doi.org/10.58931/cct.2025.113

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The Importance of Hypertriglyceridemia: Risk of Atherosclerosis and Available Treatments

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Introduction

Serum triglycerides are derived from both exogenous and endogenous sources.[1] Exogenous triglycerides are obtained through the diet and circulate post prandially within large, intestinally-derived chylomicron particles, which are normally cleared within 3 to 4 hours after eating.[1] Endogenous triglycerides are hepatically produced and circulate in smaller very low density lipoprotein (VLDL) particles, which are remodelled in plasma to form even smaller triglyceride-depleted low density lipoprotein (LDL) particles.[1] While the atherogenic impact of LDL and its cholesterol content are well appreciated, the atherogenic role of triglyceride-rich lipoprotein particles, including VLDL and various remnant lipoprotein species, had only recently come into focus.

Approximately 25% of the population has mild-to-moderate hypertriglyceridemia, characterized by triglyceride levels ranging from 2 to 9.9 mmol/L, while approximately 1 in 500 has severe hypertriglyceridemia, defined as triglyceride levels >10 mmol/L.[2] Pathogenic DNA variants within the gene encoding the triglyceride clearing enzyme lipoprotein lipase (*LPL*) or one of its co-factors (*APOC2*, *APOA5*, *GPIHBP1* or *LMF1*) can cause severe hypertriglyceridemia, that presents in childhood.[2] Adults with milder forms of genetic predisposition in combination with secondary factors, can also express triglyceride levels this high.[3]

The risk to health of severe hypertriglyceridemia is acute pancreatitis, which is related to the pathological persistence of chylomicron particles. However, chylomicrons are not considered to increase the risk of atherosclerotic cardiovascular disease (ASCVD).[3] In contrast, the cholesterol carried within VLDL and remnant particles in patients with mild-to-moderate hypertriglyceridemia does increase ASCVD risk.[2,3] Therapies aimed at lowering LDL cholesterol, such as statins, ezetimibe, and inhibitors of proprotein convertase subtilisin kexin 9 (PCSK9) are relatively ineffective at reducing triglycerides.[2,3] Historically, agents such as fibrates, niacin derivatives, and omega-3 fatty acids have been used to reduce

triglyceride levels, but their efficacy varies, and they do not reduce the risk of either acute pancreatitis or ASCVD.[2,3]

Secondary Causes of Hypertriglyceridemia

Many cases of adult-onset hypertriglyceridemia result from secondary causes, as summarized in **Table 1**. These factors or conditions either increase hepatic triglyceride production or impair the clearance of triglyceride-rich lipoproteins, or both.[1-3] Secondary factors associated with elevated triglyceride levels include lifestyle factors, a diverse list of medical conditions, and a wide range of medications. For patients with hypertriglyceridemia, it is important to mitigate secondary causes, including potentially controllable medical conditions and/or culprit medications for which metabolically neutral alternatives are available.[2,3]

Severe Hypertriglyceridemia and Chylomicronemia Syndrome

Severely elevated triglycerides are related to the pathological presence of chylomicrons.[4] Often, there are no symptoms or physical findings, but when these are present, the condition is referred to as chylomicronemia syndrome.[5] Clinical features of chylomicronemia include failure to thrive in infants, eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, recurrent abdominal pain, nausea and vomiting, and an increased risk of acute pancreatitis. Less common clinical features include intestinal bleeding, pallor, anemia, irritability, diarrhea, seizures, and encephalopathy. In children, severe hypertriglyceridemia and chylomicronemia syndrome can be genetically determined by autosomal recessive Mendelian inheritance and is referred to as "familial chylomicronemia syndrome" (FCS).[4] The causal genes for FCS can now be detected on DNA sequencing panels that are becoming more accessible clinically.[4] In adults, severe hypertriglyceridemia and chylomicronemia syndrome are multifactorial, with a complex contribution of polygenic predisposition plus a significant influence of the secondary factors mentioned above.[5] Genetic testing in adults with severe hypertriglyceridemia is usually non-informative and is not currently recommended.[3]

