

## REVIEW ARTICLE

# Hypertriglyceridemia - Common Causes, Prevention and treatment Strategies

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**Abstract: Background:** Prevention and treatment of dyslipidemias represent the key issues of Cardiovascular Disease (CVD) prophylaxis. Consequently, the effective management of different types of lipid disorders, including hypertriglyceridemia, should be a priority for the healthcare practitioners (*e.g.*: cardiology and endocrinology specialists, primary care physicians, dietitians, and pharmacists), who provide medical care, as well as for the patients, who receive this care, and need to be directly engaged in it, in order to improve their outcomes. The aim of this review is to facilitate the translation of current trends in hypertriglyceridemia management into a daily practice. The article focuses on the common causes and consequences of hypertriglyceridemia, and discusses diagnostic evaluation and therapeutic options for patients with high Triglyceride (TG) levels and CVD risk.

**Conclusion:** This review presents the main practice-related strategies, based on the current guidelines for the management of dyslipidemias and CVD risk, according to the European Society of Cardiology (ESC), the European Atherosclerosis Society (EAS), and the American College of Cardiology (ACC)/American Heart Association (AHA), including both non-pharmacological, and pharmacological approaches. It also addresses the beneficial impact of pharmaceutical Care (PC) interventions on clinical outcomes of patients with lipid disorders and CVD risk (in light of Randomized Controlled Trials (RCT) data), and underlines the importance of close cooperation between physicians and pharmacists, who manage such patients.

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## 1. INTRODUCTION

Cardiovascular Diseases (CVD) due to atherosclerosis and thrombosis are the largest cause of premature morbidity, mortality, disability, and financial burden, not only in the European Union (EU) and the U.S., but also in a growing number of developing countries, worldwide [1]. It has been well established that lipid disorders promote the development of atherosclerosis and its clinical consequences, such as CVD, including the main clinical conditions: Coronary Heart Disease (CHD), ischemic stroke, Peripheral Arterial Disease (PAD), heart failure, and sudden cardiac death [1]. Although CVD have multifactorial causes, their common denominator is often relevant to lifestyle, which involves typical risk factors, such as inappropriate nutritional habits, physical inactivity, tobacco smoking, lack of adherence to medical advice, and poor coping strategies in response to chronic stress. These risk factors, as well as elevated blood pressure, diabetes mellitus, and dyslipidemias can be modified [1, 2].

Traditionally, the SCORE (Systematic COronary Risk Evaluation) scale has been recommended as a basic instrument for calculating cardiovascular (CV) risk, and the therapeutic guidelines for dyslipidemia were focused on low-density lipoprotein cholesterol (LDL-C) goals [1]. However, the new guidelines of American College of Cardiology (ACC)/American Heart Association (AHA), from 2013, rather than LDL-C targets used the intensity of statin therapy as the goal of treatment. According to the ACC/AHA guidelines, the decision about individual patient management has to be made by the medical practitioner and engaged patient. This review focuses on hypertriglyceridemia (as an important component of dyslipidemia) and discusses evidence-based strategies to reduce the risk of atherosclerotic CVD [3].

## 2. NEW APPROACH TO DYSLIPIDEMIA MANAGEMENT BASED ON ACC/AHA GUIDELINES OF 2013

The new guidelines of American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, from 2013, differ significantly from the previous ones, by abandoning the traditional LDL-C treatment goals (that were easy

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to follow by physicians and patients) [3]. Instead, the new ACC/AHA guidelines recommend a CVD risk reduction via moderate to intense statin therapy in four groups of patients: 1) with atherosclerotic CVD, 2) with diabetes mellitus (T2DM), 3) with primary elevations of LDL-C above 4.9 mmol/l (190 mg/dl), and 4) without clinical CVD, who are 40 to 75 years of age, with LDL-C level from 1.8 to 4.88 mmol/l (70 and 189 mg/dl), and with an estimated 10 year CVD risk above 7.5% (calculated by the Pooled Cohort Equations) [3]. It should be pointed out that first, the ACC/AHA guidelines are based on the randomized controlled trials (RCTs) data that did not include patient populations in some geographic locations (*e.g.*: the Indian subcontinent, and the Asia-Pacific region) [3, 4]. Second, due to absence of specific treatment targets, there is some concern that initiation and monitoring of the therapy might be more difficult for clinicians [3, 4]. Third, since the statin regimens (aimed at 30-50% reduction in LDL-C) will be promoted, it can be expected that a reduction of the treatment threshold (from 20 to 7.5%), in primary CVD prevention, will result in a larger number of patients receiving statin therapy [3, 4]. This would be beneficial, especially for young patients with high life time CV risk. On the other hand, however, this could result in a greater number of elderly patients on statins (creating a potential for overtreatment, and adverse effects) [3, 4]. In addition, measurements of LDL-C levels will be performed during treatment, only as an assessment of adherence and response to therapy [3]. At present, it appears that the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines from 2011 appear to represent the most pragmatic strategy, since they consider evidence beyond RCTs, and provide management recommendations for practice in various patient populations, worldwide [1, 4]. Also, current statements of the American Association of Clinical Endocrinologists, the International Lipid Society, and the previous National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) of 2001 (based on the Framingham algorithm) are generally in agreement with the ESC/EAS guidelines [5, 6].

