Korean Circ J. 2018 Dec;48(12):1097-1119
https://doi.org/10.4070/kcj.2018.0343
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Review Article

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Triglyceride-Rich Lipoproteins and Novel Targets for Anti-atherosclerotic Therapy

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OPEN ACCESS

Received: Oct 1, 2018
Accepted: Oct 22, 2018

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Conflict of Interest
The author has received honoraria from Sanofi Aventis and Akcea.

ABSTRACT

Although elevated serum low-density lipoprotein-cholesterol (LDL-C) is without any doubts accepted as an important risk factor for cardiovascular disease (CVD), the role of elevated triglycerides (TGs)-rich lipoproteins as an independent risk factor has until recently been quite controversial. Recent data strongly suggest that elevated TG-rich lipoproteins are an independent risk factor for CVD and that therapeutic targeting of them could possibly provide further benefit in reducing CVD morbidity, events and mortality, apart from LDL-C lowering. Today elevated TGs are treated with lifestyle interventions, and with fibrates which could be combined with omega-3 fatty acids. There are also some new drugs. Volanesorsen, is an antisense oligonucleotid that inhibits the production of the Apo C-III which is crucial in regulating TGs metabolism because it inhibits lipoprotein lipase (LPL) and hepatic lipase activity but also hepatic uptake of TGs-rich particles. Evinacumab is a monoclonal antibody against angiopoietin-like protein 3 (ANGPTL3) and it seems that it can substantially lower elevated TGs levels because ANGPTL3 also regulates TGs metabolism. Pemafibrate is a selective peroxisome proliferator-activated receptor alpha modulator which also decreases TGs, and improves other lipid parameters. It seems that it also has some other possible antiatherogenic effects. Alipogene tiparvovec is a nonreplicating adeno-associated viral vector that delivers copies of the LPL gene to muscle tissue which accelerates the clearance of TG-rich lipoproteins thus decreasing extremely high TGs levels. Pradigastat is a novel diacylglycerol acyltransferase 1 inhibitor which substantially reduces extremely high TGs levels and appears to be promising in treatment of the rare familial chylomicronemia syndrome.

Keywords: Triglycerides; Cardiovascular diseases; Fibrates; Omega-3 fatty acids; Volanesorsen

INTRODUCTION

It is well known that elevated serum concentration of low density lipoproteins (LDLs), which are lipoprotein particles carrying most of the total circulating cholesterol, and their main lipid component low-density lipoprotein-cholesterol (LDL-C), are a well-known risk factor for atherosclerotic cardiovascular disease (CVD), particularly for coronary heart disease (CHD). It is also generally accepted that both primary and secondary prevention of CVD by decreasing elevated LDL-C can decrease CVD morbidity, CVD events and mortality.[1)2)] This is especially true when serum levels of LDL-C are extremely elevated which occurs in

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patients with familial hypercholesterolemia, either homozygotes or severe heterozygotes.[3-6] Nevertheless, elevated LDL-C (of course apart from arterial hypertension, cigarette smoking, central obesity etc.) cannot explain all CVD events. Among other lipoprotein risk factors triglyceride (TG)-rich lipoproteins are repeatedly and extensively investigated as a possible independent risk factor for CVD. When discussing the importance of TG-rich lipoprotein particles, it has to be mentioned that hypertriglyceridemia is commonly accepted to be fasting TGs serum level ≥1.7 mmol/L (≥150 mg/dL).[7][8]

The aim of this paper is to critically appraise the current evidence relating to elevated TG-rich lipoproteins as a risk factor for CVD and to consider possible therapeutic strategies for their management.

METABOLISM OF TRIGLYCERIDE-RICH LIPOPROTEINS

TG-rich lipoprotein particles contain exogenous and endogenous TGs and represent the transport module for fatty acids which provide an essential source of energy upon oxidation in mitochondria. A major source of TGs is derived from dietary fat consumption. Dietary TGs are absorbed by enterocytes in which they combine with apolipoprotein (Apo) B48 to form the largest lipoprotein particles – chylomicrons. They are 80–95% built of TGs. Chylomicrons are transported first via perimesenteric lymphatic vessels and then enter the blood circulation via ductus thoracicus. By moving through circulation chylomicrons acquire Apo C-II, Apo C-III, and Apo E. Heart is the first organ for delivery of fatty acids from TG-rich particles to fulfil energy requirements.

