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Cardiovascular Risk Assessment in Patients with Hypertriglyceridemia

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Abstract

Purpose of Review Assessing the cardiovascular risk associated with hypertriglyceridemia can be challenging due to frequent confounding conditions such as hypertension, diabetes mellitus, and hyperlipidemia. We sought to quantify this risk by examining several meta-analyses as well as subgroup analyses of previously published major randomized controlled trials that focused on the treatment of hyperlipidemia.

Recent Findings Recent trials measuring the effects of PCSK9 inhibitors such as evolocumab and alirocumab on cardiovascular outcomes have demonstrated a high degree of residual cardiovascular risk even after profound reductions in low-density-lipoprotein cholesterol (LDL-C).

Summary Despite optimization of LDL-C through the use of statins, PCSK9 inhibitors and adjunctive therapies such as ezetimibe, bile acid sequestrants and niacin, residual cardiovascular risk remains significant. Several ongoing trials are assessing the efficacy of pemafibrate and omega-3 fatty acids for the treatment of hypertriglyceridemia and their effects on major cardiovascular outcomes.

Keywords Hypertriglyceridemia · Hyperlipidemia · Risk assessment

Introduction

Historically, when it comes to decreasing cardiovascular disease (CVD) risk, most lifestyle and pharmacologic interventions have focused on reducing low-density-lipoprotein cholesterol (LDL-C). There is evidence, however, that despite significantly reducing LDL-C levels and even achieving what are considered optimal levels, considerable CVD risk remains. Part of this risk is thought to be attributed to hypertriglyceridemia (HTG) and compelling evidence suggests a significant association between HTG and CVD.

According to the American Heart Association national statement on triglycerides and CVD, a fasting triglyceride (TG) level < 100 is optimal, 100–149 mg/dL is normal, 150–199 mg/dL is borderline high, 240–499 mg/dL is high, and levels at or exceeding 500 mg/dL are very high [1]. Based on data collected by the National Health and Nutrition Examination Surveys (NHANES) between 2009 and 2012, 25.1% of the adult population in the USA had borderline to elevated TG levels. Among ethnic populations, Mexican-Americans had the highest prevalence, followed by non-Hispanic whites and finally non-Hispanic blacks. When comparing survey data from 2009 to 2012 to data from 2001 to 2004, the percentage of Mexican-American women with elevated TGs decreased from 39.6% (2001–2004) to 27.8% (2009–2012) while there was not a significant difference between Mexican-American men. Additionally, obese men and women had increased rates of elevated TGs compared to their normal-weight counterparts. 38.7% of obese men (body mass index (BMI) ≥ 30 kg/m^2) and 31.9% obese women had elevated rates while 17% of normal-weight men (BMI 18.5–24.9 kg/m^2) and 9.3% of normal-weight women did [2, 3].

Triglyceride and cholesterol are the two primary lipids in plasma and due to their hydrophobic nature are transported with other lipids and proteins that collectively form as lipoproteins. In addition to the hydrophobic TG and cholesterol ester core, lipoprotein surfaces contain phospholipids, free

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cholesterol, and apolipoproteins. Apolipoproteins not only play an important structural role, but also act as ligands for lipoprotein receptors, serve as nascent derivatives of lipoproteins, and participate in the activation and inhibition of enzymes involved in lipoprotein metabolism. Based on the type of apolipoproteins, size, and lipid composition, plasma lipoproteins are divided into various classes (chylomicrons, chylomicron remnants, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL)). HDL and LDL are relatively small, cholesterol-enriched particles whereas chylomicrons and VLDL are TG-enriched. The by-products of TG-rich particle hydrolysis are cholesterol-enriched remnant particles [4]..

Triglyceride-enriched particles are derived from endogenous and exogenous sources. Endogenous sources are derived from the liver, which produces and secretes triglyceride-rich VLDL particles. Upon entering the circulation, VLDL is metabolized by lipoprotein lipase (LPL) into free fatty acids that are either stored in adipocytes or used as an energy source by muscle. Exogenous sources are represented by dietary fats that upon intestinal absorption are repackaged in lymph as chylomicrons. Upon entering the bloodstream, these TG-rich particles are avidly hydrolyzed by LPL and under physiologic conditions, the resulting remnant particles are cleared by the liver [5].

