

RISK OF FASTING AND NON-FASTING HYPERTRIGLYCERIDEMIA IN CORONARY VASCULAR DISEASE AND PANCREATITIS

Andrew Messersmith, MD, MPH., Fellow, Division of Endocrinology, Diabetes and Metabolism, University of Kentucky, Lexington, KY 40536. andrew.messersmith@uky.edu

Rahul Purbey, MD, Fellow, Division of Endocrinology, Diabetes and Metabolism, University of Kentucky, Lexington, KY 40536. rahul.purbey@uky.edu

Lisa R. Tannock, MD, Professor, Queen's University, Kingston, Ontario, Canada, deanfhs@queensu.ca

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ABSTRACT

Cardiovascular disease (CVD) remains a major cause of mortality in the Western world and in spite of the reduction of CVD risk by the use of lipid lowering agents per current treatment goals there remains substantial residual and absolute risk of CVD in high-risk populations. Focus on elevated triglyceride (TG) levels deserves renewed attention, particularly as one-third of all adults in the United States suffer from elevated TG and a growing number of people are diagnosed with metabolic syndrome or type 2 diabetes mellitus (T2DM). The dyslipidemia of metabolic syndrome and T2DM is characterized by low high-density lipoprotein cholesterol (HDL-c) concentrations and marked elevations in triglyceride rich lipoproteins (TRL). There has been growing data that points towards an association of fasting and non-fasting TGs with CVD, including a number of genetic studies suggesting causality. However, the association of TG as an independent risk factor in CVD is confounded by its inverse metabolic relationship with HDL-c and the heterogeneity of TG lipoproteins. Current guidelines suggest diagnosis of hypertriglyceridemia based on fasting levels where the length of fasting is recommended to be 9-12 hours. Although non-fasting TG levels may be a better indicator of risk, the lack of

standardization of non-fasting TG measurements, lack of specific reference ranges, and the variability of postprandial lipid measurements have hampered their routine clinical use. Current guidelines focus mainly on LDL-c levels; however, lowering TG may provide additional benefit for CVD prevention. Lifestyle changes including dietary changes and exercise play an important role in the treatment of hyperlipidemia. Pharmacological agents used in the treatment of hypertriglyceridemia include niacin, fibrates, fish oil, and statins. Most guidelines recommend treating elevated TG for prevention of pancreatitis. This chapter will discuss the role of elevated TG in pancreatitis and CVD risk.

INTRODUCTION

Cardiovascular disease (CVD) remains a major cause of mortality in the Western world, especially in individuals with obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM). With increasing incidence of the metabolic syndrome and T2DM worldwide, the global burden of CVD will also increase (1). In spite of the reduction of CVD risk by 25-35% with the use of lipid lowering agents, especially statins, there remains substantial residual and absolute risk of CVD in high-risk populations such as T2DM (2). Elevated low-

density lipoprotein (LDL-c) is a well-established CVD risk factor and has been the primary target for lipid lowering treatment. However, growing evidence suggests that an elevated triglyceride (TG) level is also an independent risk factor (3,4). Borderline high TGs or high TGs defined by National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) as TG concentration (150 – 199 mg/dL) and (200 – 499 mg/dL) respectively are present in 30% of the US adult population (5) and these levels have been associated with increased risk of CVD. The dyslipidemia of metabolic syndrome and T2DM is characterized by raised TG concentrations, low high-density lipoprotein cholesterol (HDL-c) concentrations and marked elevations in triglyceride rich lipoproteins (TRL). This triad is termed mixed or atherogenic dyslipidemia (6). Impaired metabolism of TRLs in the postprandial state have been observed in insulin resistant states such as visceral obesity, metabolic syndrome, and T2DM and this has been linked to the development of atherosclerosis (7).

Severe hypertriglyceridemia and very severe hyperlipidemia defined by Endocrine Society Clinical Practice Guideline on Evaluation and Treatment of Hypertriglyceridemia as TG concentration (1000 – 1999 mg/dL) and (>2000 mg/dL) carries an increased risk for pancreatitis (8). Case series and uncontrolled studies have shown that severely elevated TG levels are associated with the chylomicronemia syndrome and an increased risk of pancreatitis. Serum TG levels of 1000 mg/dL and higher have been observed in 12% to 38% of patients with acute pancreatitis (9). Hence, understanding the role of hypertriglyceridemia in CVD, chylomicronemia syndrome and risk of pancreatitis is important.

METABOLISM OF TRIGLYCERIDE RICH LIPOPROTEINS AND TRIGLYCERIDEMIA

Triglyceride Rich Lipoprotein Metabolism

Triglyceride rich lipoproteins (TRL) consist of chylomicrons carrying triglycerides from the diet,

VLDLs synthesized in the liver, and their respective remnant particles. After a fatty meal, dietary triglycerides are hydrolyzed in the intestine to free fatty acids and monoglycerides. Fatty acids and monoglycerides are then absorbed by enterocytes and resynthesized to form triglycerides. Triglycerides within the intestinal enterocytes are assembled with apolipoprotein (apo) B-48 into large chylomicrons which are released from the cells into the lymphatic system. They access the plasma via the thoracic duct and are rapidly metabolized by lipoprotein lipase (LPL) to yield chylomicron remnants. These are taken up by remnant receptors and by LDL receptors in the liver. Free fatty acids liberated by the action of LPL are available to adipose tissue for storage and to other tissues (e.g., skeletal muscle, heart) for use as energy substrates. Lipids derived from chylomicron remnants, from de novo lipid synthesis, and from lipolysis of adipose tissue are reassembled in the liver as very-low-density lipoprotein (VLDL) particles, which are secreted into the plasma. VLDL particles are metabolized by LPL to yield intermediate density lipoprotein (IDL) particles, which are metabolized by LPL and hepatic lipase to yield low density lipoprotein (LDL) particles. IDL can be taken up by the liver through an apo E-dependent process, and LDL is taken up by the liver through the binding of apoB100 to LDL receptors. Small VLDL particles, IDL particles, and LDL particles may be taken up by peripheral tissues to deliver nutrients, cholesterol, and fat-soluble vitamins (10-12).

Hypertriglyceridemia

Hypertriglyceridemia is a normal physiological state that occurs post ingestion of a meal where lipids undergo the above-mentioned metabolism. In insulin-resistant states there is an exaggerated lipid response leading to pathological hypertriglyceridemia which is thought to be atherogenic. In insulin-resistant states there is an increase in the production of VLDL by the liver and decreased hepatic uptake of VLDL, IDL and LDL. There is a reduction in LPL activity resulting in high triglyceride concentrations, especially in the

postprandial state. The over secretion of VLDL, which competes with chylomicron remnants for clearance through the common pathway, can exacerbate the post prandial response. The large amount of TRLs and their prolonged residence time in the circulation leads to increased exchange of cholesteryl ester for triglycerides between TRL and LDL or HDL particles mediated by cholesteryl ester transfer protein (CETP). This process enriches LDL and HDL with triglyceride, and these particles are subsequently more readily hydrolyzed by hepatic lipase resulting in smaller, denser LDL particles and lower concentrations of HDL (13). These abnormalities result in a characteristic dyslipidemia in insulin resistant states, which is now recognized to be atherogenic.

Apo C-III

Apolipoprotein C-III (APOC3) has a key role in lipoprotein metabolism and regulation of triglyceride levels. APOC3 is synthesized in the liver and transported on triglyceride-rich lipoproteins. It inhibits LPL mediated hydrolysis of triglycerides, and at high concentrations can also inhibit hepatic lipase activity. In addition, APOC3 impairs the hepatic uptake of triglyceride rich lipoproteins by remnant receptors. Thus, increased APOC3 levels are an independent risk factor for CVD (14-16); genetic variants of APOC3 leading to lower levels are associated with a reduced risk for CVD (17-19).

