

Correction of hypertriglyceridemia and ways to improve the prognosis of patients

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Individuals with high triglyceride levels remain at high risk for premature cardiovascular disease despite reductions in low-density lipoprotein cholesterol levels. This review discusses the causes of hypertriglyceridemia (HTG) and its association with atherosclerosis. Non-pharmacologic and pharmacologic means of correcting HTG are presented. The results of the major randomized trials of fibrates, omega-3 polyunsaturated fatty acids, and nicotinic acid are reviewed to assess the efficacy, safety, and impact of treatment on cardiovascular outcomes. The first data from clinical trials of new drugs for the treatment of HTG are reported.

Keywords: hypertriglyceridemia, cardiovascular complications, statins, fibrates, omega-3 polyunsaturated fatty

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Introduction

Currently, low-density lipoprotein (LDL) cholesterol (C) levels are the primary target of most available hypolipidemic therapies because of their established direct association with cardiovascular disease (CVD) risk [1]. In recent years, triglyceride (TG) levels have also become an important focus of researchers and physicians because of their association with the incidence of myocardial infarction (MI), unstable angina, and the need for arterial revascularization [2]. In addition, the risk of premature CVD remains high in individuals with high TG levels despite decreasing LDL-C levels [3].

A fasting TG level <1.7 mmol/L is considered normal, mild/moderately elevated — 1.7 – 5.6 mmol/L; severe hypertriglyceridemia (HTG) is recognized when the level is ≥ 5.7 mmol/L [4]. HTG is associated with a linear increase in the risk of major adverse cardiovascular events (MACE), and severe HTG (especially >10 mmol/L) is associated with the risk of acute pancreatitis (AP) [5, 6]. Mild to moderate HTG is found in 1/3–1/4 of the population, about half of patients with type 2 diabetes mellitus (DM), and requires treatment for primary and secondary prevention [7]. Typically, people with HTG have a combination of genetic causes and modifiable factors, most commonly obesity, insulin resistance, and type 2 DM.

Current beliefs about the role of HTG correction are rather contradictory. On the one hand, the cardiovascular risk assessment system SCORE-2/SCORE2-OR has a parameter “C not related to high-density lipoprotein (HDL)” (the difference between total C and HDL-C), which now takes into account the influence of not only total C (as in SCORE) and LDL-C on clinical outcomes, but also other lipid fractions — very-low-density lipoproteins, intermediate-density lipoproteins, chylomicrons and their remnants, collectively termed “TG-rich lipoproteins” (TGRL), which contain atherogenic apolipoprotein B (apoB) [8]. On the other hand, even in the SCORE2-Diabetes version for type 2 DM patients, HTG is not mentioned among the major cardiovascular risk factors [9]. Meanwhile, experts from the European Society of Cardiology and the European Atherosclerosis Society in 2019 noted that a TG level >2.3 mmol/L is a risk factor for CVD and recommended TG-lowering therapy in such cases [1]. In the Russian guidelines “Dyslipidemia. Clinical Recommendations 2023”, the problem of HTG is given sufficient attention and con-

tains similar European principles for the management of such patients [10].

This review discusses the influence of HTG on the development of atherosclerosis and the possibilities of its correction, as well as the influence of available treatment methods on cardiovascular outcomes.