Triglyceride levels >10 mmol/L are a risk factor for acute pancreatitis, which can be life-threatening. Triglyceride elevation in this range requires assertive management including significant dietary fat restriction, cessation of alcohol, and correcting secondary factors, especially obesity and diabetes. Plasmapheresis or intravenous infusions of insulin or heparin are not recommended for treating severe hypertriglyceridemia. Two novel biological therapies, olezarsen and plozasiran, have been shown to effectively treat severe hypertriglyceridemia and reduce pancreatitis risk.[6-8] While adult patients with severe hypertriglyceridemia or chylomicronemia also have an increased ASCVD risk, it is relatively less significant than their pancreatitis risk.[5]

Mild-to-moderate Hypertriglyceridemia and ASCVD Risk

The more pertinent concern in cardiology is common mild-to-moderate hypertriglyceridemia, defined as triglyceride levels between 2 and 9.9 mmol/L, but typically <5 mmol/L.[2,3] These levels are observed in approximately 1 in 25 people, and while they are not associated with any physical findings, they are associated with an increased risk of atherosclerosis end points.[2,3] The link between elevated triglycerides and atherosclerosis is complex.[1] For instance, the atherogenic potential of liver-derived triglyceride-rich VLDL particles comes from their cholesterol content, which can be deposited within the arterial wall to form atherosclerotic plaques.[1] Furthermore, elevated triglycerides often co-exist with other adverse metabolic parameters, such as obesity, insulin resistance, hepatosteatosis, depressed high-density lipoprotein (HDL) cholesterol, and increased atherogenic small dense LDL particles, as well as a pro-coagulant and pro-inflammatory state.[2,3] All of these factors can amplify atherosclerosis risk.

For many years it was believed that triglycerides were not a direct cause of atherosclerosis and that their relationship with adverse cardiovascular outcomes was because triglycerides "kept bad company".[2,3] Today however, the balance of experimental evidence suggests that hypertriglyceridemia is itself an independent risk factor for ASCVD.[2,3] Several observational studies have demonstrated a graded association of elevated triglyceride levels with ASCVD risk, although this association is somewhat attenuated following adjustments for such confounders as obesity and insulin resistance. However, recent Mendelian randomization studies

— essentially genetic epidemiology studies in large populations — indicate that triglycerides play a direct causal role in atherosclerosis.[7] In contrast, previously suspected pathogenic factors such as reduced HDL cholesterol are now considered to be bystanders in the process.[7]

Mendelian randomization studies have linked genetic elevations in triglycerides to an increased risk of ASCVD outcomes, although there are some caveats inherent to these types of indirect studies that attempt to infer risk. For instance, studies of individuals with rare, large-effect loss-of-function variants in the APOC3 gene, which encodes apolipoprotein (apo) C-III have naturally low triglyceride levels and reduced rates of ASCVD compared to the general population.[7] However, these individuals also have reduced levels of LDL cholesterol, which could also be contributing to the reduced ASCVD risk.[7] Nonetheless, many researchers have speculated that new drugs which reduce apo C-III levels by targeting APOC3 mRNA, such as olezarsen and plozasiran,[8,9] might pharmacologically recapitulate the benefit seen in individuals with lower triglycerides by virtue of having been born with a natural genetic deficiency of the apo C-III protein.

In fact, the evidence of the benefit of lowering triglycerides pharmacologically with existing drugs to improve ASCVD outcomes is currently quite scarce. Most agents that lower triglycerides also affect other components of the lipid profile, making it a challenge to isolate the effect of triglyceride lowering alone from clinical trial data. For instance, a meta-analysis of 49 lipid trials was conducted and a multivariable meta-regression determined a relative risk of 0.84 (95% CI 0.75-0.94) per 1 mmol/L reduction in triglycerides, which was judged to be rather marginal and confounded by other variables, as mentioned above.[10] In contrast, the REDUCE-IT trial, a randomized trial of icosapent ethyl in high-risk individuals on statin therapy, showed that triglycerides were reduced by 20% with markedly improved ASCVD outcomes.[11]