ANGPTL

Angiopoietin-like proteins (ANGPTL) are regulators of lipoprotein metabolism. ANGPT3 and ANGPTL4 are natural inhibitors of LPL. Loss of function variants in these proteins have been associated with decreased triglyceride levels and decreased CVD. Murine studies have found that the suppression of ANGPTL3 decreases atherosclerosis (20).

Severe Hypertriglyceridemia

In severe or very severe TG levels (> 1000 mg/dL), which occur as a result of defective lipolysis or excessive production of *endogenous* triglyceride, the LPL removal system is saturated. There is decreased degradation of dietary TGs incorporated into chylomicrons and a rapid increase of TG levels post fat-rich meals (worsened by dietary simple sugars, fructose, and alcohol) in susceptible individuals causing pancreatitis. The mechanism by which hypertriglyceridemia causes pancreatitis is not understood, but could include local accumulation of free fatty acids and serum hyperviscosity (8).

HYPERTRIGLYCERIDEMIA AND RISK OF PANCREATITIS AND CHYLOMICRONEMIA SYNDROME

Severe hypertriglyceridemia (> 1000 mg/dL) is an infrequent laboratory finding and is generally associated with genetic disorders of lipid metabolism or TG levels exacerbated by secondary causes. Familial chylomicronemia is a rare monogenic disorder that can cause severe hypertriglyceridemia. It is defined as the presence of chylomicronemia (TG > 1000 mg/dL) along with one or more of the following: eruptive xanthomas, lipemia retinalis, or abdominal findings of pain, acute pancreatitis and/or hepatosplenomegaly (21). Multifactorial chylomicronemia syndrome (MFCS) which is a much more common cause of severe hypertriglyceridemia is caused by the accumulation of genetic, non-genetic, and environmental factors. Individuals with severe hypertriglyceridemia may present with these classic findings and pancreatitis or may be asymptomatic. The mechanisms by which hypertriglyceridemia may lead to acute pancreatitis are not known. Possible mechanisms include intra-pancreatic hydrolysis of high triglycerides by pancreatic lipase leading to accumulation of fatty acids in the pancreas which may be toxic and lead to inflammation and ischemia. Another proposed mechanism is increased viscosity by high chylomicron levels leading to ischemia (22). A study looking at the frequency of signs and symptoms of hypertriglyceridemia including pancreatitis found

that the incidence of pancreatitis and eruptive xanthomas was low unless TG levels were significantly elevated, e.g. > 1700 mg/dL (20 mmol/l); patients with extreme hypertriglyceridemia had a combination of primary and secondary factors (T2DM, obesity, alcohol intake, pregnancy) contributing to their high TG levels (23). Murphy et al. in their cohort study estimated the risk of pancreatitis with differing degrees of TG elevations and showed that the crude incidence of pancreatitis was 0.91 per 1000 person years (95% CI, 0.76 – 1.09) in individuals with TG levels <150 mg/dL, 1.24 (95% CI, 1.07 – 1.44) with TG levels 150 – 499 mg/dL and 2.48 (95% CI, 1.79 – 3.42) with TG levels >500 mg/dL (24). Increased incidence is seen with increased TG levels. The level of TG at which pancreatitis can be attributed to hypertriglyceridemia is not well defined nor is the level of TG reduction that is associated with reduced risk known. A study by Lindquist et al. (22) looked at the association of moderately elevated serum TG levels and acute pancreatitis. In this study, 33,260 individuals were followed for a median 25.7 years where overall incidence of acute pancreatitis in the cohort was 35.5/100,000-person years. There was a statistically significant association between TG levels and risk of pancreatitis with adjusted HR for pancreatitis of 1.21 (95% CI, 1.07 – 1.36) per 1 mmol/l (~88.5 mg/dL) increment in TG and a significant increased risk for acute pancreatitis in individuals with TG levels > 1.64 mmol/l (145 mg/dL). The analysis in this study was restricted to individuals with TG levels < 6 mmol/l (530 mg/dL) producing statistically significant results and showing that TG levels much lower than previously believed can be associated with an increased risk of acute pancreatitis. Another study evaluated the association between lower follow-up TG levels and the incidence of recurrent clinical events for patients with severe hypertriglyceridemia (>500 mg/dL). This study included 41,210 individuals with < 1% having a history of pancreatitis. Individuals with severe hypertriglyceridemia with follow up TG levels <200 mg/dL experienced a lower rate of recurrent pancreatitis episodes, with an adjusted rate ratio of 0.45 (95% CI, 0.34 – 0.60) compared to those with TG

levels >500 mg/dL (25). There is an increased risk of pancreatitis with severe hypertriglyceridemia and in individuals with elevated dietary TG levels and in some cases pharmacological intervention is necessary to prevent severe complications such as pancreatitis.

HYPERTRIGLYCERIDEMIA AS A CARDIOVASCULAR RISK FACTOR

Epidemiological Data Supporting TG as a CVD Risk Factor

The association of elevated TG values with CVD remains controversial. Establishing TG level as an independent risk factor for CVD is confounded by its inverse metabolic relationship with HDL-c and the heterogeneity of TG risk lipoproteins. Growing evidence suggests that an elevated TG level is an independent risk factor for CVD and represents an important biomarker of CVD risk because of their association with atherogenic remnant particles. A meta-analysis by Hokanson and Austin (4), showed increased plasma TG levels are associated with a significant increase in the risk of CVD independent of HDL-c level. An overall relative risk (RR) for CVD of 1.32 for men and 1.76 for women per 1 mmol/L (~88.5 mg/dL) increase in TGs was noted. However, this analysis was limited to Caucasian study subjects. A non-overlapping meta-analysis involving data from 26 prospective studies in Asian and Pacific populations reported a RR for CVD of 1.8 (95% CI, 1.49 – 2.19), comparing subjects in the top fifth with the bottom fifth of TG levels (26). Sarwar et al. (27) reported data from two prospective cohort studies: the Reykjavik study and the European Prospective Investigational of Cancer (EPIC) - Norfolk study, which together comprised 44,237 Western middle-aged men and women and a total of 3582 incident cases of CVD. Comparing individuals with TGs in the top tertile with the bottom tertile, the adjusted odds ratio for CVD was 1.76 (95% CI, 1.39 – 2.21) in the Reykjavik study and 1.57 (95% CI, 1.10 – 2.24) in the EPIC-Norfolk study.

However, adjustment for HDL-c substantially attenuated the magnitude of association of TG level with CVD. They also performed an updated meta-analysis of the Western population studies adding information to include a total of >10,000 CVD cases from 29 Western prospective studies involving a total of > 260,000 participants, and report an adjusted odds ratio of 1.72 (95% CI, 1.56 – 1.90) comparing top and the bottom tertiles of TG values (27). A more recent meta-analysis by Murad, et al. (9), included 35 studies with a total of 927,218 subjects who suffered 132,460 deaths and 72,654 cardiac events, myocardial infarctions or pancreatitis; with odds ratio of 1.80 (95% CI, 1.31 – 2.49) for cardiac events, 1.31 (95% CI, 1.15 – 1.49) for myocardial infarctions, and 3.96 (95%, CI 1.27 – 12.34) for pancreatitis.

