Fellow’s voice: Hypertriglyceridemia: Understanding the current guideline

Sri Charitha Koneru *

Clinical Research Assistant, Division of Cardiology, Baylor Scott & White Heart Hospital Baylor Plano, Plano, TX United States

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Triglycerides are an important measure of cardiovascular health. Studies have shown that elevated triglycerides increase the risk of atherosclerosis due to their association with an increase in very low-density lipoprotein (VLDL) particles, which in turn results in increased low-density lipoprotein cholesterol (LDL-C) and decreased high-density lipoprotein cholesterol (HDL-C) [1–3]. The 2018 AHA/ACC/multisociety cholesterol guideline lists elevated triglycerides as a “risk-enhancing factor”, which may influence decisions regarding initiation or intensification of statin therapy in primary prevention patients who are at borderline or intermediate risk for atherosclerotic cardiovascular disease (ASCVD) based on the 10-year risk from the pooled cohort equations [4].

Persistent hypertriglyceridemia is defined as non-fasting levels of ≥175 mg/dL after a minimum of 4 to 12 weeks of lifestyle intervention on a stable dose of maximally tolerated statins when indicated and after evaluation/management of potential secondary causes. In patients with severe triglyceride levels >500 mg/dL, it is essential to initiate fibrate therapy to lower levels to reduce the risk of pancreatitis.

There are several secondary causes of hypertriglyceridemia, which include poorly controlled diabetes, chronic kidney disease, uncontrolled hypothyroidism, and autoimmune conditions. Triglyceride-raising medications such as beta blockers, diuretics, bile acid sequestrants, glucocorticoids, HIV protease inhibitors, estrogens, atypical antipsychotics and immunosuppressive agents should be evaluated and monitored in patients with hypertriglyceridemia.

Aggressive lifestyle intervention is the first line of therapy to lower triglyceride levels in all patients. Emphasis on weight loss (5%-10% reduction in body weight) through healthy diet and physical activity (at least moderate 150 minutes/week or vigorous 75 minutes/week) can substantially lower triglyceride levels by 20% to 50%. A low carbohydrate, high protein diet is particularly beneficial for weight loss. A healthy dietary pattern includes lean protein, fish, fresh fruits and vegetables, legumes, avoidance of refined foods with high glycemic index and added sugars and restricting alcohol intake [5]. Given the importance of healthy lifestyle in managing hypertriglyceridemia, referral to a registered dietician or nutritionist is recommended.

Statins, fibrates, and omega 3 fatty acids (OM-3FA) are the cornerstone of pharmacotherapy for triglyceride lowering. Statins provide a 10%-30% dose dependent reduction in triglycerides [6] and also reduce ASCVD events, so they are the first line-therapy. To date, fibrates have not been demonstrated to reduce ASCVD events on a background of statin therapy, although the PROMINENT trial is still on-going (NCT03071692). Therefore, fibrates are generally not indicated for mild to moderate hypertriglyceridemia (150-499 mg/dL), but rather prioritize statin therapy, lifestyle changes, and glycemic control.

The JELIS and REDUCE-IT trials have shown that the use of eicosapentaenoic acid (EPA, an ethyl ester found in OM-3FA), reduced the risk of major cardiovascular events. The REDUCE-IT trial evaluated icosapent ethyl (IPE), a highly purified form of EPA at a dose of 2 g twice a day, among high risk patients with ASCVD or diabetes with risk factors who had elevated triglycerides on a background of statin therapy with controlled LDL-C levels [7]. The REDUCE-IT trial showed a highly
significant 25% reduction in the primary composite ASCVD endpoint—a reduction that was greater than would be anticipated by the achieved 20% lowering of triglycerides alone, suggesting other non-lipid mechanisms for benefit. IPE is the only fish oil therapy with an U.S. Food and Drug Administration (FDA) indication for reduction of ASCVD in patients with ASCVD and diabetes with moderately elevated triglyceride levels.

The 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients with Persistent Hypertriglyceridemia provides the most current guidance on the management of hypertriglyceridemia [8] and identifies four patient management groups:

- **Adults with ASCVD and mild to moderate hypertriglyceridemia.** Optimizing diet, lifestyle and glycemic control, ruling out secondary causes and starting high intensity statins is the first step of management. In patients with known clinical ASCVD, assessing the patient’s risk level and levels of LDL-C is essential. Further management depends on the LDL-C levels. If LDL cholesterol levels are well controlled at <70 mg/dL, IPE may be considered. For LDL-C levels higher than 70 mg/dL, triglyceride or LDL-C risk-based therapies are considered on shared decision making and patient preference.

- **Adults aged ≥40 with diabetes mellitus and mild to moderate hypertriglyceridemia and without ASCVD.** After initial optimization of diet and lifestyle the next step is to continue LDL-C risk-based approach among patients <50 years or ≥50 years with no additional ASCVD risk enhancing factors. In patients aged ≥50 years with 1 or more ASCVD high risk features, shared decision making is advised based on patient preference and IPE may be considered.

- **Adults aged ≥20 years with mild to moderate hypertriglyceridemia and with no ASCVD or diabetes mellitus.** First, the 10-year ASCVD risk should be assessed and other risk enhancing factors should be considered. In patients with <5% ASCVD risk, emphasis should be given to implementing healthy diet and increased physical activity along with periodic ASCVD risk assessment. In patients with ASCVD risk ≥5%, shared decision making is encouraged to determine whether to initiate or intensify statin therapy.

- **Adults aged ≥20 years with severe hypertriglyceridemia.** Weight loss, glycemic control, optimizing carbohydrate consumption, alcohol restriction and physical activity should be strongly encouraged in these patients with triglycerides ≥500 mg/dL. For adults aged 20-39 years or 40–75 years with 10-year ASCVD risk <5% without ASCVD and diabetes, emphasis should be given to consuming low-fat diet (20% to 25% calories from fat) and using pharmacological agents such as fibrates and prescription grade OM-3FA to reduce the risk of pancreatitis. In adults with 10-year ASCVD risk ≥5%, known ASCVD and diabetes among those aged 40-75 years, it is advised to initiate and intensify statin therapy along with consumption of low-fat diet. Fibrates and OM-3FA can be considered. Adults with severe hypertriglyceridemia with levels >1000 mg/dL are at even greater risk of developing pancreatitis. Hence it is essential to implement lifestyle counseling with emphasis on very low-fat diet (10% to 15% of calories from fat) along with addition of statins, fibrates and OM-3FA in these patients.

Management of hypertriglyceridemia has a key role in cardiovascular disease prevention. Hence it is crucial to spread awareness on this topic in order to improve cardiovascular health. Lifestyle interventions such as optimizing diet, weight loss if overweight or obese, and increasing physical activity are the first line of management.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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