It has to be stressed that neither TG-rich lipoproteins nor TGs cannot pass through cell membranes, including those of endothelial cells. Therefore, intravascular lipolysis is a necessary process for release of free fatty acids (FFAs). Chylomicrons and other TG-rich particles are hydrolysed by lipoprotein lipase (LPL) along the luminal surface of capillaries. LPL is synthesized mostly in macrophages but also parenchymal cells, particularly those of the heart, adipose tissue and skeletal muscle. Then, it is transported to the endothelial cells surface and secreted into the vasculature of these tissues where it binds to glycosylphosphatidylinositol high-density lipoprotein (HDL) binding protein 1 (GPIHBP1).[9-11] Lipase maturation factor 1 (LMF1) is necessary for the secretion of LPL from the cells and it's absence causes severely elevated plasma TG levels.[12]

LPL requires activation with Apo C-II, and its activity is highly regulated by various proteins, including Apo C-III, Apo A-V, and angiopoietin-like proteins 3 and 4 but also 8 (ANGPTL3, 4, and 8).[13][14] It is important to mention that ANGPTL3 and 4 are well recognized as inhibitors of LPL.[15] Apo C-II is a 79 amino acid peptide containing 3 amphipathic α-helices which is synthetized in hepatic cells. The lipid-binding domain of Apo C-II is located in the N-terminal, whereas the C-terminal helix of Apo C-II is responsible for the interaction with LPL. Apo C-II circulates in blood on TG-rich lipoprotein particles but also on HDL particles and is the rate-limiting protein required for normal LPL activity. One of the possible roles of Apo C-II may be to influence binding TG-rich particles to the active site of LPL at the endothelial surface.

LPL is also regulated at the level of transcription by both peroxisome proliferator-activated receptor (PPAR) α and PPARγ through binding to a peroxisome proliferator response element

https://doi.org/10.4070/kcj.2018.0343

(PPRE) in the 5′-regulatory region of the LPL gene.[16][17] PPARα is involved in lipid metabolism in the liver cells, while PPARγ is more involved in adipose tissue lipid homeostasis, thereby regulating LPL action. LPL gene single nucleotide polymorphisms (SNPs) are associated with TG concentrations but the functionality of many of these SNPs remains poorly understood. Relatively recently, it has been shown that different microRNAs (miR-29, miR-1277 and miR-410) might be important for posttranslational regulation of LPL. However, their exact mechanism(s) has not as yet been elucidated. FFAs which are result of LPL activity are then oxidized by a variety of cell types, such as skeletal and myocardial myocytes, or are resynthetized together with glycerol in TGs and in this form stored in adipose tissue.[18] On the other hand, the chylomicron remnants, which are rich in cholesterol esters and Apo E, are removed from circulation by binding to the LDL receptors or the LDL receptor-related proteins on the liver cells. LMF1 is a gene product that regulates TGs metabolism influencing LPL and hepatic lipase (HL).

The liver plays a central role in TGs homeostasis and maintains a steady state between TGs synthesis, secretion and oxidation. In contrast to adipose tissue, the liver cells do not store TGs under normal physiologic conditions. They can take up FFAs derived from lipolysis in adipose tissue or from circulating lipoproteins but may equally synthesize fatty acids from carbohydrates in the process of de novo lipogenesis. In the liver cells, fatty acids can be partly stored as TGs (particularly in some conditions in lipid droplets - fatty liver) or oxidised to generate energy in mitochondria in the process of beta-oxidation. They can also be packaged together with glycerol in Apo B100-containing very low-density lipoprotein (VLDL) particles which are secreted into the systemic circulation where they serve as a source for energy for peripheral tissues. Glycerol-3-phosphate dehydrogenase 1 (GPD1) is needed for TGs synthesis. Apo C-I, Apo C-II, Apo C-III, and Apo E are added to the surface of VLDL particles during their secretion from liver cells. The molecular pathway involved in the packaging of TGs into both chylomicrons and VLDL particles is remarkably similar, involving microsomal triglyceride transfer protein (MTTP) as described in detail elsewhere.[19][20]

Following secretion, VLDL particles are also hydrolyzed by LPL in the plasma, producing progressively smaller VLDL particles and then eventually intermediate-density lipoproteins (IDLs). The size of VLDL particles is important since large VLDL particles and chylomicrons cannot transverse endothelial barrier and thus cannot start the process of atherogenesis.[21] However, smaller VLDL and other TG-rich remnant particles which can influx into artery wall play an important role and might be, if their concentration in plasma is elevated, a risk factor for atherosclerosis and CVD.[22]

As just described, during the above explained process, chylomicrons and VLDL particles are remodelled so that their TGs are hydrolysed by LPL producing TG-rich remnant particles and IDL. The expression “TG-rich lipoprotein remnants” relates to chylomicron and VLDL particles which have undergone dynamic remodelling in the plasma after secretion from the intestine cells (chylomicrons) or liver cells (VLDL).[23]