Genetic Data Linking TG to CVD

Recent human genetic studies show that elevated TGs and TRLs are causal risk factors for CVD. A Mendelian randomization study based on several genetic variants affecting remnant cholesterol and/or HDL showed that a 1 mmol/l (39 mg/dL) increase in non-fasting remnant cholesterol is associated with a 2.8-fold causal risk for ischemic heart disease, independent of reduced HDL cholesterol (28). A meta-analysis of 46 lipid genome-wide-association studies (GWAS) together comprising >100,000 individuals of European descent identified four novel loci associated with CVD that were related to HDL-c and TG levels suggesting elevated TG metabolism may also be associated with CVD risk (29). Another large Mendelian randomization study based on a single APOA5 variant (-1131T>C) that regulates TG showed an association with CVD risk. The odds ratio for coronary heart disease was 1.18 (95% CI 1.11–1.26; $p=2.6 \times 10^{-7}$) per C allele, which was concordant with the hazard ratio of 1.10 (95% CI 1.08–1.12) per 16% higher TG concentration recorded in prospective studies (30). This finding is similar to that seen in the study by Jorgensen et al. (31), where doubling of genetically raised remnant cholesterol and TG levels due to APOA5 genetic variants was associated with

an increased risk of myocardial infarctions. In addition, a study using individuals from the Copenhagen City Heart Study with genetic variants in lipoprotein lipase (LPL), tested whether low concentrations of non-fasting TG were associated with reduced all-cause mortality in observational analyses ($n = 13,957$). The results showed that each genetically-derived 1 mmol/l (~88.5 mg/dL) reduction in TG levels was associated with a halved risk of all-cause mortality (32). Two large studies examining the relationship between the gene encoding apolipoprotein C3 (APOC3) found that loss of function mutations in APOC3 were associated with low levels of TG and reduced risk of CVD (17,19). ANGPTLs have also been linked to CVD. A large human study found that individuals with loss of function variants in ANGPTL3 had lower TG levels, as well as lower levels of HDL-c and LDL-c compared to control subjects, and decreased odds of CVD (20). Similarly, individuals with loss of function variants of ANGPTL4 also had lower TG levels and decreased risk for CVD (33). A study by Ference et al did a randomization analysis of a total of 654,783 participants to determine if there was any association with risk of CVD per unit of change in ApoB from either LDL-C lowering variants in the LDL receptor gene (LDLR) or TG-lowering variants in the lipoprotein lipase gene. It showed that there was a similar decrease in risk of CVD per unit difference in ApoB from either TG-lowering LPL variants or LDL-C lowering LDLR variants. Due to differences in the composition of LDL and VLDL, TG levels must be decreased to a much greater extent than LDL-c to achieve a comparable decrease in ApoB levels. This has important implications in the interpretation of TG lowering trials, as studies may not sufficiently lower TG to effectively decrease ASCVD risk. To be noted, the results from this study are from genetic variants and not lipid lowering therapies (34). A genetic cause of lower LDL-c confers a lifetime reduction with associated decline of ASCVD risk up to three to four times greater than with statin therapy, which has a shorter period of lower LDL-c. This finding is likely similar for TG. Collectively, these studies strongly point to a causal effect of elevated TG and TRLs with

CVD.

Clinical Trial Evidence Supporting Lowering TG Reduces CVD

Results with clinical outcomes trials of fibrate therapy have been variable but primarily indicate a reduction in CV events. Post hoc analysis of several of these trials provides consistent evidence showing a clinical benefit in subgroups with elevated TG levels. A meta-analysis of the effect of TG lowering in 18 trials providing data for 45,058 participants showed that fibrate therapy produced a 10% RR reduction (95% CI 0-18) for major cardiovascular events ($p=0.048$) and a 13% RR reduction (95% CI 7-19) for coronary events ($p<0.0001$) (35). The Helsinki Heart Study (HHS), a primary prevention trial showed that in an average follow up of 5 years, there was a 34% (95% CI 8.2-52.6, $P=0.02$) RR reduction in CVD in those treated with gemfibrozil compared to placebo (36). In an 18 year follow up of this study, individuals randomized to gemfibrozil had a 24% adjusted RR reduction ($p=0.05$) in CVD, and individuals with elevated TG and body mass index (BMI) showed significant benefit from treatment with gemfibrozil. Those with TG level in the highest tertiles had a 71% lower RR of CVD mortality ($p<0.001$) (37). The Bezafibrate Infarction Prevention (BIP) study assessed the role of fibrates in secondary prevention. The initial reports showed no significant RR reductions in CVD outcomes in bezafibrate treated vs. placebo-treated subjects. However, a post-hoc analysis of individuals with TG ≥ 200 mg/dL demonstrated significant RR reduction by 39.5% ($p=0.02$); there was no significant RR in those with TG values < 200 mg/dL (38,39). In a subgroup analysis of patients in the BIP study by Tenenbaum et al. (40), patients with CVD, metabolic syndrome and TG > 150 mg/dL experienced significant benefits from the treatment with bezafibrate. Bezafibrate was associated with a reduced risk of any MI and nonfatal MI with HRs of 0.71 (95% CI, 0.54-0.95) and 0.67 (95% CI, 0.49-0.91), respectively. The cardiac mortality risk tended to be lower in patients taking bezafibrate (HR, 0.74; 95% CI, 0.54-1.03). The

Veterans Affairs High-Density Lipoprotein Intervention (VA-HIT) involved 2531 males with CVD with low HDL-c and relatively low LDL-c who were treated with gemfibrozil or placebo and monitored for 5.1 years. Gemfibrozil safely reduced the risk of death from CVD or nonfatal myocardial infarction by 22 percent (41). For every 100 mg/dL increment in baseline TG there was a 14% increase in coronary risk ($p=0.045$). Further, those with highest tertile of TG values (>180 mg/dL) exhibited a more marked decrease in coronary risk with gemfibrozil compared with those in lower tertiles (42). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid study using statin + fibrate combination therapy, fenofibrate + simvastatin had no effect on the primary outcome vs. simvastatin alone for all patients. However, in the fenofibrate + simvastatin group, there was a 31% reduction in CV risk in the subgroup with baseline TG levels in the upper tertile vs. simvastatin monotherapy (43).

Pemafibrate, a new selective PPAR- α activator, approved in Japan in 2017 for hyperlipidemia, is metabolized by cytochromes CYP2C8, CYP2C9, and CYP3A4, indicating potential drug interactions (44). The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial evaluated its cardiovascular benefits in patients with high TGs, including those with diabetes. While pemafibrate significantly reduced TGs, remnant cholesterol, and apo C-III after 4 months, it also raised LDL cholesterol and apo B and did not improve HDL cholesterol. Adverse effects included renal issues and a risk of venous thromboembolism (45). This trial found no significant difference in major cardiovascular events among patients treated with pemafibrate compared to placebo. Despite initial promise, the trial's findings diminished support for combining fibrates like pemafibrate with statins for cardiovascular risk reduction.

PPAR alpha activators may decrease atherosclerosis by various pathways, not limited to affecting circulating lipid levels. Plutzky and Zandbergen discuss the

reduction of acute phase reactants produced in the liver, including C-reactive protein, serum amyloid A, and fibrinogen, by PPAR alpha agonists. These agents may also limit endothelial dysfunction through inhibition of the vasoconstrictor endothelin-1 and by promoting vasodilation by enhanced expression of endothelial nitric oxide synthase. PPAR α agonists may also limit early atherogenesis by inhibiting cytokine-induced expression of a key molecule, vascular adhesion molecule-1, required for adhesion of leukocytes to injured vasculature (46). Additionally, PPAR alpha activators may activate PPARs differently, resulting in variable effects.

The Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention (REDUCE-IT) and Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trials present examples of conflicting cardiovascular outcomes in patients receiving omega-3 fatty acid therapy. The REDUCE-IT trial with 8,179 patients showed a decrease in major cardiac events with high dose icosapent ethyl (4g/d EPA), while the STRENGTH trial with 13,086 patients showed no effects on cardiac events with high dose EPA/DHA carboxylic acid (4g/d) (47,48). A difference in the two studies could be due to the EPA levels achieved in each study. REDUCE-IT achieved an EPA level of 144 (mg/mL) while the STRENGTH trial achieved an EPA level of 89.6 (mg/mL) (49). Another issue is that in the REDUCE-IT trial, mineral oil was used as the placebo in the control group which resulted in higher atherogenic lipoproteins in that arm. This raised concerns that both the negative effects from the mineral oil in the control group and the positive effects of EPA in the treatment group underlies the observed reduction in major cardiac events seen in the trial. However, Olshansky et al reviewed eight studies that used mineral oil as a placebo which showed no evidence that mineral oil in the dosage used in the REDUCE-IT trial had any effect on clinical outcomes (50). Given the opposite results of the two trials, further investigation is needed in regards to EPA levels and drug formulations. A secondary analysis of the

STRENGTH trial showed no cardiovascular benefits at the highest levels of DHA or EPA (51). A meta-analysis which includes the REDUCE-IT and STRENGTH trials show that there was a higher risk of atrial fibrillation in groups treated with omega-3 fatty acids than placebo (52). These studies cast doubt on the benefits of lowering TG levels to reduce ASCVD and necessitate further evaluation in the potential adverse effects of omega 3 fatty acids.