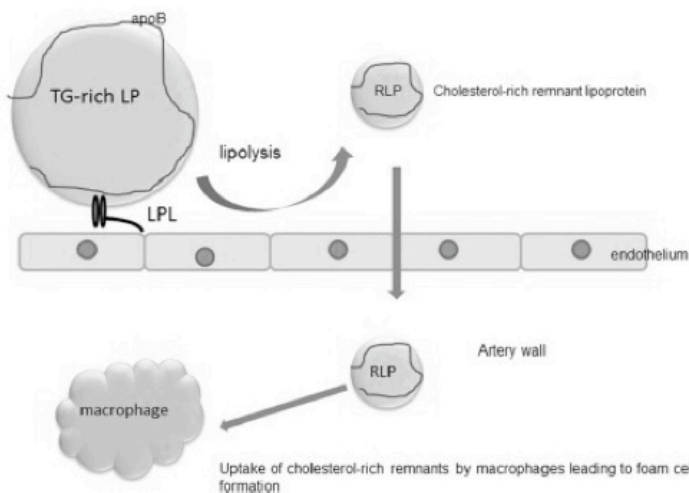
### **3. TRIGLYCERIDES - PRACTICAL ASPECTS OF THEIR BIOCHEMISTRY, METABOLISM, AND RELATIONS WITH CVD RISK**

Triglycerides (TG) are lipids that constitute three chains of fatty acids, and one molecule of glycerol, as their backbone. Since TG are hydrophobic (water insoluble), they are stored in the adipose tissue, and can be transported between variety of tissues via certain lipoproteins. TG undergo enzymatic hydrolyzation to free fatty acids (FFA) and glycerol. FFA can be oxidized by many tissues, such as muscle or myocardium, and thus, physiologically, TG play an important role as nutrients, delivered to various tissues to provide energy [2, 7]. Both TG and FFA can be mobilized from the liver and lipoproteins, and are able to migrate to different tissues, to be metabolized, according to physiologic patterns and current needs of the organism. However, elevated serum levels of TG and FFA can be associated with some negative health consequences, especially among patients with insulin resistance (IR), central (visceral) obesity, type 2 diabetes mellitus (T2DM), or inborn errors of metabolism. For instance, too much FFA in the bloodstream leads to impair-

ment in the oxidation of TG, and often causes insulin receptor insensitivity (because in the presence of excess FFA, the capacity of systemic tissues to metabolize glucose is often compromised). In consequence, hypertriglyceridemia and elevated FFA levels perpetuate IR, contributing to a cascade of cardio-metabolic derangements [2, 7]. According to a recent meta-analysis by Liu *et al.*, analyzing over sixty prospective studies, it has been indicated that the genetic predispositions to hypertriglyceridemia can lead to excess of TG in the bloodstream, or poor capacity to remove TG from the blood. In result, both of these scenarios are correlated with increased risk for future CV events [8]. As an explanation of these concepts, two mechanisms have been proposed: 1) high TG levels indicate that remnant lipoproteins (which are as atherogenic as the LDL-C) are also elevated, and 2) the increased remnant levels, including intermediate density lipoprotein (IDL), and small remnant very low density lipoprotein (VLDL) particles (which have pro-inflammatory properties) are associated with increased risk for CV events [9]. For a medical practitioner, an elevation of TG levels should signalize that there is an increase in both the number of LDL particles, and their atherogenic properties. For instance, if the LDL-C levels are the same in two different patients, the one, who has the elevated TG level, can also have a high number of small, dense LDL (sd LDL) particles, which are highly atherogenic, and predictive of increased risk of CV events [9].