Hypertriglyceridemia and atherosclerosis

The effect of HTG, especially when combined with low HDL-C levels, on the development of atherosclerosis and its complications is realized by several mechanisms. First, HTG reflects elevated concentrations of TGRL in blood, and TGRL, like other apoB-containing lipoproteins, are directly atherogenic, easily penetrating the endothelium due to their small particle size (≥ 70 nm) [11]. Second, high plasma TG concentrations contribute to several characteristic changes in the profile of circulating lipoproteins that are associated with enhanced atherogenesis. HTG stimulates the activity of C-transfer protein, which remodels the lipoproteins by exchanging TG for C esters between TGRL and TG-poor lipoproteins. This results in small, dense LDL particles that are more atherogenic than would be expected from their C content alone because there are many apoB molecules for each unit of C [11]. Smaller C-depleted HDL particles are more rapidly excreted by the kidneys, further reducing HDL-C levels. In general, despite often normal LDL-C levels, individuals with HTG tend to have elevated levels of atherogenic non-HDL-C and apoB, reflecting a high risk of atherosclerosis [12]. TGRLs have been shown to be associated with atherosclerosis through increased inflammation, oxidative stress and endothelial dysfunction. TGRLs are taken up by macrophages by phagocytosis, leading to the formation of C-rich foam cells in the arterial intima to form a primary lesion. Smooth muscle cells from the media migrate into this area, eventually forming an unstable atherosclerotic plaque [13]. In addition, by inhibiting fibrinolysis, HTG increases blood viscosity and promotes thrombosis [14].

Elevated TGRL levels are associated with a high risk of MACE in both primary and secondary prevention, even among patients receiving statins [15]. In a large retrospective study, participants in both primary ($n=373,389$) and secondary prevention groups ($n=97,832$) with TG levels ≥ 1.7 mmol/L on statin therapy had a lower adjusted risk of death but a significantly higher risk of MACE [16]. Many patients with

DM, even those successfully controlling LDL-C levels with statins, still have an increased risk of MACE due to HTG [17].

The causes of hypertriglyceridemia

Mild to moderate HTG is usually due to heredity and modifiable environmental factors. Modern diets high in calories, fat, added sugars, and ultra-processed foods contribute directly to HTG and indirectly to the development of visceral obesity, non-alcoholic fatty liver disease, insulin resistance, and type 2 DM.

Monogenic disorders causing HTG occur in approximately 0.01% of the general population and in 1–2% of individuals with the most severe HTG (TG levels >10 mmol/L) [18]. Genetic testing is generally not recommended for the detection or management of HTG because genes that regulate TG levels are often recessive with heterogeneous penetrance [19]. However, when monogenic disorders such as familial chylomicronemia syndrome, familial lipodystrophy, and familial dysbetalipoproteinemia are suspected, genetic testing may influence prognosis, management strategies, and expectations regarding response to lifestyle modifications and pharmacotherapy.

When determining an individualized strategy to reduce TG and cardiovascular risk, potential secondary causes of HTG, including a number of diseases and medications (Table 1), should be evaluated and, if possible, treated [20].

Table 1. Main causes of secondary hypertriglyceridemia

Secondary disorders	Medications
Obesity	β-adrenoblockers
Metabolic syndrome	Thiazide diuretics
Diabetes	L-asparaginase
Hypothyroidism	Bile acid sequestrants
Chronic liver disease	Atypical neuroleptics
Chronic kidney disease	Rosiglitazone
Nephrotic syndrome	Sirolimus
Lipodystrophy	Cyclophosphamide
Autoimmune disorders	Isotretinoin
Pregnancy (3 rd trimester)	Oral estrogens
Weight gain after weight loss	Tamoxifen
Rheumatoid arthritis	Glucocorticoids
Glycogen storage diseases	Retinoids
Psoriasis	Raloxifene
Sepsis	Cyclosporine
Multiple myeloma	Interferon
Systemic lupus erythematosus	Tacrolimus
Cushing's syndrome	Propofol

Hypertriglyceridemia treatment

Non-pharmacological treatment

Given the strong association of HTG with lifestyle and metabolic syndrome, many of the treatment principles for insulin resistance, type 2 DM, obesity, CVD, and non-alcoholic fatty liver disease can be successfully applied to the management of patients with HTG. Lifestyle modifications that can significantly reduce TG levels include >5% weight loss (possible ≥70% reduction in TG), dietary changes (≥70% reduction), and physical activity (≤30% reduction) [21, 22].