Collectively, studies suggest that fibrate monotherapy leading to a reduction in TG levels prevents coronary events. Many of these studies also show improvements in HDL-c levels which may contribute to the improvements in CVD seen; however, recent HDL-c raising studies (using CETP inhibitors) have not found improved cardiovascular benefits suggesting that the decrease in TG levels contributed to the reduction of CVD seen in the fibrate studies. It has been difficult to demonstrate an ASCVD benefit with TG lowering in patients taking statins. At present, guidelines have not been recommending TG lowering in patients with elevated TG levels to reduce CVD. The lack of evidence to support an ASCVD benefit for TG lowering in patients already using statins may be due to insufficient lowering of TG levels, effects that counter the beneficial effects of lowering TG levels (e.g. in the PROMINENT trial non-HDL-c increased), or perhaps inclusion of inappropriate study populations.

Post-Prandial TG as a CVD Risk Factor

There is also growing evidence that postprandial hypertriglyceridemia may be a better indicator of the presence or development of CVD than fasting hypertriglyceridemia. In the Women's Health Study, a prospective cohort of 26,330 initially healthy women with over 11 years of follow up, it was observed that higher non-fasting TG levels were strongly associated with an increased risk of future cardiovascular events independent of baseline cardiac risk factors, levels of other lipids, and markers of insulin resistance. The concentrations of lipids and apolipoproteins differed

minimally when measurements were performed on non-fasting compared to fasting blood samples, except for TG, which were higher when non-fasting. There was a > 4-fold increased risk of a cardiovascular event among individuals with postprandial TG concentrations peaking at 2-4 hours following a meal. This study showed that HDL-c, TG, total cholesterol/HDL-c ratio, and apolipoprotein B predict CVD when measured in non-fasting samples. By contrast, total cholesterol, LDL, and non-HDL cholesterol, in addition to apolipoprotein B-100 and B-100/A-I ratio, may provide less useful CVD risk information when measured non-fasting (53,54). In a Norwegian study which included 42,600 women and 43,641 men ages 20 – 50 years at inclusion, with a mean follow-up of 27 years, non-fasting TG were positively associated with CVD death in both genders, with hazard ratios being higher in women than in men. However, after adjustment for cholesterol, systolic blood pressure, and smoking, and in a sub-sample also HDL-c, the associations were distinctly attenuated (55). In another study, the Copenhagen City Heart Study, a prospective cardiovascular study of the Danish general population initiated in 1976, 7581 women and 6391 men who had lipids measured at baseline in 1976-1978, were followed for up to 31 years without losses to follow-up, and most were not taking lipid-lowering therapy. The study found that the cumulative incidence of myocardial infarction, ischemic heart disease, and death increased with increasing levels of non-fasting TG levels. Non-fasting TG level were a better predictor of coronary heart disease in women whereas non-fasting cholesterol level was a better predictor in men. However, non-fasting cholesterol levels were not found to be associated with total mortality (56,57). A Japanese study which included 4,988 participants with diabetes already on statin therapy, evaluated the relationship between fasting and non-fasting TGs and cardiovascular events. It showed that cardiac events were associated with elevated fasting and non-fasting TG. However, the study found that non-fasting TG was more helpful for risk assessment for future CVD instead of fasting TG (58). Data from these studies

provide evidence for a link between non-fasting TG and cardiovascular disease and support the concept that non-fasting TG levels may strongly predict the risk of cardiovascular events.

Mechanisms by Which TG are a CVD Risk Factor

The exact mechanism by which TG may promote vascular disease remains to be elucidated. A possible explanation for TG being associated with increased CVD is that elevated levels of postprandial TG may indicate a high content of TRLs derived from chylomicrons and VLDL. Given their relatively small size, these TRLs can enter the arterial wall, and contribute to the formation of foam cells and thus cause atherosclerosis. The remnant particles under normal conditions are rapidly taken up by the liver. However, in people with the metabolic syndrome or T2DM, hepatic clearance of remnant particles can be delayed and thus there is a predisposition towards increased production of remnant particles and small dense LDL and HDL particles. Thus, increased production along with prolonged exposure of circulating remnant particles enhances the possibility for the particles to be trapped in the arterial wall. Accordingly, remnant lipoproteins have been shown to increase the risk of atherosclerotic heart disease. This suggests a need to direct attention towards diagnosis and treatment of high TG levels in conjunction with treating high cholesterol levels (59). These studies also draw importance to further investigate independent association of fasting and non-fasting hypertriglyceridemia in CVD.

PREVALENCE AND ASSESMENT OF HYPERTRIGLYCERIDEMIA

Prevalence of Hypertriglyceridemia

There is high prevalence of hypertriglyceridemia in the US which necessitates periodic assessment of TG levels, especially in individuals with increased risk. A study looking at 5680 subjects, greater than or equal to 20 years of age who participated in the National

Health and Nutrition Examination Survey from 2001 and 2006 evaluated the epidemiology of adults with hypertriglyceridemia. This study reports about 67.8% of the study participants had a normal TG level (<150 mg/dL), 14.2% had borderline high TG levels (150 – 200 mg/dL) and 16.3% had high TG levels (200 - 500 mg/dL). The prevalence of severe high TG (500 – 2000 mg/dL) was noted to be 1.7% equating to about 2.4 million Americans. Three participants were noted to have TG levels > 2000 mg/dL. The participants with severe high TG tended to be men (75.3%), non-Hispanic whites (70.1%), and aged 40 to 59 years (58.5%), and more than 14% of those reported having diabetes mellitus, and 31.3% reported having hypertension (60). A study published in 2018 surveyed 9593 American adults between 2007-2014 to determine the TG levels in patients taking and not taking a statin. It showed almost one-third of people taking statins have unsatisfactory TG levels, as well as one-fourth of overall US adults (61).

Assessment of Hypertriglyceridemia

Plasma lipids and lipoproteins are generally measured in the fasting state and guidelines for therapy for CVD prevention are based on these measurements. The Endocrine Society clinical practice guidelines on evaluation and treatment of hyperlipidemia suggest diagnosis of hypertriglyceridemia based on fasting levels where length of fast is recommended to be 12 hours (8). In insulin resistant states postprandial TG may be more relevant to CVD risk. To assess postprandial TG there is a need to identify an accurate and standardized methodology to measure postprandial triglycerides and TRLs. Currently, the lack of standardization of non-fasting TG measurements, lack of specific reference ranges, and the variability of postprandial lipid measurements have hampered their routine clinical use (62). A Fat Tolerance Test (FTT) has been used to assess post prandial lipoproteins. An expert panel suggests that individuals with fasting TG concentrations between 1-2 mmol/l (89-180 mg/dL) would have better risk assessment by being tested with a FTT than with just

fasting TG. Individuals with fasting TG concentration of less than 1 mmol/l (88.5 mg/dL) commonly do not have exaggerated and delayed response of TGs to a FTT, whereas individuals with elevated fasting TG values above 2 mmol/l (180 mg/dL) are expected to have an exaggerated and delayed response of TG to a FTT. These two patient populations would not benefit from a FTT for better risk assessment(63).