### **4. CONTRIBUTION OF REMNANT LIPOPROTEIN PARTICLES (RLP) TO ATHEROGENICITY AND CVD RISK**

In patients with hypertriglyceridemia, elevated levels of TG in the circulation are correlated with the activation of two enzymes: Cholesteryl Ester Transfer Protein (CETP) and hepatic Lipoprotein Lipase (LPL). CETP transfers TG out of IDL and small VLDL particles into LDL particles, which subsequently undergo lipolysis by hepatic LPL. During this process, large LDL particles are converted into much more numerous, small, dense LDL (sd LDL) particles, which have high atherogenic potential [2]. It should be noted that on one hand, the TG overload in the circulation is not a typical pathological feature of atherosclerotic lesions, since the FFA (the end product of TG hydrolyzation) represent either an important energy source for myocytes and other tissues, or an inactive fuel, deposited in adipocytes [2]. On the other hand, the TG metabolism by-products, called Triglyceride-Rich Lipoproteins (TG-rich LPs), or Remnant Lipoprotein Particles (RLPs) can cause highly atherogenic foam cell depositions, similarly to the modified, pro-atherogenic LDL particles [2, 10-12]. It has been demonstrated that TG-rich LPs can execute pro-atherogenic actions in endothelial cells, and the RLPs (derived from the TG-rich LPs), can cross the endothelial barrier, and accelerate the atherosclerotic process, as presented in Fig. (1) [2, 10, 11]. Every pro-atherogenic lipoprotein particle (such as IDL, VLDL, LDL, lipoprotein (a), and chylomicrons) contains just one Apolipoprotein B (apo B) molecule, and thus, the apo B represents a direct measure of the number of atherogenic particles, circulating in the bloodstream [13]. Based on some early CHD studies, it has been documented that there is a direct connection between apo B measurements, and severity of



**Figure 1** Remnant Cholesterol and Atherosclerosis  
 Triglyceride (TG)-rich lipoproteins (LPs) containing a single molecule of apolipoprotein B (apo B) are released into the circulation by the liver or intestine and bind the LP lipase (LPL) on the surface of endothelial cells. Lipolysis of TG-rich LPs by LPL yields a TG-depleted but cholesterol-rich remnant LP (RLP). RLPs contain 5 to 20 times more cholesterol per particle than low-density LP (LDL) and can cross the endothelial barrier. Importantly, unlike native LDL, RLPs can be taken up in an unregulated fashion by scavenger receptors expressed by resident macrophages in the subendothelial space, facilitating foam cell formation and atherosclerosis.  
 Source: Modified from McPherson [10].

**Fig. (1).** Remnant cholesterol and atherosclerosis.

CVD among patients, who underwent cardiac catheterization [14]. The predictive role of apo B as CVD marker was further supported in some clinical trials [13, 15]. In addition to remnants, the other important contributor to atherosclerosis is the Apolipoprotein C3 (apo C3), which is a glycoprotein, located on the surface of TG-rich LPs (which also contain apo B). Apo C3 inhibits the enzyme LPL, exhibits pro-inflammatory properties, decreases endothelial nitric oxide production, interferes with insulin signaling pathways, and facilitates atherosclerosis [16, 17].

**5. DIAGNOSTIC CRITERIA AND COMMON PRIMARY AND SECONDARY CAUSES OF HYPERTRIGLYCERIDEMIA**

Criteria for hypertriglyceridemia (according to the Endocrine Society clinical practice guidelines, and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines) are presented in Table 1. They should help clinicians with risk assessment of premature CVD. In addition, a very severe hypertriglyceridemia (TG levels above 2000 mg/dl; 22.4 mmol/l) indicates the risk of acute pancreatitis that is a life-threatening condition, which requires immediate treatment.

Common primary and secondary causes of hypertriglyceridemia are summarized in Table 2. They include some rare congenital disorders, and more common, acquired causes of hypertriglyceridemia, usually due to medical conditions, such as diabetes mellitus, metabolic syndrome, central obesity, hypothyroidism, and chronic kidney disease, as well as medication-induced dyslipidemia (with high TG level). Physicians need to keep in mind that patients with hypertriglyceridemia should always be assessed for possible secondary causes of dyslipidemia, and in case of suspected primary hypertriglyceridemia, the patients should be evaluated for family history (genetic predispositions) of dyslipidemia and CVD [1, 2, 18].

In accordance with the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, the secondary treatment target in patients with high hypertriglyceridemia (TG levels 200 to 499 mg/dl; 2.3–5.6 mmol/l) is non-high-density lipoprotein cholesterol (non-HDL-C) (calculated by subtracting HDL-C from total cholesterol, TC). The cut-off value for the non-HDL-C should be about 30 mg/dl (0.8 mmol/l) higher than the corresponding LDL-C target value. In practice, this means that non-HDL-C level should be below 100 mg/dl (2.6 mmol/l), and

**Table 1.** Criteria for hypertriglyceridemia.

NCEP ATP III [6, 19]			The Endocrine Society 2010 [18]		
Borderline-high TG	150–199 mg/dl	1.7–2.3 mmol/l	Mild hypertriglyceridemia	150–199 mg/dl	1.7–2.3 mmol/l
High TG	200–499 mg/dl	2.3–5.6 mmol/l	Moderate hypertriglyceridemia	200–999 mg/dl	2.3–11.2 mmol/l
Very high TG	≥500 mg/dl	≥5.6 mmol/l	Severe hypertriglyceridemia	1000–1999 mg/dl	11.2–22.4 mmol/l
			Very severe hypertriglyceridemia	≥2000 mg/dl	≥22.4 mmol/l

NCEP ATP III, The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III).  
 Abbreviations: mg/dl, milligram/deciliter; mmol/l, milimol/liter; TG, triglycerides.