Treating Hypertriglyceridemia

Lifestyle

Lifestyle interventions are recommended for all individuals with hypertriglyceridemia, since triglycerides are more responsive to lifestyle changes than other elevated lipoprotein levels, such as LDL cholesterol.[2,3] Weight loss, increasing physical activity, abstaining from alcohol, reducing simple sugar intake, and reducing intake of dietary trans and saturated fats can result in significant improvements in triglyceride levels.[2,3]

Statins

Statins are highly effective at lowering LDL cholesterol but only moderately reduce triglycerides by 10-20%.[2,3] Statins also result in a qualitatively more favourable lipid profile, reducing triglyceride-rich remnant particles and shifting from small, dense particles to those that are larger and less atherogenic.[3] Despite these relatively marginal effects on triglyceride-rich lipoproteins, three decades worth of randomized clinical trials indicate that the majority of the benefit from statin therapy derives from their ability to reduce overall LDL cholesterol, which encompasses particles of all sizes.

Niacin Derivatives

While niacin and its derivatives were popular in the late twentieth century for treating dyslipidemia, including hypertriglyceridemia, a series of neutral cardiovascular outcome trials combined with intolerability and an increased adverse effect profile[12] has essentially eliminated prescription niacin and related agents from the Canadian market.

Fibrates

Fibrates are the currently available drug of choice for targeting severely elevated triglycerides in adults.[3,11] Fibrates act mainly through interacting with peroxisome proliferator activated receptor (PPAR)-alpha, which enhances fatty acid oxidation and suppresses fatty acid and triglyceride synthesis. They can lower plasma triglyceride levels by up to 60%.[3,13] Evidence from the late twentieth century suggests a cardiovascular benefit with fibrates as monotherapy and when used in combination with statins.[3,13] However, a recent randomized double-blinded clinical trial of pemafibrate added to statin therapy in patients with mild-to-moderate hypertriglyceridemia (triglyceride range 2 to 5.6 mmol/L) showed no benefit.[14] This has further dampened enthusiasm for fibrate therapy to reduce the risk of ASCVD in patients with mild-to-moderate hypertriglyceridemia who are already taking a statin. On the other hand, the use of fibrates in patients with severe hypertriglyceridemia is still considered valid by many lipidologists, with the rationale of reducing triglycerides below 10 mmol/L

in order to reduce the risk of acute pancreatitis.[2,3] However, no randomized clinical trial to date has shown that fibrates reduce the risk of pancreatitis.

Omega-3-Fattty Acids

For years, researchers have been intrigued by the potential of fish oils, which have been linked epidemiologically to populations with a low ASCVD prevalence, such as circumpolar communities.[15] Fish oils are complex mixtures of various fatty acids. Omega-3 fatty acids, a family of fats found in fish oils, derive their name from the fact that the first double bond involves the third carbon from the methyl end. The main omega-3 fatty acid with cardiovascular benefit is eicosapentaenoic acid (EPA), named for its 5 double bonds along its 20-carbon backbone.[13]

The mechanism of action for triglyceride lowering with the use of omega-3 fatty acids is unclear, but they may act on multiple molecular targets to reduce triglyceride synthesis and secretion. Proposed mechanisms of action include suppressing the expression of sterol regulatory element-binding protein (SREBP)-1c, increasing the beta-oxidation of fatty acids, and inhibiting the enzymes involved in triglyceride synthesis. These agents may also enhance triglyceride clearance through increasing LPL activity.[16]

Omega-3-fatty acids have been used for years (with little effect) in the treatment of resistant hypertriglyceridemia; however, emerging evidence suggests that these agents may have additional cardiovascular benefits beyond triglyceride lowering. There is also debate regarding which formulation is most effective, and whether the preparation method that ensures minimal oxidation of omega-3 fatty acids is an important factor that influences their clinical effect.[16]