Fat Tolerance Testing

Given that humans spend most of their awake time in a post prandial state, various factors including fasting concentrations of serum TGs, time of the day when test is undertaken, the fat content and quality of FTT need to be considered. An expert panel statement recommends measuring total TGs to evaluate the post prandial lipemia response 4 hours after a standardized FTT performed after an 8 hour fast. There has been significant variability in the fat- rich meals used for FTT ranging from dairy products, eggs, oils, to liquid formulations. An expert panel suggests a FTT meal consisting of 75 g fat including both saturated and unsaturated fatty acids (63). ApoB-48 is an alternative marker for the assessment of post prandial hypertriglyceridemia as it measures the number of circulating chylomicrons and their remnants after a meal (there is one ApoB-48 per chylomicron particle). The level of ApoB-48 is very low compared to ApoB-100 in the fasting state but it increases after a FTT. However, the lack of internationally recognized standardized assays and reference ranges, limited availability of the ApoB-48 assay, and high costs limit the utilization of ApoB-48 in clinical settings (62,64).

Secondary Causes of Hypertriglyceridemia

Individuals found to have any elevation of fasting TG should be evaluated for secondary causes including endocrine conditions and medications (Table 1) (65,66). Patients with untreated diabetes, obesity, and insulin resistant states commonly have elevated TG levels (67,68). Other endocrine disorders such as hypothyroidism, Cushing's disease, and growth hormone deficiency can also be associated with

elevated TG levels (8). TG levels can also significantly increase during pregnancy owing to estrogen-induced stimulation of the secretion of hepatic TRLs (69). In women with underlying disorders of TG metabolism, this increase in TG levels during pregnancy can be associated with pancreatitis and fetal loss. Alcohol intake increases hepatic fatty acid synthesis and decreases breakdown resulting in increased hepatic VLDL secretion and hypertriglyceridemia. Lipodystrophies, either primary or as seen in HIV treated patients or with other diseases is also associated with hypertriglyceridemia (8). There are several monogenic autosomal recessive disorders that lead to hypertriglyceridemia (table 1). LPL deficiency, apo CII deficiency, and GPIHBP1 loss of function mutations (or antibodies to LPL or GPIHBP1) are associated with impaired LPL activity and present in young patients with an increased risk of chylomicronemia and pancreatitis. Additional genetic syndromes in the differential diagnosis of hypertriglyceridemia include mixed or familial combined hyperlipidemia (FCHL), type III dysbetalipoproteinemia, and familial hypertriglyceridemia (FHTG) (70). Many patients have multiple genetic variants and combined with environmental factors, can cause hypertriglyceridemia. However, a study with 563 patients with severe hypertriglyceridemia showed that

14.4% had heterozygous rare variants known to cause hypertriglyceridemia while 3.8% of the control group had these variants as well indicating that these variants are incompletely or partly penetrant. Polygenic risk can now be assessed by a polygenic score. An elevated score increases the probability of developing hypertriglyceridemia, but it is not an absolute predictor of developing hypertriglyceridemia (71). Many drugs also raise triglyceride levels (table 1). Oral estrogens increase the hepatic secretion of VLDL causing an increase in serum TG levels (72). Other medications include Tamoxifen/Raloxifene, retinoids, beta blockers, thiazide inhibitors, corticosteroids, immunosuppressants, antipsychotics, and antiretroviral protease inhibitors (8). Clomiphene which has been successfully used to aid fertility in women with certain anovulatory disorders, is a synthetic estrogen analog whose biochemical structure is similar to that of tamoxifen. It has been noted to induce severe hypertriglyceridemia and pancreatitis in patients with baseline hypertriglyceridemia (73). If possible, individuals with secondary hypertriglyceridemia should have the secondary cause addressed, and such individuals may then not need primary, TG-lowering therapy. However, secondary causes of hypertriglyceridemia cannot always be addressed, in which case providers should consider TG-lowering therapy.

Table 1. Causes of Hypertriglyceridemia		
Disorders	Drugs	Monogenic*
Hypothyroidism	Alcohol	Lipoprotein lipase deficiency
Uncontrolled Diabetes	Estrogens	Apolipoprotein CII deficiency
Obesity	Beta blockers	Apolipoprotein AV deficiency
Chronic renal failure	Tamoxifen/Raloxifene	GPIHBP1 deficiency
Nephrotic syndrome	Glucocorticoids	Lipase Maturation factor 1 (LMF1)
Pregnancy	Atypical anti-psychotics	
HIV	Cyclosporine	
Cushing’s syndrome	Protease inhibitors	
Lipodystrophy	Clomiphene	
Inflammatory disease – rheumatoid arthritis, lupus, psoriasis, etc.		

*autosomal recessive disorders

GUIDELINES FOR TRIGLYCERIDE EVALUTION AND MANAGEMENT

The Endocrine Society Clinical Guidelines

The Endocrine Society Guidelines recommend that the diagnosis of hypertriglyceridemia be based on fasting serum triglyceride levels and defines TG levels of 150 to 199 mg/dL as mild hypertriglyceridemia; 200 to 999 mg/dL as moderate; 1,000 to 1,999 mg/dL as severe; and 2,000 mg/dL or greater as very severe hypertriglyceridemia. The screening for elevated TG levels for all adults is recommended as part of a lipid panel at least every five years. These guidelines recommend against the routine measurement of lipoprotein particle heterogeneity. The guidelines also recommend screening patients with hypertriglyceridemia for secondary causes (medications, alcohol use, endocrine diseases, renal disease, liver disease) and that patients with primary hyperlipidemia be evaluated for family history of dyslipidemia and CVD. The guidelines recommend the use of non-HDL-c (goal 30 mg/dL higher than the LDL-c goal) for both risk stratification and as a target for therapy in patients with moderate hypertriglyceridemia. Initial treatment of patients with mild to moderate hypertriglyceridemia should include lifestyle therapy. For patients with severe to very severe hypertriglyceridemia, dietary modifications in combination with drug treatment should be considered. A fibrate is recommended as a first-line agent in patients with severe or very severe hyperlipidemia (8).

American Association Of Clinical Endocrinologists (AACE) Guidelines

Similar to other guidelines, the AACE clinical practice guidelines recommend evaluating all adults >20 years of age for dyslipidemia every 5 years for risk assessment with a fasting (9 to 12-hour fast) lipid profile. In addition, it recommends more frequent assessments for patients with a family history of

premature CVD. However, unlike other guidelines, AACE also recommends Apo B measurements to assess for residual risk in patients with increased TG levels (>150 mg/dL) or low HDL-c levels (< 40 mg/dL). TG levels less than 150 mg/dL are defined as normal, 150 – 199 mg/dL as borderline high, 200 – 499 mg/dL as high, and levels >500 mg/dL or greater as very high, and AACE recommends maintaining TG levels less than 150 mg/dL. Fibrates are recommended for the treatment of severe hypertriglyceridemia (>500 mg/dL) and lifestyle changes including physical activity, weight loss, and smoking cessation are recommended as first line therapy in moderate hypertriglyceridemia (74). For adults with hypertriglyceridemia and ASCVD or at increased risk of ASCVD, the use of eicosapentaenoic acid (EPA) is recommended in addition to statins, but not combinations of EPA and docosahexaenoic acid (DHA), and niacin use is strongly discouraged. There is insufficient evidence to support pharmacologic treatment recommendations for adults with severe hypertriglyceridemia (≥ 500 mg/dL) (75).