**Table 2. Causes of hypertriglyceridemia.**

Primary [1, 2]		
Genetic syndromes presenting as chylomicronemia (rare)	Other genetic syndromes with hypertriglyceridemia (relatively common)	Primary genetic susceptibility
Lipoprotein lipase (LPL) deficiency Apolipoprotein C-II (apoC2) deficiency Apolipoprotein AV deficiency Dysbetalipoproteinemia Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) deficiency (expressed in childhood)	Familial hypertriglyceridemia (FHTG) likely polygenic (high TG due to excess hepatic VLDL production, normal cholesterol levels)  Familial combined hyperlipidemia (FCHL) (polymorphisms in molecules and enzymes participating in lipoprotein metabolism; (e.g.: apoC2, apoC3)	Metabolic syndrome
Secondary [1, 2, 18]		
Diseases	Medications	Diet
Hypothyroidism Diabetes mellitus (Poorly controlled, insulinopenic) Central obesity Renal diseases Nephrotic syndrome Autoimmune disorders e.g., systemic lupus erythematosus (SLE) HIV- associated dyslipidemia Chronic idiopathic urticaria Pregnancy (the third trimester)	Beta-blockers (nonselective) Thiazides Corticosteroids Tamoxifen Raloxifene Estrogens (oral, not transdermal) (e.g. Contraceptives, Postmenopausal hormone therapy) Protease inhibitors Retinoic acid Isotretinoin Sirolimus L-Asparaginase Bile acid resins Phenothiazines Antipsychotics (second generation) Immunosuppressants	Alcohol excess Positive-energy balanced diet with saturated fat or high glyce-mic index/load content

below 130 mg/dL (3.3 mmol/l), in patients at very high, and high CVD risk, respectively [6, 19, 20].

## 6. SIMPLE TOOLS FOR A DAILY PRACTICE: NON-HDL-C AND TG TO HDL-C RATIO, AS ADJUNCTIVE MARKERS OF CVD RISK

Searching for accurate biomarkers of dyslipidemia and CVD risk is one of the priorities in current lipidology research [21]. In particular, in patients who have high TG levels, and the discordance between LDL-C and non-HDL-C (more than 30 mg/dl (0.8 mmol/l)), non-HDL-C is a better predictor of CVD risk than LDL-C, since non-HDL-C reflects the cholesterol carried by all atherogenic lipoproteins circulating in the bloodstream (especially TG-rich remnant lipoproteins) [18, 19]. However, the use of non-HDL-C has not been sufficiently adopted by physicians, in their clinical decision-making. Also, laboratories do not provide printed non-HDL-C levels on the routine lipid panel, and unfortunately, most physicians do not calculate the non-HDL-C value, even though this equation is very simple [6, 19]. Some

studies have shown that non-HDL-C correlates with coronary artery calcification even in asymptomatic individuals with CVD [22]. The association between non-HDL-C and CVD outcomes has been investigated less extensively than the relationship between LDL-C, MI, and CV death. However, in some prospective trials it has been demonstrated that the strong correlations exist between non-HDL-C levels and CV events, both with [23, 24], and without [25] the preexisting CVD. Furthermore, longitudinal findings from the Lipid Research Clinics Follow-Up Study have clearly demonstrated that non-HDL-C levels were good predictors of CV death, after 19 years of follow-up [26]. Similarly, the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study results have indicated that non-HDL-C predicted 10-year CV mortality only in the patients with impaired fasting glucose, and not in the ones with normal fasting glucose levels [27]. In addition, non-HDL-C levels were predictors of stroke, and their predictive value has been demonstrated across all age ranges, in both males and females, with or without CVD, or some other associated CV risk factors [28]. Finally, a meta-analysis of clinical trial

data supports a 1:1 relationship between the percent of non-HDL-C lowering, and the percent of CHD risk reduction [29]. According to this evidence, non-HDL-C, as an adjunctive marker of CV risk, should be more widely used by medical practitioners.

