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Mini Review

How can we Manage Hypertriglyceridemia? Practical Insights to Interdisciplinary Approach to Patients

Rygiel Katarzyna*

Department of Environmental Medicine and Epidemiology, Medical University of Silesia (SUM), Zabrze, Poland

***Corresponding Author:** Rygiel Katarzyna, Department of Environmental Medicine and Epidemiology, Medical University of Silesia (SUM), Zabrze, Poland.

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Abstract

Hypertriglyceridemia, defined as elevated triglyceride (TG) levels (≥ 150 mg/dL; ≥ 1.7 mmol/L) is related with augmented risk of cardiovascular disease (CVD), and severe hypertriglyceridemia (characterized by TG levels ≥ 500 mg/dL; ≥ 5.6 mmol/L) represents risk factor for acute pancreatitis. Importantly, TG concentration in plasma illustrates the total amount of TG, contained in TG-rich lipoproteins (TRLs), such as: very low-density lipoproteins (VLDL), chylomicrons, and their remnants, TRLs can accelerate atherosclerotic processes through several mechanisms, including proinflammatory and procoagulant actions, as well as cholesterol deposition in the arterial walls. Despite a substantial research evidence in this area, low-density lipoprotein (LDL) cholesterol still represents the main therapeutic target for cardiovascular (CV) risk reduction. Several studies have shown that elevated TG levels are independently related with higher rate of CV events, even among patients receiving therapy with statins.

The aim of this mini-review is to present some insights to the practical (diagnostic and therapeutic) aspects of integrative hypertriglyceridemia management. It explains the pleiotropic role of omega-3 fatty acids, and presents a blend of non-pharmacologic and pharmacologic approaches in both clinical and preventive contexts. It also highlights the need for patient education that is critical for adherence to treatment.

Keywords: Hypertriglyceridemia; Cardiovascular (CV); Coronary Heart Disease (CHD); Triglyceride (TG); Prevention; Disease Management

Abbreviations

apoB: Apolipoprotein B; apoE: Apolipoprotein E; AHA: American Heart Association; CHD: Coronary Heart Disease; CVD: Cardiovascular Disease; CV: Cardiovascular; CETP: Cholesteryl Ester Transfer Protein; DGAT2: Diacylglycerol O-Acyltransferase 2; DHA: Docosahexaenoic Acid; DPP: Diabetes Prevention Program; EPA: Eicosapentaenoic Acid; FCHL: Familial Combined Hyperlipidemia; FHTG: Familial Hypertriglyceridemia; GI: Glycemic Index; GL: Glycemic Load; GISSI: The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; HDL: High-Density Lipoprotein; IDL: Intermediate-Density Lipoprotein; IR: Insulin Resistance; LDL: Low-Density Lipoprotein; Lp(a): Lipoprotein(a); LpL: Lipoprotein Lipase; MI: Myocardial Infarction; MS: Metabolic Syndrome; NEFA: Nonesterified Fatty Acid; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; P-OM3: Prescription Strength Omega-3-Acid; RCT: Randomized Controlled Trial; TG: Triglyceride; TRLs: TG-Rich Lipoproteins; VLDL: Very Low-Density Lipoprotein; T2DM: Type 2 Diabetes Mellitus

Introduction

Hypertriglyceridemia represents a common derangement in lipid metabolism, and thus, it should be properly evaluated and managed, to reduce the related risk of cardiovascular disease (CVD) and acute pancreatitis [1-3]. Triglycerides (TGs) play an important role in lipid metabolism and CVD development, even though they are not directly atherogenic. Some disorders of TG metabolism are associated with high risk for acute pancreatitis (e.g. fasting TG level exceeding 1000 mg/dL), and others are linked with increased atherosclerotic risk for CVD (Table 1) [1-3]. In patients with a history of TG-induced pancreatitis, it is paramount to control the TGs with both non-pharmacologic and pharmacologic methods. An elevation of TG levels signalizes an increased number of small, dense LDL particles, which are highly atherogenic, and predictive of increased risk of coronary heart disease (CHD) and cardiovascular (CV) events, especially among patients with central obesity, metabolic syndrome (MS), pre-diabetes, and type 2 diabetes mellitus (T2DM) (Table 2) [3,4]. To successfully manage cardio-metabolic diseases, lifestyle modifications should always be implemented, followed by pharmacotherapy including a combination of statins, fibrates, and omega-3 fatty acids [5,6]. The main components of safe and effective management of hypertriglyceridemia and high CV risk include a good foundation of knowledge and practical skills among medical practitioners, patient-centered approach, effective communication between pharmacists and physicians, and ability to clearly and convincingly convey medical recommendations to individual patients. This mini-review presents some insights to the diagnostic and therapeutic aspects of integrative hypertriglyceridemia management. It explains the pleiotropic role of omega-3 fatty acids, and displays a blend of non-pharmacologic and pharmacologic approaches, in the clinical and preventive contexts. Moreover, it underscores the importance of communication between medical providers (pharmacists and physicians), in order to improve the patient care. Finally, this brief overview highlights the need for patient education that is critical for adherence to treatment, and possible improvement of outcome.