American College of Cardiology (ACC) Statement on Triglycerides and Cardiovascular Disease

In 2021 the ACC published an Expert Consensus Decision Pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia. In this statement, persistent hypertriglyceridemia is defined as fasting triglycerides ≥ 150 mg/dL despite 4–12 weeks of lifestyle changes, stable use of maximally tolerated statins (if indicated), and management of secondary causes. Before starting non-statin therapies, at least two fasting lipid panels taken at least two weeks apart should guide clinical decisions. Both fasting and non-fasting lipid profiles are acceptable for ASCVD risk assessment in adults not on lipid-lowering therapy. However, fasting lipid testing is preferred when: a) Diagnosing metabolic syndrome (requires fasting triglycerides ≥ 150 mg/dL); b) Evaluating lipid disorders in those with a family history of premature ASCVD or genetic

lipid disorders; c) Monitoring response to lifestyle or medication therapy in patients on lipid-lowering treatment; and d) Identifying and managing triglycerides ≥ 500 mg/dL to assess pancreatitis risk. In most people, postprandial triglyceride increases are modest. For non-fasting triglycerides ≥ 400 mg/dL, a repeat fasting test is advised. The expert panel supported the 2018 AHA/ACC guidelines on lifestyle changes, statins, and LDL-C-lowering therapies, and assessed the added benefit of triglyceride-lowering non-statin treatments across four patient groups: a) Secondary prevention in patients with ASCVD and triglycerides ≥ 150 mg/dL (fasting) or ≥ 175 mg/dL (non-fasting), but < 500 mg/dL. b) Diabetes (≥ 40 years) with no ASCVD, with similar triglyceride thresholds c) No ASCVD or diabetes (≥ 20 years) with similar triglyceride thresholds. d) Severe hypertriglyceridemia (≥ 20 years) with triglycerides ≥ 500 mg/dL, especially $\geq 1,000$ mg/dL. Treatment options for these patient groups includes a combination of intensive lifestyle modifications, optimization of statin therapy, and, when appropriate, the addition of fibrates or omega-3 fatty acids to help manage triglyceride levels and reduce ASCVD risk (76).

National Lipid Association (NLA)

The National Lipid Association guidelines recommend obtaining a fasting or a non-fasting lipoprotein profile in all adults (≥ 20 years) every 5 years. It defines TG level of < 150 mg/dL as normal, 150 – 199 mg/dL borderline high, 200 – 499 mg/dL as high and levels of ≥ 500 mg/dL as very high. The NLA Expert Panel views non-HDL-c as a better primary target for medication than LDL-c and recommends levels of non-HDL-c < 130 mg/dL as the desirable level of atherogenic cholesterol for primary prevention of CVD and non-HDL-c < 100 mg/dL for high-risk patients or patients with ASCVD. An elevated TG level is not a target of therapy, except when very high (≥ 500 mg/dL). NLA recommends that when TG levels are between 200 – 499 mg/dL, the targets of therapy are non-HDL-c and LDL-c to reduce risk of CVD events

and when TG levels are very high (≥ 500 mg/dL, and especially if ≥ 1000 mg/dL), reducing the concentration to < 500 mg/dL to prevent pancreatitis becomes the primary goal. The NLA recommends lifestyle interventions as first step in efforts to reduce triglycerides. If drug therapy is indicated NLA guidelines recommend using fibric acids, omega-3 fatty acids, or nicotinic acid as first line agents if fasting TG level is ≥ 1000 mg/dL. For patients with TG levels of 500 – 999 mg/dL a triglyceride-lowering agent or a statin is considered reasonable and for TG level between 200 – 499 mg/dL a statin generally is considered first-line drug therapy with addition of a triglyceride-lowering agent if non-HDL-c is not at goal post initiation of statin (77).

European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines

The ESC/EAS guidelines also recommend checking lipid levels in the fasting state. Triglyceride levels are classified as optimal (< 1.2 mmol/L or < 100 mg/dL), borderline (1.2–1.7 mmol/L or 100–150 mg/dL), moderately elevated (1.7–5.7 mmol/L or 150–500 mg/dL), severe (5.7–10.0 mmol/L or 500–880 mg/dL), and extreme (> 10 mmol/L or > 880 mg/dL). First-line management of hypertriglyceridemia includes dietary changes and weight loss. The 2019 ESC/EAS guidelines note increased ASCVD risk at triglycerides > 1.7 mmol/L (150 mg/dL) but recommend starting pharmacotherapy only in high-risk patients with levels > 2.3 mmol/L (200 mg/dL), after ruling out secondary causes. There are no specific triglyceride treatment targets, as evidence linking triglyceride lowering to ASCVD risk reduction is limited (78). Statins are recommended as first choice for high-risk individuals with hypertriglyceridemia (triglycerides > 2.3 mmol/L or 200 mg/dL). In patients already at LDL-C goal on statins but with persistent triglycerides > 2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered. For high-risk (or higher) patients with triglycerides > 1.5 mmol/L (135 mg/dL) despite statins and lifestyle changes, omega-3 fatty acids (icosapent

ethyl 2 g/day) may be considered in combination with statin therapy (79).

TG Assessment Strategies

The different guidelines in general recommend screening for lipids using a fasting lipid profile, screening for secondary causes of dyslipidemia, and focusing on lifestyle interventions as the first approach to lower elevated TG. A practical approach is to request fasting lipid panels on patients, but to obtain non-fasting (random) panels if fasting samples cannot be provided. For any patient with a TG level that is elevated (for example, > 200 mg/dL), screen for secondary causes and address these if possible. For significantly elevated TG (e.g., > 500 mg/dL) consider the addition of TG-lowering therapy, with the goal of preventing any further elevations increasing the risk for pancreatitis. For individuals with moderately elevated TG (e.g., 150-500mg/dL) then we recommend the consideration of TG-lowering therapy on an individual basis. For example, individuals with existing CVD or at high CVD risk, or those with very low HDL levels might be candidates for therapy, whereas in those with low CVD risk, or desirable HDL levels, additional focus on lifestyle interventions to lower TG may be the appropriate first line of therapy. The use of non-HDL cholesterol levels can help guide decisions.

MANAGEMENT OF HYPERTRIGLYCERIDEMIA

We recommend different therapeutic interventions for hypertriglyceridemia dependent on the underlying etiology and triglyceride level(s).

- In patients with mild-to-moderate hypertriglyceridemia (150-499 mg/dL), statin therapy should be incorporated based on ASCVD risk. Eicosapentaenoic acid (EPA) ethyl ester can be added in adults on statins who have moderately elevated TG levels >150 mg/dL with

ASCVD or diabetes plus 2 additional risk factors to reduce risk of cardiovascular disease.

- For patients with multifactorial chylomicronemia syndrome, the primary goal of treatment focuses on achieving TG level below 500 mg/dL to prevent pancreatitis. This is achieved through fibrate therapy, with addition of omega-3 fatty acid. Niacin therapy can be added for further TG lowering, although this can worsen diabetes control.
- Individuals with familial chylomicronemia syndrome are typically nonresponsive to fibrate and omega-3 fatty acid therapy due to complete absence of lipolytic activity. Historically these individuals were treated with a low-fat diet, restricted to 10-30 g/day of fat or 10-15% of calories as fat, with further limitation of long-chain fatty acids; however, we now suggest consideration of new drugs to suppress apoCIII to reduce TG levels in patients living with familial chylomicronemia syndrome.

A more detailed discussion of the above-mentioned therapeutic agents follows below.

Lifestyle Intervention

Studies have shown that the consumption of a Western diet which includes highly processed, calorie-dense and nutrient poor foods leads to an exaggerated lipemia. In addition, factors such as physical inactivity, cigarette smoking, excessive alcohol intake, and obesity worsen lipemia (63). Hence, the control of secondary factors and lifestyle changes are considered to be the first line approach of the clinical management of both fasting hypertriglyceridemia and post prandial hyperlipidemia. Appropriate dietary changes include limiting fat and simple sugar content, caloric restriction resulting in weight loss, restriction of alcohol intake, and increased exercise are fundamental for management of hypertriglyceridemia (62,63). The type of carbohydrate

consumed may affect serum triglycerides and a diet rich in simple carbohydrates and sugar-sweetened beverages is associated with hypertriglyceridemia. As compared with starches, sugars, particularly sucrose and fructose, tend to increase serum triacylglycerol concentrations by about 60%. Because fructose bypasses a major rate-determining step in glycolysis, a high influx of fructose to the liver promotes triacylglycerol synthesis and VLDL production (80). The effects of sucrose or fructose on fasting TG may be more pronounced in men, sedentary overweight individuals, or those with the metabolic syndrome. Sucrose and fructose also increase postprandial TG levels and may augment the lipemia associated with fat-containing meals (81). There is mounting evidence that physical activity lowers risk for CVD (82). Mestek et al. (83) reported that aerobic exercise lowered the postprandial TG response to a high fat meal in subjects with the metabolic syndrome. The effects of exercise in reducing postprandial lipemia are seen both acutely right after exercise as well as delayed effects through the next day. Additionally, exercise does not need to be a single continuous bout but instead could be spread out throughout the day. Accumulated physical activity appears to be as effective in lowering postprandial TGs concentrations as a single bout (84). The mechanisms leading to decreased TG levels post meals are not completely understood and need further investigation.