The main feasible targets for dietary changes include: avoiding foods high in refined carbohydrates; including seafood, especially oily fish; increasing consumption of fiber-rich foods (fruits, vegetables, and whole grains); avoiding excessive alcohol consumption; and replacing saturated animal fats (meat) with monounsaturated and polyunsaturated fats in the form of high-quality vegetable oil. Energy intake should be adjusted to achieve and maintain a healthy body weight [1, 10]. Individuals with severe HTG and hyperchylomicronemia (TG >10 mmol/L) should reduce the total fat content of the diet and use lean seafood [23].

In light of the recent results of the PURE trial, it appears that whole milk products should not be excluded [24]. Interestingly, vegetarian and vegan diets reduce levels of total C, LDL-C and apoB, thereby reducing CVD risk, but do not affect blood TG levels [25].

The prevalence of HTG is significantly higher in regular alcohol drinkers [26]. In individuals with pre-existing HTG, excessive alcohol consumption significantly increases the risk of CVD. Therefore, it is recommended that patients with severe HTG abstain from alcohol altogether.

Aerobic and strength training can significantly reduce TG levels, but their effect depends on the baseline level of the parameter, caloric expenditure, regularity, intensity, and duration of physical activity [27].

Statins

Although statins are best known for their role in lowering LDL-C and reducing the risk of MACE, they also provide a dose-dependent reduction in TG levels of 10–30% in patients with HTG, and as much as 40% in severe HTG [28]. Current guidelines suggest that patients with mild-to-moderate HTG may benefit from lifestyle modification and consideration

of statin therapy based on individual cardiovascular risk [10, 29]. In HTG, a significant reduction in MACE risk can be achieved with statin therapy. Therefore, US experts consider a TG level ≥ 2 mmol/L as a factor that increases cardiovascular risk, favoring the prescription of statin therapy in individuals with a low or borderline 10-year risk of MACE [4]. However, in statin-treated patients with controlled LDL-C levels, elevated TG levels may account for a significant proportion of their residual risk of recurrent cardiovascular events. In a pooled analysis of 10 clinical trials ($n=5724$) in patients with atherosclerotic cardiovascular disease (ACVD) receiving statins, residual C contained in TGRL significantly correlated with changes in atheroma volume on treatment in multivariate analysis ($p<0.001$), independent of LDL-C, apoB, CRP, HDL-C levels, and clinical risk factors. Higher residual C levels also correlated with a higher risk of MACE. These data support further studies of interventions to reduce residual C levels in statin-treated patients with residual cardiovascular risk [30].

Fibrates and omega-3 polyunsaturated fatty acids (PUFAs) have been the most studied for their potential to correct HTG with putative effects on cardiovascular outcomes.

Fibrates

Fibrate monotherapy reduces TG levels by 20–50%, while reducing LDL-C levels by 5–20%, with a 50% increase in LDL particle size and a 10–20% increase in LDL-C levels [10]. A number of clinical trials of fibrates to determine their potential to reduce cardiovascular risk are known: HHS (Helsinki Heart Study), VA-HIT (VA HDL Intervention Trial), ACCORD (Action to Control Cardiovascular Risk in Diabetes), FIELD (Fenofibrate Intervention and Event Lowering in Diabetes), DAIS (Diabetes Atherosclerosis Intervention Study), BIP (Bezafibrate Infarction Prevention). A systematic review and meta-regression analysis of 9 trials of fibrates ($n=41,520$) showed that these drugs can reduce the risk of MACE by lowering TG-C levels without affecting LDL-C levels. However, the risk of transaminase elevation, myopathy, and rhabdomyolysis should be carefully considered when adding fibrates, especially with gemfibrozil (but not fenofibrate), to statin therapy [31].