An elevated serum TG level is a result of increased TG production, reduced TG catabolism, or both. Excessive adiposity, particularly visceral adiposity, leads to elevated levels of free fatty acids in the liver that drives enhanced VLDL secretion. Insulin resistance in type 2 diabetes mellitus (T2DM) inhibits LPL activity thereby reducing TG clearance and enhanced TG release from adipocytes. Other less common causes of HTG also include hypothyroidism, nephrotic syndrome, antiretroviral medications (e.g., protease inhibitors) and ethanol. Primary HTG is due to genetic defects in triglyceride synthesis and metabolism and are found in less than 5% of cases [6].

Currently, screening guidelines recommend measuring lipid levels after an 8- to 12-h fast, but more recent evidence suggests non-fasting TG levels may be a superior predictor of CVD compared with fasting levels [7, 8].

Residual CVD Risk Despite LDL-C-Lowering Therapy

The independent risk of CVD attributable to HTG can be difficult to isolate because patients frequently present with other comorbid conditions that increase risk of CVD, including hypercholesterolemia, T2DM, hypertension and the metabolic syndrome.

Over the past two decades, several large-scale randomized controlled trials (4S [9], LIPID [10], CARE [11], HPS [12], WOSCOPS [13], AFCAPS/TexCAPS [14], JUPITER [15]) have demonstrated the beneficial effects of statins, or 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, in lowering the risk of CVD. As such, statins have become a mainstay of therapy in the primary and secondary prevention of CVD events. Yet those trials have also revealed that even with LDL-C lowering, significant residual CVD risk remains [16]. For example, patients treated with statin therapy in the 4S trial experienced CVD event rates approximating 20% (compared to 28% with placebo) over the 5-year study period [9].

Subsequent analyses evaluated the effects of high-dose statin treatment for more intensive LDL-C lowering. Specifically, in the PROVE IT-TIMI 22, IDEAL, and TNT trials, high-intensity (80 mg atorvastatin daily) therapy demonstrated greater CVD risk reduction when compared to moderate-intensity statin therapy, but residual risk in the intensive treatment arms was still 22.4, 12 and 8.7%, respectively, [17–19] despite mean LDL-C levels that were not elevated (62, 81, and 77 mg/dL, respectively).

This persistently elevated CVD risk despite high-intensity statin therapy has prompted consideration of adjunctive therapies as a means for further risk reduction. The IMPROVE-IT trial was designed to assess the benefits of ezetimibe to moderate-intensity simvastatin. Once again, the rate of CVD events decreased significantly, but patients in the treatment arm exhibited a 32.7% risk (compared to 34.7% with simvastatin alone), despite mean LDL-C levels of 53.2 mg/dL [20].

More recently, the FOURIER trial compared the effects of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, evolocumab, on the rate of major cardiovascular events in patients with persistently elevated LDL-C (> 70 mg/dL) despite moderate- or high-intensity statin therapy. Despite a statistically significant risk reduction, cardiovascular events still occurred in 9.8% of those treated with evolocumab. The median LDL-C level of treated patients was just 30 mg/dL [21•].

In the ODYSSEY trial, patients who had an ACS event within the prior 12 months that were prescribed a high-intensity statin were randomized to receive either another PCSK9 inhibitor, alirocumab, or placebo. Patients in the treatment arm were found to have significantly reduced LDL-C levels at four (37.6 mg/dL) and 48 months (53.3 mg/dL), but still experienced cardiovascular events at a rate of 9.5% (compared to 11.1% with placebo) [22].

Despite optimization of LDL-C levels with statin and non-statin therapies, patients remain at high risk of CVD events, which suggests that other risk factors beyond LDL-C may be reasonable therapeutic targets. Clinicians should remain mindful that patients enrolled in these large clinical trials continue to possess other known risk factors for CVD, namely obesity,

diabetes, cigarette smoking, and poorly controlled hypertension. These factors may also contribute to the residual cardiovascular risk identified above, and thus preventative strategies should remain comprehensive beyond correction of dyslipidemia.

Evidence for Triglycerides as an Independent Risk Factor for CVD

A large meta-analysis of 29 prospective studies encompassing 262,525 patients identified serum TG concentration as a strong independent risk factor for CVD events, independent of gender [23]. This association was attenuated, but not eliminated, when adjusted for HDL-C level [16].