Statins

Statins are the most widely used lipid lowering agents and have beneficial effects on cardiovascular morbidity and mortality. Statins are effective in lowering non-HDL-c, mainly because of their LDL lowering action and to a certain extent lowering TG levels. The higher the baseline TG levels, the greater the TG lowering effect. Available data also indicate that statins can reduce postprandial TG values (66). Statins inhibit HMG-CoA reductase, hence up-regulate the LDL receptor due to the intracellular depletion of cholesterol in the liver. Increased numbers of LDL receptors may improve the removal

of TRL remnants in postprandial state. It is also postulated that statins inhibit VLDL synthesis (85). Parhofer et al showed that 10 mg of atorvastatin per day for 4 weeks improves, but does not normalize, post prandial lipoprotein metabolism in hypertriglyceridemic patients (86). Other studies have also shown that atorvastatin improved fasting as well as postprandial lipemia (87,88).

Fibrates

Fibrates have the most pronounced effect on lowering plasma TG levels of the currently available lipid lowering therapies. Through activation of peroxisomal proliferator activated receptor (PPAR) alpha, fibrates decrease TGs by increasing LPL activity and decreasing apolipoprotein CIII production leading to increased lipolysis. Fibrates also increase fatty acid oxidation in the liver leading to a decrease in VLDL secretion (63). The Endocrine Society Clinical Practice Guidelines on Evaluation and Treatment of Hypertriglyceridemia recommend that a fibrate be used as a first line agent for reduction of TGs in patients at risk for triglyceride- induced pancreatitis (8). The ACCORD trial evaluated the benefit of adding fenofibrate to simvastatin therapy concluded that the addition of fenofibrate in patients with diabetes did not reduce the rate of CVD events. However, in the fenofibrate + simvastatin group there was a significant reduction in cardiovascular risk in the subgroup with clinically significant dyslipidemia marked by elevated TG levels and low HDL levels (43). Rosenson et al. reported that fenofibrate treatment for 6 weeks significantly decreased both postprandial hypertriglyceridemia and the inflammatory response after the ingestion of a test meal consisting of a milkshake including standardized fat content (68% of energy) that was adjusted to body surface area (50 g/m²) in patients with hypertriglyceridemia and the metabolic syndrome (89). In a small study (n = 10), bezafibrate was shown to significantly decrease postprandial endothelial dysfunction and elevations of both exogenous and endogenous triglycerides in patients with metabolic syndrome (90). The effects of

fibrates in decreasing postprandial TRLs may play a role in their vascular protective effects.

Niacin

Niacin decreases TG levels and has pronounced effects on increasing HDL concentration. The mechanism of action of niacin remains unclear, but it is proposed that niacin decreases TG synthesis and hepatic secretion of VLDL. The Coronary Drug Project was a randomized controlled trial that looked at the role of immediate-release niacin as a solo agent for coronary prevention. The Coronary Drug Project showed that niacin was associated with a significant reduction in cardiovascular events (91,92). Studies have shown that both immediate-release and extended-release niacin suppress postprandial hypertriglyceridemia (93,94). The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial showed that the addition of niacin to statin therapy in patients with CVD and LDL cholesterol levels of less than 70 mg per deciliter had no incremental clinical benefit during a 36-month follow-up period, despite significant improvements in HDL cholesterol and TG levels (2). However, a trend towards benefit (hazard ratio 0.74; $p=0.073$) was found for the subset of patients with both the highest TG levels and lowest HDL levels (>198 and <33 mg/dL respectively) (95). Lipids in this study were measured in fasting state. Similarly, the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2 –THRIVE) study, which compared niacin + laropiprant (a prostaglandin D2 receptor antagonist used as an anti-flushing agent) + statin vs statin alone did not find added benefit of niacin. However, this lack of additional benefit may be related to the patient population studied which did not have elevated TG levels (96) and a possible benefit may be seen for subjects with both elevated TG and low HDL. Further studies are needed to assess the effects of niacin on hypertriglyceridemia in metabolic syndrome and patients with T2DM.

Ezetimibe

Ezetimibe is a cholesterol lowering agent that inhibits the intestinal absorption of cholesterol (97). Recent studies show that ezetimibe alone or in conjunction with statins also reduces postprandial hypertriglyceridemia. Masuda, et al. showed that ezetimibe significantly decreased TGs in the fasting state along with a decrease in postprandial elevations of cholesterol and TG levels in the chylomicrons (CM) size range, suggesting that the postprandial production of CM particles was suppressed by ezetimibe (98). In a study by Olijhoek et al, combination therapy with low dose simvastatin and ezetimibe was shown to preserve post-fat load endothelial function when compared to treatment with high-dose simvastatin monotherapy in male metabolic syndrome patients (99). The Improved Reduction of Outcomes: Vytorin Efficacy International trial (IMPROVE-IT), a multicenter, randomized, double-blind trial of 18,144 moderate-high risk patients stabilized following ACS, was conducted to investigate if the addition of ezetimibe to a statin improves cardiovascular outcomes relative to statin monotherapy in these patients. The results from this study suggest that the addition of ezetimibe to statin therapy improves cardiovascular outcomes, but likely via further LDL-c lowering (100).

Fish Oil

Omega 3 polyunsaturated fatty acids (PUFAs) have dose dependent TG lowering effects resulting from variety of mechanisms including decreased VLDL secretion and improved VLDL TG clearance (101). In the Japan EPA Lipid Intervention Study (JELIS) trial, 18,645 patients in Japan were recruited between 1996 and 1999 and assigned to receive either 1800 mg of eicosapentaenoic acid (EPA) daily with statin or statin only. A 19% relative reduction in major coronary events ($p = 0.011$) was seen in patients in the EPA group. Unstable angina and non-fatal coronary events were significantly reduced; however, sudden cardiac death and coronary death did not differ between the

groups (102). As discussed above, REDUCE-IT and STRENGTH studied the effects of high dose omega-3 fatty acids and had differing results. The REDUCE-IT trial with 8,179 patients showed a decrease in major cardiac events with high dose icosapent ethyl (4g/d EPA), while the STRENGTH trial with 13,086 patients showed no effects on cardiac events with high dose EPA/DHA carboxylic acid (4g/d) (47,48).

A few studies have examined the effects of fish oil supplementation on postprandial lipemia and found that fish oil use decreases fasting and postprandial triglyceride levels (103,104). A study looking at the effect of fish oil, exercise and the combined treatments on fasting and postprandial chylomicron metabolism showed that combining fish oil with chronic exercise, reduced the plasma concentration of pro-atherogenic chylomicron remnants; in addition it reduced the fasting and postprandial TG response in viscerally obese insulin resistant subjects (105).

For additional information on drugs to treat hyperlipidemia see the chapters on triglyceride lowering drugs and cholesterol lowering drugs in Endotext (106,107).

Therapies Targeting APOC3

APOC3 is a CVD risk factor due to its association with increased triglyceride levels. Antisense oligonucleotides (ASOs) are novel therapeutic agents that bind mRNA leading to its degradation. An ASO to APOC3 was found to lower APOC3 and triglyceride levels. A RCT evaluating this ASO in patients with hypertriglyceridemia (fasting triglyceride levels between 350-2000 mg/dL if not on triglyceride-lowering therapy, or 225-2000 mg/dL if on a fibrate) found that it led to reductions in triglyceride levels of 30-71% over the 13-week trial period. After the ASO was discontinued triglyceride levels returned towards baseline levels over the next 13 weeks. There were no safety concerns in this trial (108).