The ratio of TG to HDL-C (TG/HDL-C) represents a summary measure for either elevated TG level, low HDL-C level, or both. The joint occurrence of high TG and low HDL-C is characteristic for the atherogenic dyslipidemia, typically occurring in central (visceral) obesity, MS, pre-diabetes, and T2DM. Metabolically, the TG/HDL-C ratio is linked to IR, and preponderance of sd LDL particles [30]. In addition, some prospective trials have linked the TG/HDL-C ratio not only with CVD incidence and outcomes, but also with all-cause mortality [31, 32]. Furthermore, a recent analysis of the Very Large Database of Lipids-4 (VLDL-4) study has revealed that a higher TG/HDL-C ratio was associated with an increasingly atherogenic lipid phenotype, characterized by higher RLP-C, together with higher sd LDL and non-HDL-C levels [33]. Also, based on post hoc analysis of the Scandinavian Simvastatin Survival Study (4S), it has been suggested that patients with elevation of TG/HDL-C ratio tend to have higher benefits from pharmacotherapy than those without elevation of this ratio [34]. Based on this evidence, TG/HDL-C ratio represent another useful tool for medical practice, which can be applied in an evaluation and follow-up of patients with dyslipidemia, T2DM, MS and CVD.

**7. PHARMACOTHERAPY OPTIONS IN PATIENTS WITH ELEVATED TG LEVELS AND HIGH CV RISK, SUPPORTED BY RCT DATA**

Statins are the first-line lipid-lowering therapy that reduce CHD and CV risk in patients with dyslipidemia [1-5, 35]. Although elevated TG levels (above 200 mg/dl) are associated with a greater risk of CHD, no completed prospective outcomes trial exists to support or refute a reduction in CV risk, resulting from lipid-modifying therapy, among patients specifically selected for the presence of hypertriglyceridemia. Findings from subgroup analyses of ACCORD Lipid study [35], and results of major fibrate trials, such as FIELD, VA-HIT, BIP, and HHS [36-39] (presented in

Table 3) suggested that in subgroups of patients with TG levels above 204 mg/dl and HDL-C levels below 34 mg/dl, clinical outcomes (in terms of CV event reduction), were most beneficial among patients using fibrate therapy. In addition, it has been documented that fibrates, as monotherapy, provided the strongest reduction of TG levels (30%-50%), followed by omega-3 methyl esters (20%-50%), and statins (10%-30%) [40]. Recently, two major CVD outcomes studies: AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes), and HPS2 THRIVE (The Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) using extended-release niacin (a vitamin B3) against a background of statin therapy (with optimal control of LDL-C levels) were unable to demonstrate an incremental benefit of niacin beyond the treatment with statin [41, 42]. It should be pointed out that the results of both AIM-HIGH and HPS2 THRIVE studies differ from the reports of the previous Coronary Drug Project (CDP) clinical trial, which was conducted in the “pre-statin era”, and demonstrated a good effectiveness of niacin on CVD morbidity and mortality, and modification of lipid levels (reduction of TG, and elevation of HDL-C levels) when niacin was used in patients not treated with statins [43]. Unfortunately, niacin can worsen glucose metabolism (contributing to hyperglycemia or new onset diabetes mellitus), and can cause possible side effects (e.g., skin flushing, or liver damage) [44, 45].

In addition, it should be highlighted that the low levels of LDL-C and TGs of the enrolled participants in both the ACCORD and the HPS-2 trials, significantly reduced the impact of these trials on decision-making in the clinical setting. However, the extension of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) - the ACCORDION (a large, prospective, observational follow-up study of participants who were treated and followed in the ACCORD study) trial - has shown benefits of using the statin and fibrate combination in diabetic patient population. Furthermore, the reported heterogeneity of treatment response (by baseline lipid fractions) may indicate that the treatment with fibrates could reduce the CVD incidence among patients with T2DM and concurrent hypertriglyceridemia and low level of HDL-C. Also, it should be kept in mind that a dedicated study, fo-

**Table 3. Major randomized controlled trials (RCTs) on fibrates and their outcomes.**

Name of the Trial (RCT)	Primary Endpoint (Outcome)	Therapy	Sample Size (n)	Follow-up (Years)
ACCORD [35] Action to Control Cardiovascular Risk in Diabetes (Lipid)	Nonfatal MI, or stroke, death from CV cause	Fenofibrate vs. placebo (Simvastatin background)	5518	5
FIELD [36] Fenofibrate Intervention and Event Lowering in Diabetes	CV event rates	Fenofibrate vs. placebo	9795	5
VA-HIT [37] Veterans Affairs High-density lipoprotein Intervention Trial	CV events	Gemfibrozil vs. placebo	2531	5
BIP [38] Bezafibrate Infarction Prevention	Mortality	Bezafibrate vs. placebo	3090	6
HHS [39] Helsinki Heart Study	CV risk	Gemfibrozil vs. placebo	6126	5

Outcomes (reduction of CV events) of the ACCORD, FIELD, VA-HIT, BIP, HHS trials were most beneficial in patient subgroups with TG above 204 mg/dl and HDL-C below 34 mg/dl, on fibrate therapy [35-39].

Abbreviations: CV, cardiovascular; HDL-C, high density lipoprotein-cholesterol; MI, myocardial infarction; mg/dl, milligram/deciliter, TG, triglycerides.

cused on fibrate therapy, in such a patient population would be necessary to confirm these preliminary results.