NCEP ATP III [1,2]		The Endocrine Society [3]	
Borderline-high TG	150 - 199 mg/dl 1.7 - 2.3 mmol/l	Mild hyperTG	150 - 199 mg/dl 1.7 - 2.3 mmol/l
High TG	200 - 499 mg/dl 2.3 - 5.6 mmol/l	Moderate hyperTG	200 - 999 mg/dl 2.3 - 11.2 mmol/l
Very high TG	≥ 500 mg/dl ≥ 5.6 mmol/l	Severe hyperTG	1000 - 1999 mg/dl 11.2 - 22.4 mmol/l
		Very severe hyperTG	≥ 2000 mg/dl ≥ 22.4 mmol/l

Table 1: Diagnostic criteria for hypertriglyceridemia. Abbreviations: ATP III: Adult Treatment Panel III; NCEP: The National Cholesterol Education Program; hyperTG: Hypertriglyceridemia; TG: Triglycerides; mg/dl; Milligram/Deciliter; mmol/l: Milimol/Liter

The main causes of hypertriglyceridemia

The main primary (inherited) hypertriglyceridemia syndromes are presented in table 2 [3-6]. The first, and most common of them is familial combined hyperlipidemia (FCHL), in which TG levels are in the 150 to 500 mg/dL range, and the phenotype can include low-density lipoprotein (LDL) elevated levels, or combined very low-density lipoprotein (VLDL) and LDL increased levels that pose high risk of CHD. The second disorder, familial dysbetalipoproteinemia, is relevant to the premature CHD, and the affected patients have abnormal catabolism of remnants, and may also display an apolipoprotein E (apoE) variant. If this is the only lipid disorder present in such patients, they may not have increased lipid levels. However, if they simultaneously suffer from metabolic problems, such as: central obesity, T2DM, hypothyroidism, or chronic renal disease, they can have increased levels of remnants and TGs. The third disorder, the familial hypertriglyceridemia (FHTG), is characterized by TGs in the 250 to 1000 mg/dL range. However, if such patients also have elevated chylomicrons, their TG levels can be high, as well as their risk of premature CHD. Familial chylomicronemia is usually manifested in childhood, and should be correctly diagnosed at that time. Such patients have very high TGs, mild CHD risk, and high risk of acute pancreatitis. For this reason, they require continuous lipid lowering therapy (Table 2). Secondary causes of hypertriglyceridemia involve conditions, such as: central obesity, T2DM, hypothyroidism, or chronic renal disease, as well as increased carbohydrate ingestion, iatrogenic causes (e.g. intake certain medications), excessive alcohol consumption and physical inactivity (Table 2) [3-6]. It is important to identify secondary causes of hyperlipidemia, especially among patients with multiple comorbid conditions, and on multiple medications. In patients with hypertriglyceridemia the LDL particles are abnormal (small, depleted of cholesterol, and TG enriched), and have higher density than the typical LDL. Cholesteryl ester transfer protein (CETP) (also known as plasma lipid transfer protein) moves cholesterol and TG between HDL and VLDL. Furthermore, CETP can also move TG from VLDL into LDL, take cholesterol ester out of LDL, and put it back into VLDL. When LDLs are TG enriched, the TG can be enzymatically removed by the lipoprotein lipase and the hepatic lipase. These reactions cause shrinking of the LDL. Small dense LDL particles are accompanied by elevated VLDLs, chylomicrons, and decreased high-density lipoproteins (HDLs). These abnormalities usually coexist in patients with insulin resistance (IR), MS, central obesity or T2DM [3,4]. Both fasting and non-fasting TG levels are related to the risk of CHD [5,6]. In particular, the non-fasting TGs seem to be more closely associated with CHD, since atherosclerosis has been linked with postprandial metabolic abnormalities [6].