Volanesorsen is an antisense oligonucleotide inhibitor of apolipoprotein CIII (apoCIII) mRNA, designed to decrease triglycerides by reducing hepatic apoCIII production (109). In Europe, Volanesorsen was approved in 2019 for the treatment of adults with genetically confirmed familial chylomicronemia syndrome (FCS) at high risk of pancreatitis and for which diet and triglyceride lowering therapy was insufficient. In the US, Volanesorsen received orphan drug status in 2015. Two multicenter international phase three randomized, placebo-controlled, double-blind trials, COMPASS and APPROACH, evaluated the efficacy and safety of Volanesorsen in patients with multifactorial severe hypertriglyceridemia or FCS (110,111). Injection-site reactions and thrombocytopenia were observed in both studies. In the APPROACH trial 77% of individuals who received 300 mg volanesorsen subcutaneously once weekly, had fasting triglyceride levels less than 750 mg/dL compared to 10% in the placebo group at 3 months (OR, 186.16; 95% CI, 12.86 to could not be estimated; $P < 0.001$) (111). A common side effect with volanesorsen is thrombocytopenia and it is currently only approved for use in Europe. Volanesorsen at 300 mg once weekly, decreased mean fasting plasma triglyceride concentration by 71.2% (95% CI-79.3 to -63.2) after 3 months of therapy compared to 0.9% (-13.9 to 12.2) in participants in the placebo group ($p < 0.0001$) in the COMPASS trial (110). Inhibition of APOC3 may be a therapeutic option in individuals with LPL deficiency (112); at present there are no effective therapies except for extreme dietary restrictions for these individuals.

Olezarsen (Tryngolza™) is another antisense oligonucleotide inhibitor of apoCIII manufactured by Ionis Pharmaceuticals, Inc. and FDA approved for treatment of FCS as an adjunct to diet on December 19, 2024. The composition of olezarsen incorporates the nucleotide sequence and backbone chemical composition found in volanesorsen, differing only by inclusion of Triantennary N-acetylgalactosamine (GalNAc3) (113). GalNAc3 is a carbohydrate ligand for asialoglycoprotein receptors found on the surface of

hepatocytes which promotes uptake of the drug into hepatocyte nuclei where olezarsen binds APOC3 mRNA prompting degradation by ribonuclease H1-mediated cleavage of the sense strand. The BALANCE trial was a multicenter international Phase III, randomized, double-blinded, placebo-controlled study examining the safety and efficacy of olezarsen (113). Participants were assigned to receive 50 or 80 mg olezarsen, or a placebo every 4 weeks for 49 weeks. Fasting triglycerides at 6-months were significantly decreased in the 80 mg cohort as compared with placebo (−43.5 percentage points; 95% confidence interval [CI], −69.1 to −17.9; $P < 0.001$) but not with the 50-mg dose (−22.4 percentage points; 95% CI, −47.2 to 2.5; $P = 0.08$).

Plozasiran (ARO-APOC3) is a small interfering RNA (siRNA) therapy targeting cytoplasmic APOC3 mRNA, differing from nucleus-acting drugs like volanesorsen and olezarsen (114). In the phase 3 PALISADE trial involving patients with FCS with severe hypertriglyceridemia, plozasiran significantly reduced triglyceride levels by up to 80%, independent of sex or genetic background. At 10 months, reductions in median triglyceride levels of 2044 mg/dL (23.0 mmol/L) reached −80 and −78% in the 25 and 50 mg plozasiran groups, respectively ($p < 0.001$) (115). It also lowered non-HDL cholesterol and increased HDL and LDL cholesterol (with LDL remaining below 55 mg/dL). The treatment reduced the risk of acute pancreatitis and showed a similar safety profile to placebo, though it caused a transient rise in liver enzymes and a possible increase in HbA1c in diabetic or prediabetic patients. Plozasiran has been designated an orphan drug by the EMA and received FDA breakthrough therapy status in 2024. A phase 3 cardiovascular outcomes trial is planned.

Inhibition of APOC3 may be a therapeutic option in individuals with LPL deficiency (112); at present there are no effective therapies except for extreme dietary restrictions for these individuals.

Therapies Targeting ANGPTL3

ANGPTL3 is another potential target for triglyceride lowering. Genetic causes of decreased activity are associated with lower TG, HDL, and LDL levels as well as a decreased risk for CVD. A small trial using a human monoclonal antibody to target ANGPTL3 reported decreases in triglycerides up to 76% (20). A recent study by Harada-Shiba et al, a phase 1 study took a total of 96 Caucasian and Japanese patients and randomized them to receive varying doses and routes of evinacumab or placebo. In the evinacumab cohorts, reduced TGs were rapidly seen in a dose-dependent manner. The study showed no serious or severe treatment emergent adverse events (116). Further clinical trials using either monoclonal antibody or antisense technology are ongoing. Zodasiran, a GalNAc-conjugated siRNA targeting ANGPTL3 mRNA, was evaluated in the phase 2 ARCHES-2 trial involving 204 patients with mixed hyperlipidemia. It produced dose-dependent triglyceride reductions of up to 63%, with 88% of patients on the highest dose (200 mg) achieving target TG levels. The treatment also lowered LDL-C, non-HDL-C, HDL-C, remnant cholesterol, lipoprotein(a), and apoB, though LDL-C reductions were less in patients with higher baseline TG levels. Zodasiran was generally well tolerated, with no major safety concerns. A transient HbA1c rise and increased urinary tract infections were observed in diabetic patients at the highest dose (117).

New Agents on the Horizon

FGF21 is a key metabolic regulator that enhances insulin sensitivity, promotes fatty acid oxidation, and facilitates triglyceride-rich lipoprotein (TRL) clearance, ultimately lowering non-HDL cholesterol and improving atherosclerosis in animal models (118-120). Its analog, pegozafermin, developed to extend FGF21's half-life and reduce off-target effects, significantly reduced triglycerides (up to 54%) and increased HDL-C in clinical trials involving patients with elevated triglycerides (121). In the phase 2 ENTRIGUE trial, nearly 80% of treated patients achieved TG levels below 500 mg/dL, with additional

improvements in apoB, apoC-III, and HDL-C (122). Pegozafermin was well tolerated, with only mild-to-moderate GI side effects. A phase 3 trial (ENTRUST) is ongoing to further evaluate its long-term efficacy and safety.

Weight Management Therapies and Hypertriglyceridemia

Please see other chapters for further discussion of the role of weight management (68).

CONCLUSION

Recent data strongly indicate that fasting as well as non-fasting hypertriglyceridemia is a risk factor for atherosclerosis and CVD. Current treatment goals aimed at lowering LDL-c still do not eliminate residual risk of CVD. Current guidelines focus mainly on LDL-

c levels and correction of hypertriglyceridemia is not the focus of current treatment. However, focus on elevated hypertriglyceridemia deserves renewed attention, particularly as one-third of all adults in the United States suffer from elevated TG and growing number of people are diagnosed with metabolic syndrome or T2DM. There is a need for more studies specifically testing the benefits of lowering hypertriglyceridemia. Additionally, the usefulness of “fat tolerance test” using a standardized meal, analogous to a glucose tolerance test, warrants further evaluation as potential indicator of a metabolic state identifying individuals at higher risk for cardiovascular events. Given the association with CVD, elevated postprandial TGs levels may represent a particularly attractive therapeutic target and further studies particularly looking at the effect of various lipid lowering agents on postprandial along with fasting TGs are necessary.

Table 2. Targeted Treatment of Hypertriglyceridemia		
	Primary Treatment	Secondary Treatment
ASCVD (150-499 mg/dL)	Statin	Omega-3 Fatty Acid
MFCS	Fibrate	Omega-3 Fatty Acid, Niacin
FCS	Olezarsen	

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