Recently, it has been reported that ezetimibe (a cholesterol-absorption-inhibitor), when added to statin therapy, resulted in incremental lowering of LDL-C levels, and improved CV outcomes. Moreover, a simvastatin-ezetimibe combination therapy has shown some positive effects on lowering TG levels, and decreasing the risk of CV events, as illustrated by the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) trial [46]. Similarly, a combination of ezetimibe with atorvastatin, has revealed beneficial effects on the coronary plaque regression (compared to monotherapy with a statin), as reflected by the findings from the PRECISE-IVUS (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial [47]. Nevertheless, it should be underscored that even high intensity statins do not sufficiently lower high TG levels. For instance, a recent study by Schwartz *G et al.* supports the predictive role of TG levels among patients with Acute Coronary Syndromes (ACSs), who were treated with baseline statins. Despite the effective therapy with statins, fasting TG levels turned out to be useful in predicting both short-term and long-term CV risk. Furthermore, TG-rich lipoproteins could be an additional therapeutic target, especially for patients with CHD, who suffered from prior ACSs. Hopefully, on-going or future clinical trials will elucidate the relationship of fasting TG levels with CV risk and outcomes after ACS, among patients using statins.

## 8. THE NEWEST CLINICAL TRIALS EVALUATING THE EFFECTS OF OMEGA-3 FATTY ACIDS ON HIGH TG AND CV OUTCOMES

Although, statins and fibrates are usually well tolerated, some patients might experience their adverse effects, of different severity, due to various factors [2, 40]. In case of patients with hypertriglyceridemia or mixed hyperlipidemia, who cannot take statins or fibrates, a therapy with omega-3 fatty acids should be considered. One such therapeutic intervention was examined in the Japan EPA Lipid Intervention Study (JELIS) [48]. According to the data from JELIS, the use of an omega-3 fatty acids preparation (icosapentaenoic acid (EPA) 1.8 g/day), in combination with a statin therapy, resulted in 19% reduction in CV death, MI, and cardiac revascularization procedures, as well as in beneficial modification of lipid levels (*e.g.*, decrease of TG, and increase of HDL-C levels) compared with the statin therapy alone [48]. Until now, no specifically designed clinical outcome trial, focused on primary hypertriglyceridemic patient population, was conducted. Hopefully, two pioneering trials: STRENGTH (Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia) and REDUCE IT (Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia) that are now in progress will provide some new evidence related to decreasing CVD risk among patients with hypertriglyceridemia [49, 50]. The STRENGTH trial addresses a common clinical scenario, concerning patients with elevated TG levels and high CV risk, and investigates whether or not the implementation of omega-3 fatty acids will be beneficial for them. The STRENGTH trial enrolls patients with TG levels from 200

to 500 mg/dL, who are taking a statin, despite having LDL-C levels below 100 mg/dL. The participants are randomized to receive a prescription strength omega-3 fatty acid product, Epanova (the combination of an EPA/DHA), or the comparator, which is a corn oil based product. The study endpoints, including CVD outcomes will be examined [49]. The REDUCE IT study uses a concentrated EPA product (AMR101, 4 g/day), and focuses on the hypertriglyceridemic patient population, receiving a standardized treatment with statins. This trial is going to determine whether the patients, who have established CVD or high CV risk might benefit from taking the AMR101 (compared with placebo), with regard to preventing the occurrence of their first major CV event [50].

## 9. THE IMPACT OF PHARMACEUTICAL CARE (PC) INTERVENTIONS IN PATIENTS WITH DYSLIPIDEMIA AND HIGH CVD RISK ON THERAPEUTIC OUTCOMES, IN LIGHT OF RCT EVIDENCE

In order to successfully translate both nonpharmacological and pharmacological approaches, based on the best-available RCT evidence, into a daily management of numerous, often asymptomatic patients with hypertriglyceridemia and high CV risk, it is crucial to create a common path for physicians and pharmacists, who constantly communicate with their patients within a diagnostic and therapeutic spectrum of care. The collaboration between physicians and pharmacists can improve treatment outcomes, as supported by evidence from several research studies in the pharmaceutical care (PC) field. Some trials, exemplifying practical implications for the patient management are presented below [51-54]. In the IMPROVE study, the impact of a PC intervention, provided by pharmacists, in the ambulatory setting, on clinical and economic outcomes of over 400 older patients with dyslipidemia and high risk of drug-related problems (DRP), randomized between the intervention and the control group), was examined [51]. Approximately 70% of patients from both groups required secondary CV prevention, based on the NCEP ATP III guidelines. In addition to the routine medical care, rendered for both groups, the pharmacists were in charge of providing PC (a consultation) for patients in the intervention group, while the control group did not receive PC. The results of this study have revealed that the beneficial changes in TC and LDL-C levels were significantly higher in the intervention than in the control group [51]. The findings of this trial suggest that the community pharmacists can significantly improve dyslipidemia management, in the setting designed to consult elderly patients with complex medical conditions, requiring multiple medication therapy. It should be pointed out that the medication utilization review, conducted by the pharmacists during PC consultations, especially for older patients with multimorbidity, polypharmacy, and coexistent DRPs, requires a good cooperation between physicians, pharmacists, and patients, as well as well-organized healthcare facilities, with access to necessary medical records. The Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP) that enrolled 675 patients demonstrated an advantage of the community-based intervention PC program, in which the pharmacists were involved in close collaboration with both patients and physicians [52]. In this RCT, patients were ran-