Primary causes of hypertriglyceridemia [4,5]		
Genetic syndromes with chylomicronemia	**Genetic syndromes with hypertriglyceridemia**	**Genetic susceptibility**
Familial dysbetalipoproteinemia, abnormal catabolism of remnants, apolipoprotein E (apoE) variant, risk of premature CHD Familial chylomicronemia very high TGs, mild CHD risk, high risk of acute pancreatitis, expressed in childhood, requires continuous lipid-lowering therapy Lipoprotein lipase (LPL) deficiency Apolipoprotein C-II (apoC2) deficiency Apolipoprotein AV deficiency	Familial combined hyperlipidemia (FCHL) (polymorphisms in molecules and enzymes participating in lipoprotein metabolism; (e.g.: apoC2, apoC3), high risk of CHD; the most common defect Familial hypertriglyceridemia (FHTG) likely polygenic, (high TG due to excess hepatic VLDL production, risk of premature CHD	Metabolic syndrome

Secondary causes of hypertriglyceridemia [3-6]		
Diseases and conditions	**Medical therapies causing iatrogenic effects**	**Adverse lifestyle factors**
Hypothyroidism Diabetes mellitus (Poorly controlled) Central obesity Kidney diseases Nephrotic syndrome Autoimmune disorders e.g., systemic lupus erythematosus (SLE) Chronic idiopathic utricaria HIV- associated dyslipidemia Pregnancy (the third trimester)	Beta-blockers (nonselective) Thiazide diuretics Corticosteroids, Glucocorticoids Tamoxifen Raloxifene Estrogens (e.g. contraceptives, postmenopausal hormone therapy) Protease inhibitors Retinoic acid Isotretinoin Sirolimus Cyclophosphamide L-Asparaginase Bile acid resins Phenothiazines Antipsychotics (e.g. clozapine, olanzapine) Interferon Immunosuppressants (e.g., cyclosporine)	Physical inactivity Excessive alcohol intake Positive-energy balanced diet (rich in saturated fat or high glycemic index/load content)

Table 2: Primary and secondary causes of hypertriglyceridemia.

Nonpharmacological approaches to hypertriglyceridemia - dietary modifications and physical activity

In general, the impact diet of and physical exercises on TG levels differs, depending on the baseline TG levels, caloric and nutritional modifications, as well as type, intensity level, and duration of physical activity, for each individual patient. According to data from a randomized controlled trial (RCT), a restriction in energy intake of approximately 300 kcal/d resulted in a 23% reduction in fasting TG levels, during the first year of the study. This substantial TG decrease was subsequently followed by some additional benefits, such as reduction in the postprandial TG levels, among the trial participants [7]. This should convince medical providers to addressing lifestyle changes, as a baseline component of comprehensive therapy, for patients with elevated TG levels and high CV risk. The most important dietary interventions should include decreased intake of high glycemic index/load carbohydrates, abstinence from alcohol, restricted use of high fructose, sweetened beverages or snacks, and highly processed food, containing large quantities of trans fatty acids or saturated fats. Simultaneously, the Mediterranean-style diet (containing predominantly monounsaturated and polyunsaturated fatty acids, especially omega-3 fatty acids, vegetables, fruits, whole grains, and fish), and increased intake of dietary fiber should be implemented. Moreover, a sustained weight reduction (5% - 10% of the initial body weight) that often accompanies such dietary modifications, will also have beneficial influence on elevated the TG levels [3,5]. Furthermore, it is crucial to point out to patients that regular, moderate to intense level of physical activity, combined with moderate reduction of daily caloric intake is the most effective technique for lowering TG by approximately 20% - 30%, when the baseline TG levels are above 150 mg/dL [8].