Both primary components of omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), effectively lower triglycerides. However, DHA has shown a greater triglyceride lowering ability and HDL cholesterol-raising capacity compared to EPA, but it also resulted in larger increases in LDL cholesterol compared to EPA.[14]

Studies using over-the-counter fish oils and omega-3 supplements have produced contradictory results, likely because studies are of variable quality and the laxness of regulations does not guarantee adequate quality or quantity of EPA in these supplements. Furthermore, some prescription forms of omega-3 fatty acids, available in the US but not in Canada, contain other types of fats that can neutralize EPA's benefits.[17]

The aforementioned REDUCE-IT trial was inspired by an earlier trial from Japan, the JELIS study, which showed a cardiovascular benefit of high dose pure EPA. In that study, 18,645 patients were randomly assigned to receive either 1.8 g EPA daily plus statin (N=9326) or statin alone (N=9319).[18] After 4.6 years, there were 262 major coronary events in EPA-treated patients compared to 324 events in controls, indicating that EPA reduced events by 19% (p=0.011). This suggested that high doses of pure EPA can prevent ASCVD.[18] Because EPA lowered plasma triglycerides, it was logical to focus on patients with mild-to-moderate hypertriglyceridemia when designing the REDUCE-IT trial.

The REDUCE-IT trial was a multinational study that randomized 8179 high-risk statin-treated patients to receive either 4 g of IPE daily or a placebo.[9] Among the participants, 58% had type 2 diabetes. The entry criteria included well-controlled LDL cholesterol (mean baseline level of 1.94 mmol/L) but elevated triglycerides between 1.5 and 5.6 mmol/L.[9] After 4.9 years, there was a 20% reduction in triglycerides and a 25% relative risk reduction in the composite primary end point, which included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, revascularization procedures, and hospitalization for angina. The number needed to treat was 21 patients to prevent one event.[9] The composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke was reduced by 26%, corresponding to a number needed to treat of 28.[9] Subsequent subgroup analyses of the REDUCE-IT trial have indicated that the cardiovascular benefits extend across a wide range of patients, largely irrespective of baseline demographics and clinical features. Because of the REDUCE-IT trial, IPE is recommended in the current Canadian Lipid Guidelines in the algorithm for the secondary prevention of ASCVD.[19]

Apolipoprotein C-III (APOC3) Inhibitors

The development of inhibitors against apo C-III (designated hereafter as APOC3 inhibitors) has shown proven efficacy at lowering triglycerides across different patient populations. Two agents that target *APOC3* mRNA –olezarsen and plozasiran– are in advanced stages of development. Both olezarsen and plozasiran have

shown efficacy in Phase 3 clinical trials of patients with severe hypertriglyceridemia due to FCS or persistent chylomicronemia, reducing triglyceride levels by up to 80% and reducing pancreatitis risk by up to 88%.[8,9] Olezarsen (Tryngolza) received approval for this indication by the US Food and Drug Administration in late 2024, while approval for plozasiran for a similar indication is imminent. However, neither agent has been evaluated in clinical trials for patients with mild-to-moderate hypertriglyceridemia with the goal of reducing ASCVD risk. Therefore, while this mechanism and these agents are theoretically very attractive for cardiology, much work remains to validate them for reducing cardiovascular risk.

How to Approach the Patient With Hypertriglyceridemia

The current approach to diagnosing, treating, and monitoring a patient with hypertriglyceridemia, with a focus on reducing ASCVD risk, is shown in **Figure 1**. In any adult with newly recognized hypertriglyceridemia, there are often contributing secondary causes **(Table 1)**. Addressing these secondary causes often goes a long way toward correcting the biochemical disturbance and should be the first-line management **(Figure 1)**.

