu Y, Kang HM, Xue C, Goel A, Farrall M, Duga S, Merlini PA, Asselta R, Girelli D, Olivieri O, Martinelli N, Yin W, Reilly D, Speliotes E, Fox CS, Hveem K, Holmen OL, Nikpay M, Farlow DN, Assimes TL, Franceschini N, Robinson J, North KE, Martin LW, DePristo M, Gupta N, Escher SA, Jansson J-H, Van Zuydam N, Palmer CNA, Wareham N, Koch W, Meitinger T, Peters A, Lieb W, Erbel R, Konig IR, Kruppa J, Degenhardt F, Gottesman O, Bottinger EP, O'Donnell CJ, Psaty BM, Ballantyne CM, Abecasis G, Ordovas JM, Melander O, Watkins H, Orho-Melander M, Ardissino D, Loos RJF, McPherson R, Willer CJ, Erdmann J, Hall AS, Samani NJ, Deloukas P, Schunkert H, Wilson JG, Kooperberg C, Rich SS, Tracy RP, Lin D-Y, Altshuler D, Gabriel S, Nickerson DA, Jarvik GP, Cupples LA, Reiner AP, Boerwinkle E, Kathiresan S. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med*. 2014;371:22–31.
173. Bergmark BA, Marston NA, Prohaska TA, Alexander VJ, Zimerman A, Moura FA, Murphy SA, Goodrich EL, Zhang S, Gaudet D, Karwatowska-Prokopczuk E, Tsimikas S, Giugliano RP, Sabatine MS, Bridge–TIMI 73a Investigators. Olezarsen for Hypertriglyceridemia in Patients at High Cardiovascular Risk. *N Engl J Med*. 2024;390:1770–1780.
174. Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, Hegele RA, Arca M, Ballantyne CM, Soran H, Prohaska TA, Xia S, Ginsberg HN, Witztum JL, Tsimikas S, Balance Investigators. Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. *N Engl J Med*. 2024;390:1781–1792.
175. Watts GF. Shooting the Messenger to Treat Hypertriglyceridemia. *N Engl J Med*. 2024;390:1818–1823.
176. Gaudet D, Pall D, Watts GF, Nicholls SJ, Rosenson RS, Modesto K, San Martin J, Hellawell J, Ballantyne CM. Plozasiran (ARO-APOC3) for Severe Hypertriglyceridemia: The SHASTA-2 Randomized Clinical Trial. *JAMA Cardiol*. 2024;e240959.
177. Ballantyne CM, Vasas S, Azizad M, Clifton P, Rosenson RS, Chang T, Melquist S, Zhou R, Mushin M, Leeper NJ, Hellawell J, Gaudet D. Plozasiran, an RNA Interference Agent Targeting APOC3, for Mixed Hyperlipidemia. *N Engl J Med*. 2024;
178. Raal FJ, Rosenson RS, Reeskamp LF, Hovingh GK, Kastelein JJP, Rubba P, Ali S, Banerjee P, Chan K-C, Gipe DA, Khilla N, Pordy R, Weinreich DM, Yancopoulos GD, Zhang Y, Gaudet D, ELIPSE HoFH Investigators. Evinacumab for Homozygous Familial Hypercholesterolemia. *N Engl J Med*. 2020;383:711–720.
179. Eli Lilly and Company. A Study of LY3561774 in Participants With Mixed Dyslipidemia (PROLONG-ANG3) [Internet]. ClinicalTrials.Gov. [cited 2024 Jul 8];Available from: https://clinicaltrials.gov/study/NCT05256654
180. U.S. Food & Drug Administration. FDA approves add-on therapy for patients with genetic form of severely high cholesterol. *FDA* [Internet]. 2021 [cited 2024 Jul 8];Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-add-therapy-patients-genetic-form-severely-high-cholesterol-0
181. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan G-A, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, Rubini Gimenez M, Thiele H, Vranckx P, Wassmann S, Wenger NK, Ibanez B, ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44:3720–3826.

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

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

athero.org

These resources were produced independently by the society, college, university or other institution that is named as the author of these guidelines, with an unrestricted educational grant from CSL Seqirus. Responsibility for these resources remain with the named author of these resources. Whilst CSL Seqirus has provided funds for these guidelines to be produced, all the content of these resources were developed under the full control of the named author with no bias attributed to them. Although these resources will not be accredited, the named author has applied this standard in the development of all elements of this initiative and has adhered to accepted standards of commercial support.