A new member of the fibrate class — a selective modulator of the peroxisome proliferator-activated receptor alpha, pemafibrate at a dose of 0.2 mg twice

daily was evaluated in the double-blind, randomized, placebo-controlled PROMINENT trial in 10 497 patients with type 2 DM, mild or moderate HTG (TG level 2.3–5.7 mmol/l), HDL-C ≤ 1 mmol/l and LDL-C ≤ 2.6 mmol/l. They were already taking statins. At a median follow-up of 3.4 years, when TG, residual C and apolipoprotein C-III (apoC-III) levels were reduced by 1/4 but apoB by only 4.8%, the sum of events of the primary efficacy endpoint (non-fatal MI, ischemic stroke, coronary revascularization or death from cardiovascular causes) was observed with equal frequency in the pemafibrate and placebo groups. The overall incidence of serious adverse events was not significantly different between the groups, but the use of pemafibrate was associated with a higher incidence of renal adverse events, venous thromboembolism, and a lower incidence of non-alcoholic fatty liver disease [32].

Retrospective and secondary analyses of fibrate trials have suggested that fibrate-treated patients with HTG and low HDL-C levels may achieve improved cardiovascular outcomes despite overall neutral trial results, which served as the hypothesis for a large prospective project [33]. However, the PROMINENT trial in such a population confirmed that fibrates may reduce the risk of MACE when used as monotherapy, but not when added to statins. TG-lowering therapy is likely to reduce the risk of MACE if it increases TGRL clearance rather than simply converting remnant lipoproteins to LDL. Lowering TG levels without lowering apoB levels is not sufficient to improve cardiovascular outcomes, so fibrates should not be used to reduce the risk of MACE in individuals receiving statins, although they may still be used to reduce the risk of AP associated with severe HTG [34]. Based on these findings, the combination of statin plus fibrate is not recommended by the American Diabetes Association experts for patients with type 2 DM to reduce the risk of adverse atherosclerotic cardiovascular events [35]. A recent meta-analysis confirmed the lack of improvement in cardiovascular outcomes when fibrates are added to statins in patients with type 2 DM [36].

Omega-3 polyunsaturated fatty acids

Omega-3 PUFAs, including the combinations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), purified EPA (icosapent ethyl), reduce high TG levels by 20–45% without unidirectional effects on LDL-C levels [10]. A number of clinical trials

investigating the role of omega-3 PUFAs in reducing the risk of MACE are well known: GISSI-P (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione), JELIS (Japan EPA Lipid Intervention Study), ORIGIN (Outcome Reduction with an Initial Glargine Intervention), ASCEND (A Study of Cardiovascular Events in Diabetes), REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial), VITAL (the Vitamin D and Omega-3 Trial), STRENGTH (A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia), and OMEMI (Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction). In a meta-regression analysis including 42 studies of omega-3 PUFAs ($n=149,359$), administration of 1 g/day of EPA was associated with a 9% relative risk reduction of MI [37].

In the GISSI-P trial in patients with recent MI (<3 months), EPA/DHA at a dose of 1 g/day reduced the risk of MACE, but only a small subgroup of participants were receiving statins [38]. In the ASCEND, VITAL, and OMEMI trials, low doses of EPA/DHA did not significantly reduce the incidence of MACE during baseline statin treatment [39–41].

The JELIS and REDUCE-IT trials evaluated the effects of EPA alone at moderate and high doses, respectively. In JELIS, 18,645 patients with elevated LDL-C levels treated with statins were randomized to receive 1.8 g/day of EPA or conventional treatment. The mean baseline plasma TG level was normal (1.7 mmol/L), and the overall treatment-related reduction in this parameter was only 9%. At a mean follow-up of 4.6 years, the EPA group showed a 19% relative risk reduction in major coronary events ($p=0.011$) [42], and patients in the EPA treatment group with baseline HTG and low HDL-C levels had a 53% reduction in the risk of major cardiac events ($p=0.043$) [43]. In JELIS, participants with high (≥ 150 $\mu\text{g/L}$) plasma EPA concentrations had a significantly lower risk of MACE than participants with low (<87 $\mu\text{g/L}$) concentrations [44].