Epidemiologic and observation studies have also established a causal relationship between HTG and CVD risk. A Mendelian randomization study of individuals enrolled in the Copenhagen City Heart Study (CCHS) demonstrated an association between reduced all-cause mortality in patients with reduced concentrations of non-fasting plasma TG [24]. In a similar analysis, there was a causal association between elevated levels of non-fasting TG and increased risk of myocardial infarction (MI) among CCHS patients with genetic variation in the apolipoprotein A5 (APOA5) gene [25].. Combining samples from the CCHS and the Copenhagen General Population Study (CGPS) demonstrated high (> 500 mg/dL) non-fasting TG were associated with high risk of CVD and all-cause mortality [26].

Post hoc analyses of several of the previously mentioned statin trials have also suggested a correlation between HTG and CVD risk. In 4S, patients in the highest TG (> 159 mg/dL) and lowest HDL-C (< 39 mg/dL) subgroup had the highest risk for CVD events on placebo and experienced significantly greater event reduction (52%) than either the isolated LDL-C elevation subgroup (14%) or the total study population (34%) [27].

Similar subgroup analyses of PROVE IT-TIMI 22 demonstrated low TG levels (< 150 mg/dL) were associated with reduced CVD risk and each 10 mg/dL decrement in serum triglycerides conferred a 1.5% reduction in the incidence of death, MI, and recurrent acute coronary syndrome (ACS) [28]. In addition, the beneficial effect of reducing LDL-C to less than 70 mg/dL was maximal in subjects with TG levels less than 150 mg/dL.

Additionally, a meta-analysis of 8 studies between 1994 and 2008 illustrated that in statin-treated patients, non-HDL-C ≥ 130 mg/dL had a stronger association with risk of future major cardiovascular events than LDL-C ≥ 100 mg/dL. Patients with non-HDL ≥ 130 and LDL-C ≤ 100 at 12-month follow-up had a hazard ratio (HR) of 1.32 and patients with non-HDL ≥ 130 and LDL-C ≥ 100 had a HR of 1.21. In patients with non-HDL-C < 130 mg/dL and LDL-C ≥ 100, the HR was lower at 1.02; HRs were adjusted for sex, age, smoking, diabetes, and systolic blood pressure. In another meta-analysis of 14 studies and 100,827 patients receiving a statin, niacin or fibrate, there was a 1:1 relationship between percent non-HDL-C lowering and CVD reduction.

Reduction in CVD Risk Through Treatment of Hypertriglyceridemia

Lifestyle Modification

For patients with borderline HTG (150–199 mg/dL), appropriate first line therapy consists of individualized adjustments to nutrition and physical activity. Intake of processed foods that contain refined carbohydrates as well as beverages with a high fructose content (e.g. cola), should be restricted [29]. In addition, numerous studies have demonstrated the beneficial effects of diets rich in marine sources of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), such as anchovies, herring, salmon, and mackerel [30]. One prospective cohort of women in the Nurses' Health Study found that higher consumption of fish and omega-3 polyunsaturated fatty acids was associated with a decreased risk of thrombotic stroke [31].

Triglyceride reduction is the first and most notable effect of increased physical activity on the lipid profile [32]. In 2014, the American College of Cardiology (ACC) and American Heart Association (AHA) released guidelines for the management of obesity in adults, in which they recommended counseling all overweight and obese adults with CVD risk factors (such as hypertension, hyperlipidemia and hyperglycemia) that sustained weight loss of 3–5% can produce clinically meaningful reductions in serum TG [33]. Within those same guidelines, the American College of Sports Medicine (ACSM) recommended 30–60 min of exercise per day, 5–7 days per week for these patients.

Pharmacologic Management

When TG levels are between 200 and 499 mg/dL despite lifestyle modification, pharmacologic therapy should be considered, particularly if patient-specific LDL-C and non-HDL-C targets have not been met. In addition to the known TG-lowering effects of statins, numerous investigations have sought to determine additional potential treatment options.

The benefits of omega-3 fatty acids such as EPA and DHA on serum TG levels have been well-described, as mentioned above. Polyunsaturated fatty acids, such as omega-3 and omega-6 fatty acids are incorporated into cell membranes, where they modulate membrane protein function, cellular signaling, and gene expression. In addition to reducing TG levels, EPA and DHA are thought to exert cardioprotective effects via attenuation of atherosclerotic plaques, lowering of

systolic and diastolic blood pressure, and improvement in endothelial function [34].