Pharmacological management of elevated TG - bringing patients to treatment goals

There is a group of patients, for whom the primary target of therapy is the reduction of very high levels of TG, and prevention of acute pancreatitis. For such patients, a combination of various lipid-lowering strategies is necessary, including non-pharmacological and pharmacological approaches. It is essential to remove any possible exogenous factors, which can promote or exacerbate severe hypertriglyceridemia. This can be accomplished via: dietary restriction of saturated and trans fats, no alcohol use, good glycemic control in diabetic patients, and minimizing the estrogen content in birth control pills, or post-menopausal preparations (among women taking contraceptives or post-menopausal hormonal therapies) [9]. A pharmacological approach to very high TG includes: fibrates, omega-3 fatty acids, and nicotinic acid (with caution), in addition to statins, and non-pharmacological strategies. According to the results of the study conducted among patients with hypertriglyceridemia, the combined treatment with omega-3 fatty acids and simvastatin caused greater reductions in non-HDL-C levels, comparing to simvastatin monotherapy [10]. From the safety perspective, it should be highlighted that the addition of omega-3 fatty acids to statin therapy involves the lowest risk for myalgia, myopathy or elevation in liver function tests, comparing with other lipid-lowering agents [10]. Lack of these annoying adverse effects is particularly important from the patient point of view. Data from clinical studies on lipid-lowering treatments have indicated that fenofibrate, used in severely hypertriglyceridemic patients with the MS, resulted in a 7.5% reduction in non-HDL-C levels [11], and a combination therapy of fenofibrate with simvastatin resulted in an additional 5% lowering of non-HDL-C levels, among patients with moderate to severe TG elevation, and the MS [12]. Moreover, an addition of niacin to simvastatin therapy resulted in non-HDL-C lowering of approximately 10% for each gram of the daily dose of niacin [13]. On the other hand, it is important to keep in mind that according to the AIM-HIGH trial data, the treatment with extended-release niacin was associated with significantly increased rates of serious adverse events (e.g. ischemic stroke), and high rates of dose reductions or medication discontinuation, related with niacin side effects [14]. Medical providers should remember that the individually tailored blend of intensive lifestyle changes, combined with pharmacotherapy, needs to be promptly and effectively implemented, in order to reduce very high TG levels, and possibly prevent acute pancreatitis events.

The role of omega-3 fatty acids in the management of patients with high TG levels

It is crucial to understand the main biochemical and physiologic pathways of lipoprotein metabolism, as well as pleiotropic effects exerted by the omega-3 fatty acids (long-chain polyunsaturated fatty acids, present in the fish oil), in order to provide the most appropriate interventions for the above mentioned group of patients [15,16]. Omega-3 fatty acids reduce TG biosynthesis in hepatocytes, by blocking an enzyme diacylglycerol O-acyltransferase 2 (DGAT2), which reduces TG supply for loading into VLDL particles (the lipoproteins secreted by the liver, responsible for lipid and energy distribution to systemic tissues) [15]. In this way, omega-3 fatty acids decrease the amount of TG in the VLDL particles, and reduce hepatic VLDL secretion. Furthermore, the omega-3 fatty acids activate the serum lipolytic enzyme - LPL, which hydrolyzes TG in the core of pro-atherogenic apo B-containing lipoproteins, such as VLDL, IDL and LDL [15]. In result of these metabolic actions, omega-3 fatty acids reduce the elevated TG, TC, and non-HDL-C levels, and increase HDL-C levels, in addition to exerting their pleiotropic effects for cardiovascular system, and beyond [15,16]. Omega-3 fatty acids can slightly elevate LDL-C levels in hypertriglyceridemic patients; however, they concurrently reduce non-HDL-C levels. This action is clinically significant, since non-HDL-C is a better predictor of atherogenic CV risk than the LDL-C. Therefore, in patients with TG equal or above 200 mg/dl, who attained their LDL-C treatment goals, and non-HDL-C is recommended as their secondary lipid target, the omega-3 fatty acids should be added to a baseline statin therapy [16,17]. The greatest features of the omega-3 fatty acids include their safety and pleiotropic effects that increase their potential usefulness in the management of patients with CVD, co-morbidities and multidrug therapies [16,17]. Based on the findings of the GISSI (The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) trial, the use of 1 gram of omega-3 fatty acids, has revealed positive effects on total mortality, CV mortality, and sudden cardiac death (probably due to the anti-arrhythmic role of omega-3 fatty acids, during 3-4-months after acute MI) [18]. In general, the American Heart Association recommends that patients with documented CHD take approximately 1g of eicosapentaenoic acid (EPA) and docosahexaenoic (DHA) acid per day [15,16].