The aim of the REDUCE-IT project was to confirm the results of JELIS and address its limitations in a double-blind, randomized, placebo-controlled trial in 8179 patients with established CVD or DM and other risk factors on statin therapy using a higher dose (2 g twice daily) of purified EPA. Baseline fasting TG levels were 1.52–5.63 mmol/L and LDL-C lev-

els were 1.06–2.59 mmol/L. At a median follow-up of 4.9 years, EPA was associated with a 25% reduction in the risk of the primary endpoint (cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization or unstable angina) compared to placebo ($p<0.001$). At the same time, the risk of CVD death was reduced by 20%, MI by 31% and stroke by 28%. Hospitalizations for atrial fibrillation or flutter were more frequent in the EPA group than in the placebo group (3.1% vs. 2.1%, $p=0.004$) [45]. No association was found between lower TG levels with EPA treatment and a reduced incidence of adverse events. However, higher plasma EPA levels after treatment were strongly associated with a reduced risk of MACE. In this regard, an important role may be attributed to the pleiotropic effect of icosapent ethyl, resulting in slowing the progression of atherosclerotic plaques and altering their structure [46].

In the STRENGTH trial of 13,078 patients at high cardiovascular risk, with HTG and low HDL-C levels, the addition of EPA/DHA at a dose of 4 g/day to statins did not reduce the risk of MACE compared with placebo [47]. Possible explanations for the discrepancy between the results of the REDUCE-IT and STRENGTH trials include 1) differences in the omega-3 PUFA formulations used (EPA and EPA/DHA); 2) follow-up periods (STRENGTH was stopped early due to no perspectives); 3) proportions of patients with established ACVD; and 4) differences in the placebo used (mineral oil vs. corn oil) [29]. The last point is of concern because the use of mineral oil as placebo in REDUCE-IT was associated with adverse effects on lipid and inflammatory biomarkers and reduced statin absorption [48]. However, the 25% difference in MACE risk between the groups is too large to be explained by the adverse effect of the chosen placebo alone.

Apolipoprotein C-III inhibitors

Individuals with elevated levels of apoC-III, a member of the TGRL, have reduced hepatic uptake of TG-rich particles, resulting in HTG, accelerated development of atherosclerosis, and significantly increased risk of its complications. Therefore, apoC-III is one of the main targets of emerging treatments for severe HTG to reduce the risk of MACE and AP [49]. The first apoC-III inhibitor, volanesorsen, effectively reduced TG levels in 77% of patients with familial chylomicronemia syndrome, in whom fibrates, omega-3 PUFAs and statins are usually in-

effective, but cause thrombocytopenia in half of the cases [50]. Olesarsen, which targets matrix apoC-III ribonucleic acid in the liver to inhibit apoC-III synthesis, was used subcutaneously for 6–12 months in a randomized, double-blind, placebo-controlled phase 2 study in 114 patients with fasting serum TG levels of 2.26–5.65 mmol/L, with varying degrees of good tolerability [51]. Olesarsen dose-dependently reduced TG levels by 23–60%, while significant reductions in apoC-III, very-low-density lipoprotein C, non-HDL-C and apoB levels were observed. These data suggest that apoC-III inhibition may reduce TG levels in a population with established ACVD or at high risk of developing it. In addition, the beneficial effects of such therapy on other atherogenic lipoproteins when added to standard therapy may suggest the possibility of reducing the risk of adverse cardiovascular outcomes.

Angiopoietin-like protein inhibitors 3

Angiopoietin-like protein 3 (ALP-3) inhibits both lipoprotein lipase and endothelial lipase in humans, which may lead to elevated plasma TG and C-LDL levels with increased risk of ACVD. In this regard, ALP-3 may be another target for novel lipid-modifying therapies [52]. Vupanorsen, which inhibits ALP-3 synthesis in the liver, was compared to placebo for efficacy and safety in a randomized phase 2 study in 286 patients with non-LDL-C levels ≥ 2.6 mmol/L and TG levels 1.7–5.7 mmol/L on statin therapy [53]. The vupanorsen group showed a 22.0–27.7% reduction in non-HDL-C and a 41.3–56.8% reduction in TG, but only a 6.0–15.1% reduction in apoB. Higher doses of vupanorsen resulted in significantly increased levels of alanine aminotransferase or aspartate aminotransferase and increased liver fat fraction, which requires careful evaluation of the safety of this new drug.