For the patient with mild-to-moderate hypertriglyceridemia, the primary concern is the potential for excess ASCVD risk. It is important to manage ASCVD risk factors, such as hypertension, obesity, sedentary lifestyle, smoking, and diabetes concurrently. If pharmacological treatment is required, medications with proven cardiovascular benefit, such as statins, ezetimibe, and icosapent ethyl are preferred initially. Despite the fact that these medications are less effective at lowering triglyceride levels than fibrates, the evidence supporting an ASCVD benefit is tenuous as discussed above. Due to technical reasons, LDL cholesterol levels may be impossible to determine in a statin-treated patient with persistently elevated triglycerides. For these situations, non-HDL cholesterol and/or apo B are recommended as alternative laboratory tests to determine treatment thresholds and for monitoring the effects of therapy, according to the Canadian Lipid Guidelines.[19]

For the patient with severe hypertriglyceridemia and a history of acute pancreatitis, or an individual whose fasting triglyceride levels remain >10 mmol/L on repeated fasting lipid profiles without an obvious and treatable secondary cause, e.g., alcohol binge or decompensated diabetes, treatment is likely warranted to protect against pancreatitis. The first-line drug of choice in these cases should be a fibrate, with APOC3 inhibitors becoming a consideration in the near future for patients with persistent severe hypertriglyceridemia.

For those with a past history of hypertriglyceridemia-associated pancreatitis, who currently have only mild-to-moderate hypertriglyceridemia, an argument can still be

Lifestyle
• Diet with high positive energy-intake balance and high fat or high glycemic index • Obesity • Physical inactivity • Excess alcohol intake
Medical Conditions
• Metabolic syndrome • Insulin resistance • Diabetes mellitus (principally type 2) • Metabolic dysfunction-associated steatotic liver disease (MASLD) • Renal disease (proteinuria, uremia, or glomerulonephritis) • Cushing syndrome • Pregnancy (particularly third trimester) • HIV infection • Systemic lupus erythematosis • Paraproteinemia • Lipodystrophy
Medications
• Corticosteroids • Oral estrogen • Tamoxifen • Thiazide diuretics • Non-cardioselective beta-blockers • Bile acid sequestrants • Cyclophosphamide • L-asparaginase • Protease inhibitors • Second generation antipsychotic agents (e.g. clozapine and olanzapine)

Table 1. Secondary causes of hypertriglyceridemia; *courtesy of Robert A. Hegele, MD, FRCPC, Cert Endo, FACP*