Consideration of prescription forms versus supplements of omega-3 fatty acids for patients with hypertriglyceridemia

Input of pharmacists to a decision-making process, related to a selection of prescription strength omega-3-acid ethyl ester compounds versus omega-3 fatty acids supplements, in patients with high TG and non-HDL-C levels, and associated risk for CVD or acute pancreatitis, can play an important role in the adherence to treatment, especially in cases involving multi-morbidity and polytherapy, or elderly patients. Prescription strength omega-3-acid (P-OM3) ethyl esters are fish oil formulations, that undergo the rigorous quality control and regulatory steps, required to obtain an approval for prescription medications. In general, P-OM3 are derived from cold water fish, which are high in omega-3 fatty acids [15,19]. Unlike some lipid-lowering pharmaceutical agents, there is no known toxicity, related to the use of omega-3 fatty acids. However, it should be kept in mind that heavy metal contamination can be a problem, especially in some supplements of fish oil. In contrast, in the pharmacologic-grade omega-3 fish oil products, the risk of impurity is rather negligible [19]. Moreover, omega-3 fatty acids contain polyunsaturated fatty acids chains that can be oxidized, and thus, their taste can be not appealing to patients. In contrast, in the purified, pharmaceutical form, fish oils are more palatable, and therefore, addressing such a nuance by pharmacists, can increase the patient adherence to therapy [19]. A choice of a prescription form versus a supplement preparation of the omega-3 fatty acids can be illustrated, using an exemplary patient with very severe hypertriglyceridemia (fasting TG of 1300 mg/dl, posing risk for pancreatitis), who needs omega-3 fish oil therapy, in addition to his multiple medication regimen, which include fibrates and statins. Such a patient, after a brief consultation with his “very busy” physician, was using the omega-3 fish oil capsules, containing 50 mg each. Unfortunately, due to some miscommunication with his doctor, a daily dose of the omega-3 fish oil was not properly specified. In fact, this patient needed 2 - 4 grams as a daily dose, and this would require of him to swallow 40 - 80 capsules per day. Of course, this choice was not feasible. This scenario reflects a common situation, since many supplement preparations contain only a small percentage of the therapeutically required quantity of omega-3 fatty acids. Also, supplements do not undergo the rigorous investigation during clinical trials, and thus, there might be some variability in the quantity of omega-3 fatty acids in them, as well as some contaminants, such as oxidized lipids

or phospholipids [20]. In addition, the manufacturer's information about doses can be misleading, especially when at the supplement package, on the front, it is written: "1000 mg omega-3 fatty acids", but directly on the bottle, it is written: "300 mg of EPA and DHA". At this point, a clarification by a pharmacist can ensure the use of a right dose of this preparation, for a given patient. Furthermore, using prescription strength omega-3 fatty acids can eliminate most of these potential problems.

Prevention of CVD and acute pancreatitis in patients with high TG levels

Nutritional modifications and regular physical activity are necessary steps for prevention of CVD and acute pancreatitis [3,20]. Since these non-pharmacologic changes are difficult to achieve in many patients with hypertriglyceridemia, it is imperative that medical staff, including physicians, pharmacists, dietitians, and physical therapists will provide long-term support their patients, struggling with these problems. There is substantial evidence that many lifestyle oriented strategies can be successfully applied among in patients with hypertriglyceridemia, to improve the management of their lipid disorders, and the associated medical risk. In particular, in the Diabetes Prevention Program (DPP), the patients with IR, at elevated risk of developing diabetes mellitus, were randomized to receive either metformin, or lifestyle modifications, such as weight reduction program and physical exercises. The DPP findings have revealed that these non-pharmacologic modalities decreased the risk of developing diabetes to a much greater extent than did metformin [21]. In addition, the DPP results were consistent with a significant decrease of TG levels, as a result of non-pharmacologic interventions (such as diet, exercise, and weight loss). In consequence, the DPP has important implications for the reduction of high TG levels, and relevant CV risk, thanks to an early start, followed by maintenance of therapeutic lifestyle changes, to sustain target TG levels [22]. It should be highlighted that for the patients with high TG levels, very low-fat diets, which are related with consuming high amounts of carbohydrates, and bigger caloric intake [5] that can exacerbate hypertriglyceridemia. For this reason, it is imperative to underscore that a strict low-fat, and high-carbohydrate diet is usually not helpful. In contrast, the best strategy is to reduce the total caloric intake (mostly derived from high glycemic index (GI) and high glycemic load (GL) carbohydrates), to decrease the amount of saturated fat, and to eliminate trans-fats (as much as possible) [5]. The patients should be encouraged by their providers to consume a diet low in high GI and GL carbohydrates, by restricting highly processed fast food, and sweetened beverages intake. In addition, their menu needs to be high in monounsaturated and polyunsaturated fatty acids, rich in vegetables, fruits and grains [3,5,23]. Simultaneously, it should be emphasized that the "best exercise" means the one that the patient likes, and will perform systematically. This in turn, should enhance successful weight loss, and long-term maintenance of recommended body mass. Moreover, it can be encouraging for some patients that the equivalent energy expenditure, even during slow walking, can be as advantageous, as long-distance running [24]. Contrary to that, a sedentary lifestyle, which is often related with obesity, poor glycemic control, and IR (leading to MS, or worsening of CV risk factors) has to be discouraged. In fact, patients should have recommendations to get up from their sitting position every 15 minutes. Furthermore, dietary education, focused on healthy food choices and behaviors, as well as cooking workshops, promoting "heart-healthy" fats need to be arranged. Medical providers should emphasize, during routine appointments with their patients that these nonpharmacological solutions for dyslipidemia management are also useful for glycemic and blood pressure control [23]. Practical implementation of lifestyle interventions requires coordinated efforts by medical staff and patients. However, such efforts are mandatory, in order to reduce a degree of hypertriglyceridemia, and impending risk of CVD and pancreatitis [5,20].