Finding new ways to correct monogenic hypertriglyceridemia

Lipoprotein lipase deficiency is a rare monogenic autosomal recessive disease characterized by mutations in the gene for this enzyme, accumulation of chylomicrons in the blood, and HTG. Lipoprotein lipase deficiency has been corrected by replacement gene therapy using adenovirus as a vector. Intramuscular administration of human transgene to mice provided effective gene transfer to skeletal muscle and liver with normalization of plasma TG

levels within 6 months [54]. The developers of this therapy now hope to be able to use it in the future not to treat HTG but to reduce LDL-C levels.

Another option for correction of familial chylomicronemia syndrome caused by lipoprotein lipase deficiency is inhibition of diacylglycerol acyltransferase 1, which mediates TG synthesis. Pradigastat, a drug with this mechanism of action, reduced TG levels by 41% at the 20 mg dose and 70% at the 40 mg dose after oral administration once daily in 6 patients. Pradigastat caused only mild transient gastrointestinal side effects and may be considered a promising treatment for this rare pathology [55].

European Society of Cardiology guidelines for the management of cardiovascular diseases in patients with diabetes (2023)

Experts from the European Society of Cardiology have identified DM-specific changes in the ratio of individual lipids in the blood, as well as disturbances in lipoprotein structure and function. In patients with DM, statins are recommended as first-line therapy to achieve LDL (or non-HDL-C) target levels determined on the basis of the cardiovascular risk profile (Class I recommendation, Level of Evidence A). In patients with HTG, high-dose EPA (2 g twice daily) in combination with statins may be considered (class of recommendation IIb, level of evidence B). The potential use of fibrates to reduce TG levels is very limited because of the risk of myopathy when administered concomitantly with statins and negligible benefit according to randomized trials [56].

American Diabetes Association's Standards of Diabetes Care (2024)

The American Diabetes Association recommends to evaluate secondary causes of HTG and consider medication to reduce CVD risk in people with fasting TG levels ≥ 5.7 mmol/L (level of evidence: C). It is recommended that lifestyle factors (obesity and metabolic syndrome), secondary factors (DM, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase TG levels be considered and corrected in adults with moderate HTG (2.0–5.6 mmol/L fasting or nonfasting, level of evidence C).. In individuals with ACVD or cardiovascular risk factors with statin-controlled LDL-C levels but elevated TG levels (1.5–5.6 mmol/L), supplementation with EPA may be

considered to reduce the cardiovascular risk (level of evidence A) [57].

Conclusion

HTG is commonly found in patients with type 2 DM and other cardiometabolic disorders, contributes to an increased risk of ACVD and CVD, and requires correction, as recognized in current clinical guidelines. Management of patients with HTG includes exclusion or possible elimination of its secondary causes and individualized lifestyle counseling. In severe HTG, TG-lowering pharmacotherapy should be used along with lifestyle modification to reduce the risk of developing AP. In those at high risk of ACVD, statin-based dyslipidemia therapy to reduce LDL-C, non-HDL-C and apoB levels is indicated. Fibrates and low-dose omega-3 PUFAs (<1.5 g/day) do not reduce the risk of

MACE in patients taking statins, but may be useful to lower TG levels in patients with severe HTG to reduce the risk of AP. Patients with HTG often have type 2 DM and should receive optimal therapy with proven ability to reduce the risk of cardiovascular complications.

Traditional approaches to treating HTG with available drugs do not address the residual risk of MACE in patients receiving statins. New drugs currently being investigated for the treatment of HTG (apoC-III inhibitors, ALP-3, pradigastat, gene therapy) under the control of the most informative biochemical marker (apoB) may potentially provide an additional reduction in the risk of cardiovascular complications.

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