domized to PC intervention (that included educational session, brochure on CV risk factors, referral to a physician, lipid panel measurement, and regular follow-up visits for 4 months), versus usual care (that included the same brochure, and minimal follow-up) [52]. According to the results of SCRIIP, the lipid management, among high CV risk patients (with CHD or T2DM with another CV risk factor), who received the described PC intervention, was significantly improved. It appears that the concise suggestions written by the pharmacists, and then conveyed to the participating primary care physicians, who in turn, translated them into diagnostic and therapeutic actions, were main contributors to overall success of this study [52]. This trial reflects the beneficial effects of the PC program, conducted in the community pharmacy that represents the “real-world” setting, interrelated with medical practice, on the dyslipidemia management, among patients with high risk for CV events. Similarly, the effectiveness of PC management program, provided by clinical pharmacists for patients with dyslipidemia, was assessed in a retrospective cohort study, conducted in two primary care clinics, where an intervention (IT) cohort (213 patients) had the dyslipidemia management provided by clinical pharmacists, and a control cohort (219 patients) received the usual care (UC) only. In this study, medical records relevant to pharmacotherapy, laboratory lipid profiles, and patient demographic and clinical characteristics were examined [53]. A comparison of mean values of the LDL-C, TC, HDL-C, and TG, in both groups, during the final follow-up visit was analyzed. In addition, the proportion of patients attaining the NCEP ATPIII LDL-C goals, and the time periods to achieve these LDL-C goals, were compared between the two groups. The results of this study have revealed that the patients referred to the clinical pharmacists for PC service, focused on treatment of dyslipidemia, achieved significant decreases in their TC and LDL-C levels [53]. Also, a greater proportion of patients achieved the NCEP ATPIII targets for LDL-C, and the time period to attainment of the LDL-C goals was shorter in the pharmacist-managed group. These results clearly support a valuable contribution of PC to the effective management of patients with dyslipidemia [53]. Furthermore, a PC program designed for patients with lipid disorders, in the community pharmacy setting, which offers patient education, focused on compliance with medications use and lifestyle modifications, with emphasis on attaining the lipid target levels, was conducted [54]. Out-patients participating in this 4-month study, were randomly selected to the PC intervention or control group. The patients in the intervention group were interviewed by the pharmacists more often, and in more comprehensive manner than the ones in the control group. In both groups, the measurements of: TC, TG, glucose levels, and body weight, as well as CV risk factors, DRPs, and quality of life scores were assessed at the beginning of the study, and then in regular intervals, until the study's conclusion. The findings of this trial indicate that even the short-term PC programs, implemented in a community pharmacy, which is properly equipped to deliver such a service, can contribute to the improvement of lipid profiles, reduction of CV risk factors, and better quality of life of the patients [54]. Also, from a patient-compliance point of view, the pharmacists can convey or reinforce an important, practical advice that the administration of fibrates in the morning, and short-duration statins at the bedtime would significantly

reduce the number and severity of possible adverse effects, due to the combination therapy.

In health care systems, in which PC services are not formally established, on-going close cooperation of physicians and pharmacists, involved in the management of patients with lipid disorders can positively impact the patient adherence to treatment and clinical outcomes.

## **10. PREVENTION IS THE KEY - RESULTS FROM MAJOR RCT, AND THEIR IMPLICATIONS FOR PATIENTS WITH HIGH TG LEVELS AND CVD RISK**