Key practical recommendations related to diagnosis and management of patients with hypertriglyceridemia

- Screening patients for hypertriglyceridemia, as an important component of lipid panel, should be done at least every five years.
- A diagnosis of hypertriglyceridemia should be based on fasting and non-fasting TG levels.
- Patients with high fasting TGs need assessment for secondary causes of hypertriglyceridemia, such as endocrine disorders or iatrogenic effects of medications. Further therapy needs to directed at these secondary causes.
- Patients with primary hypertriglyceridemia should be assessed for usual CV risk factors (e.g.: arterial hypertension, pre-diabetes, type 2 diabetes mellitus (T2DM), central obesity, and liver dysfunction or diseases.
- Possible genetic causes or future CV risk, among patients with primary hypertriglyceridemia have to be evaluated (e.g., starting from medical interview focused on family history of dyslipidemia and CVD).
- Measurement of apolipoprotein B (apoB) or lipoprotein(a) (Lp(a)) levels has clinical value in some patients, with elevated CV risk.
- In the comprehensive therapy of hypertriglyceridemia, it has been recommended that the following interventions should be implemented, based on individual patient clinical status, goals, and needs:
    - Lifestyle therapy (e.g. dietary modifications, physical exercises, and weight reduction program), for mild-to-moderate hypertriglyceridemia,
    - Combination of reduction of dietary fat and simple carbohydrate intake with pharmacotherapy, to decrease the risk of acute pancreatitis, in severe and very severe hypertriglyceridemia (>1000 mg/dl) cases
    - A fibrate, as a first-line medication to reduce TG levels in patients at risk for acute pancreatitis (induced by very high TGs)
    - Statins, for the treatment of mild to moderate hypertriglyceridemia (to decrease CV risk); however, statins should not be used in monotherapy for severe or very severe hypertriglyceridemia.
    - Fibrates and omega -3 fatty acids, alone or in combination with statins are therapeutic options for moderate to severe TGs

Conclusion

Mild or moderate hypertriglyceridemia can be a risk factor for cardiovascular disease (CVD), while severe or very severe hypertriglyceridemia increases the risk for acute pancreatitis. In patients with hypertriglyceridemia, CHD risk is often augmented by concomitantly increased levels of LDL cholesterol (e.g. in mixed hyperlipidemia), and with decreased levels of HDL

cholesterol (e.g. in the atherogenic lipid triad, often present among patients with central obesity, MS, pre-diabetes, and T2DM). It is imperative to early detect patients with high TG and increased CV risk, in order to implement interdisciplinary therapies directed at normalizing lipid profile, and CV risk reduction. Well-educated patients, who are engaged in their care, and have confidence in their physicians and pharmacists, will have a better chance to achieve lipid-related therapeutic goals, and to decrease CV risk. It remains to be determined, to what degree, the application of combined therapeutic approaches will have a beneficial impact on CVD outcomes, beyond proven pharmacotherapy (e.g. statins or fibrates). Hopefully, further clinical outcome trials will answer this question, and will provide valuable implications for clinical practice.

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