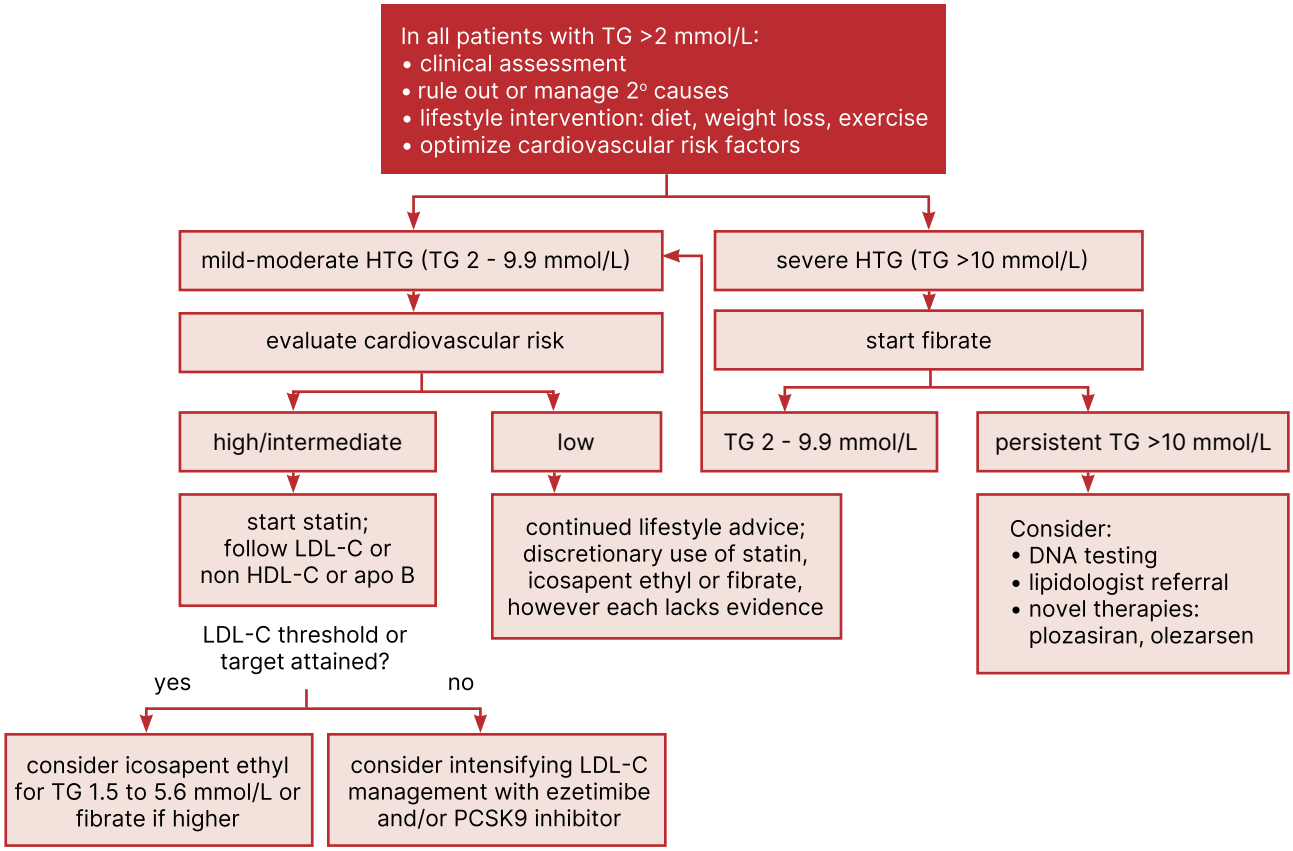

Figure 1. Approach to the patient with hypertriglyceridemia; *courtesy of Robert A. Hegele, MD, FRCPC, Cert Endo, FACP*

made for treatment with a fibrate to reduce the future risk of pancreatitis. Mild-to-moderate triglyceride elevation is also a predictor of future severe hypertriglyceridemia and the development of pancreatitis. Finally, for those at low cardiovascular risk with triglyceride levels below the pancreatitis threshold of 5 mmol/L, management of secondary contributors is the recommended course of action.[2,3]

Conclusion

Hypertriglyceridemia is characterized by elevated serum triglyceride levels, with varying degrees of severity and associated risks. Severe hypertriglyceridemia (triglycerides >10 mmol/L) significantly increases the risk of acute pancreatitis, while mild-to-moderate hypertriglyceridemia (triglycerides 2 to 9.9 mmol/L) is associated with an increased cardiovascular disease risk. In all cases of hypertriglyceridemia, it is essential to manage the underlying secondary factors such as diabetes, obesity, and alcohol consumption. Treatment for severe hypertriglyceridemia focuses on reducing triglyceride levels to <5 mmol/L to prevent future episodes of acute pancreatitis. This is primarily accomplished by severe dietary fat restriction, the use of fibrates in some cases, and new biological therapies directed against APOC3, namely plozasiran and olezarsen. For mild-to-moderate hypertriglyceridemia, the primary goal is to reduce cardiovascular risk through lifestyle modifications and pharmacological interventions. These include weight loss, dietary modifications, regular physical activity, and limiting alcohol consumption. For patients with diabetes or established atherosclerotic cardiovascular disease, with mild-to-moderate hypertriglyceridemia on statin therapy, adding icosapent ethyl has been shown to reduce 3- and 5-point MACE as seen in the REDUCE-IT trial and recommended by the Canadian Lipid Guidelines.[19]

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Financial Disclosures

R.H.: The author has received consulting fees and honoraria from Akcea/Ionis, Amgen, Arrowhead, HLS Therapeutics, Medison, Pfizer, Novartis, Regeneron, Sanofi and UltraGenyx.

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