Unquestionably, the implementation of nutritional modifications and regular physical exercise into a daily routine of the hypertriglyceridemic patients is a big challenge. Nevertheless, these modalities represent necessary, initial steps toward prevention of CVD [2, 18, 55]. Therefore, it is desirable that the physicians, pharmacists, dietitians, and physical therapists would continuously support their patients in making these efforts. There is a substantial body of research on cardiometabolic diseases and their risk factors, revealing some remarkable effects of lifestyle interventions on various CV markers [19, 55-58]. Apparently, many of these strategies can also be, to some degree, adopted in patients with hypertriglyceridemia, to successfully manage their lipid disorders, and the relevant CVD risk. In the Diabetes Prevention Program (DPP), the patients with IR, who had a high risk of developing diabetes were randomized to either pharmacotherapy with metformin, or lifestyle change, including weight loss and physical activity interventions. The DPP results have shown that the lifestyle modifications reduced the risk of developing diabetes to a much greater extent than did pharmacotherapy [56]. Moreover, the DPP findings were consistent with a significant reduction in TG levels, as a result of non-pharmacologic interventions, including diet, exercise, and weight loss program. Therefore, the DPP has strong practical implications for the effective reduction of high TG levels, and associated CV risk, via an early introduction, and then systematic continuation of therapeutic lifestyle changes, in order to maintain the recommended TG levels in the long run [57]. Some common misconceptions with regard to very low-fat diets are primarily related to consuming excessive amounts of carbohydrates that contribute to the significantly increased caloric intake that in turn can perpetuate hypertriglyceridemia [2]. Instead, the best approach is to decrease the total caloric intake (especially from high glycemic index and load carbohydrates), to reduce the amount of saturated fat, and to eliminate trans-fats (as much as possible) [2]. It has been established that the combination of the dietary modifications, physical activity, and weight loss contributes to successful reduction of elevated TG levels [2]. Consequently, the patients should always be encouraged by their practitioners to restrict highly processed fast food, and sweetened beverages intake, and incorporate nutrition that are high in monounsaturated and polyunsaturated fatty acids, rich in vegetables, fruits and grains [2, 18, 58-60]. Simultaneously, patients need to introduce into their daily schedule a moderate intensity physical activity. It should be kept in mind that the “best exercise” practically means the one that the patient likes, and will perform on a regular basis. This will also ensure a successful long-term weight maintenance. Although implementation of lifestyle interventions

will require coordinated efforts by medical practitioners and patients, they are absolutely necessary as the first step to reduction of hypertriglyceridemia, and impending CVD risk [2, 55]. The next step in this direction consists of pharmacotherapy with on-going monitoring of the therapeutic outcomes.

## 11. LEARNING POINTS

1. Hypertriglyceridemia signalizes an increased number of small dense LDL (sd LDL) particles that are highly atherogenic, and predictive of high risk of CV events.
2. Patients with hypertriglyceridemia should always be evaluated for common secondary causes of dyslipidemia (*e.g.*: hypothyroidism, chronic kidney disease, autoimmune disorders, and HIV infection). In case of suspected primary hypertriglyceridemia, the patients need to be evaluated for genetic predispositions to dyslipidemia and CVD.
3. Review of medications, focused on pharmacotherapy-induced dyslipidemia (*e.g.*: nonselective beta-blockers, thiazide diuretics, corticosteroids, estrogens, tamoxifen, raloxifene, protease inhibitors, retinoic acid, phenothiazines, antipsychotics, and immunosuppressants) should be conducted, and the most appropriate therapeutic and dietary regimen should be established.
4. Measurements of non-HDL-C and TG/HDL-C represent simple tools that are particularly useful in the assessment of patients with atherogenic dyslipidemia, characteristic for central obesity, insulin resistance, metabolic syndrome, pre-diabetes, and T2DM, as conditions associated with elevated CVD risk.
5. Treatment of hypertriglyceridemia, including statins, fibrates, and omega-3 fatty acids needs to be selected, based on the safety and effectiveness of lipid-modifying medications, in the context of each individual patient.

## CONCLUSION

Hypertriglyceridemia, as an important component of atherogenic dyslipidemia, and CVD risk factor (associated with central obesity, metabolic syndrome, diabetes mellitus, insulin resistance, and hypothyroidism) that should be carefully evaluated and managed, via lifestyle modification and pharmacotherapy. Although, statins are a basis of the contemporary lipid-modifying treatment, the major RCTs on fibrates support the therapy with fibrates that is most beneficial in patients with TG levels above 204 mg/dl and HDL-C below 34 mg/dl. Since statins, fibrates, and omega-3 fatty acids regulate serum lipids concentration by different mechanisms of action, a combined therapy, based on the effectiveness and safety of chosen medications, as well as on the individual patient factors is most useful in achieving a comprehensive control of dyslipidemia, and CV risk reduction. An implementation of the new ACC/AHA guidelines into a daily practice remains challenging, and medical practitioners should remember that these recommendations are not a replacement for clinical judgment. Furthermore, a personalized, patient-centered strategies to mitigate CVD risk

should further improve adherence to treatment and medical outcomes. For this purpose, a close cooperation between physicians and pharmacists, focused not only on the treatment, but also on the patient engagement in monitoring of the therapy effects plays an essential role in the lipid-modifying therapeutic process. Hopefully, further outcome trials will provide more implications for medical practice, to stem the tide of hypertriglyceridemia and CVD.

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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