The GISSI-Prevenzione trial was a prospective study of 11,324 patients post-MI randomly assigned to receive either omega-3 fatty acid supplementation (1 g of EPA plus DHA), vitamin E (0.3 g daily), both, or none for 3.5 years. Patients in the EPA/DHA group had a 15% reduction in the primary outcome of death, non-fatal MI and stroke [35]. Similarly, the JELIS trial randomized 18,645 Japanese patients with hypercholesterolemia to receive either statin monotherapy or combination therapy with a statin and 1.8 g daily of EPA. Patients in the EPA group experienced a 19% relative reduction in major coronary events [36].

More recent studies, including OMEGA, ALPHA OMEGA, and ORIGIN, failed to reproduce the outcomes of GISSI and JELIS. Notably, however, the investigational doses in all three trials were less than the 1 g/day of omega-3 fatty acids currently recommended by the AHA for patients with established coronary artery disease (0.84, 0.40, and 0.90 g/daily, respectively) [37–39].

There are three FDA-approved omega-3 fatty acid agents available, omega-3 fatty acid ethyl esters (OM-3 A EE) (Lovaza®), icosapent ethyl (IPE) (Vascepa®), and omega-3 carboxylic acids (Epanova®). In the COMBOS trial, addition of OM-3 A EE to simvastatin resulted in significantly reduced non-HDL-C. In addition, treatment when compared to placebo resulted in significantly reduced triglyceride levels (27.5 vs 7.2%) [40]. The efficacy of IPE was assessed in the MARINE and ANCHOR trials, where patients experienced statistically significantly reductions in serum triglyceride levels. In MARINE, patients with baseline TG levels > 500 mg/dL were randomized to receive either 4 g/daily, 2 g/daily, or placebo over 12 weeks and experienced reductions in serum triglyceride level of 33.1 and 19.7%, respectively [41]. In ANCHOR patients with baseline TG levels between 150 and 499 mg/dL experienced reductions of 21.5 and 10.2% with the 4 and 2 g daily dosage, respectively compared to placebo [42•].

While there is clear evidence that these two omega-3 products significantly reduce TG levels, as mentioned, there are no CVD outcomes data currently available to support their routine use for HTG patients with or at increased CVD risk. Two ongoing randomized controlled trials, REDUCE-IT (evaluating IPE 4 g/daily with a primary outcome of cardiovascular death, MI, stroke, coronary revascularization and hospitalization for unstable angina), and STRENGTH (assessing the effects of omega-3 carboxylic acids on the same primary outcome) are expected to report results within the next 1–2 years [34].

Although additional adjunct therapies such as fibrates and niacin have previously been recommended by the AHA, clinical outcome trials have failed to demonstrate improvement in CVD outcomes. The ACCORD study failed to demonstrate a significant effect on cardiovascular outcomes in simvastatin-treated patients receiving fenofibrate vs placebo [43], but a post hoc analysis demonstrated a benefit in those with baseline dyslipidemia (triglycerides > 204 mg/dL and HDL-C < 34 mg/dL) [44]. The ongoing PROMINENT trial will assess the effect of pemafibrate on the incidence of non-fatal MI, non-fatal stroke, hospitalization for unstable angina requiring unplanned coronary revascularization or CV death. The HPS2-THRIVE study sought to assess the benefits of extended-release niacin/laropiprant in simvastatin-treated patients with CAD, but no significant reductions in CVD outcomes were observed and safety analyses demonstrated an increased risk of myopathy in the treatment arm, which later led to the drug being removed from the market [45].

Conclusion

In summary, patients being treated with the highest-intensity statin therapy remain at considerable CVD risk even when combined with ezetimibe and a PCSK9 inhibitor. Mendelian randomization studies support HTG as an independent risk factor for CVD. Weight loss through reduction of saturated fat and simple carbohydrates coupled with aerobic activity can effectively reduce elevated TG levels, while novel agents may support further CVD risk reduction. The results of the ongoing REDUCE-IT and STRENGTH trials will offer additional outcomes data for omega-3 fatty acid therapy while PROMINENT will determine whether the novel fibrate, pemafibrate, effectively reduces CVD risk in HTG.

Compliance with Ethical Standards

Conflict of Interest Matthew C. Evans, Tapati Stalam, and Michael Miller declare that they have no conflict of interest.

Michael Miller is a member of the Steering Committee for the REDUCE IT Study and consultant for Amarin.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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