Some IDL particles are taken up by the liver cells and catabolized in them while some of these particles undergo further catabolism by LPL and hepatic TG lipase to generate LDL particles. VLDL and LDL, but remnant particles as well, acquire additional cholesteryl esters (CEs) in plasma via the action of cholesteryl ester transfer protein (CETP), which exchanges TGs in them for CE in HDL. HDL particles have the main role to mediate reverse cholesterol transport to the liver. When TGs levels are high, CETP-mediated transfer of TGs from

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chylomycrons and VLDL to LDL and HDL in exchange for CE from LDL and HDL leads to TG-enriched VLDL remnants, IDL and small LDL particles. Remnant particles are atherogenic primarily as a result of their progressive enrichment with cholesterol during the above described process and they are linked to the development and progression of CVD.[24-26] It has been also shown that that small dense LDL particles are highly atherogenic.[27]

WHAT CAN CAUSE ELEVATED CONCENTRATIONS OF TRIGLYCERIDE-RICH PARTICLES?

In many patients mild-to-moderate elevated plasma TGs levels are a result of unhealthy diet and unhealthy lifestyle, e.g. alcohol overuse. This can also occur due to hypothyroidism, pregnancy, hepatosteatosis, weight regain after significant weight loss, nephrotic syndrome and some medicines (glucocorticoids, older types of oral estrogens, etc.). Nevertheless, most often such elevated levels of TGs occur as a part of the metabolic syndrome and/or type 2 diabetes (T2D).

Autosomal recessive monogenic severe hypertriglyceridemia is rare. It can result from large-effect mutations in six different genes either homozygous or heterozygous in combination with other lesser genes.[28] Two most important forms of genetically elevated TGs are familial combined hyperlipidemia (FCHL) and familial hypertriglyceridemia (FHTG). FCHL was first described 45 years ago in families of survivors of MI who presented with variable lipid disturbances.[29] Some of these patients have predominantly elevated plasma total and LDL-C and much less elevated TGs, some have elevated TGs alone or predominantly elevated TGs and just slightly elevated LDL-C, but most of these patients have elevated both lipids. FCHL is characterized by elevated not only TGs levels but also elevated Apo B and an increased number of very atherogenic small dense LDL particles but the phenotype of the disease may vary even among members from the same family.[30] This lipid disturbance is similar to the one that occurs in metabolic syndrome and/or T2D. These lipoprotein changes occur as a result of overproduction of VLDL particles in liver cells due to an increased Apo B synthesis in the setting of disordered adipose metabolism, insulin resistance and accumulation of fat in the liver cells, but also due to an impaired clearance of Apo B containing particles.[31] Long residence time of VLDL particles in the circulation favors the formation of very atherogenic small dense LDL particles. FCHL is a multigenic disease with insulin resistance in the background. No single genes have been identified or confirmed so far to be the cause of it.

FHTG is also an inherited disease. It occurs because of an increased TGs synthesis, where normal numbers of very large TG-enriched VLDL particles are secreted.[31] Patients have elevated VLDL levels, but kept normal levels of LDL-C and high-density lipoprotein-cholesterol (HDL-C). Therefore, patients are generally asymptomatic unless extremely elevated levels of TGs cause acute pancreatitis, which is often. FHTG is an extremely rare lipoprotein disorder caused by mutations in at least 5 genes of the LPL complex. Most recently 5 novel pathogenic mutations have been identified: 2 in LPL, 1 in GPIHBP1, and 2 in the APOA5 gene but the possibility of involvement of new genes in the manifestation of this disease cannot be excluded.[32] Extremely elevated levels of TGs cause often acute pancreatitis. Recently it has been developed a pragmatic clinical scoring, by standardizing diagnosis, which may help differentiate FHTG from multifactorial chylomicronemia syndrome (MCS), which may alleviate the need for systematic genotyping in patients with severely elevated TGs and may help identify high-priority candidates for genotyping.[33]

https://doi.org/10.4070/kcj.2018.0343

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Familial dysbetalipoproteinemia (type III hyperlipoproteinemia or remnant removal disease) is a rare disease as well. Most patients are homozygous for the E2-isoform of Apo E which is important for hepatic clearance of chylomicron TG-rich remnant particles and IDL.[34] Patients often develop a characteristic clinical syndrome in which both total cholesterol and TGs are extremely elevated, usually both in the range of 7–10 mmol/L with an increased risk of CVD but it seems that a multigenic background is needed to convert E2/2 to type III hyperlipoproteinemia.

As mentioned earlier, elevation of TGs levels could be also caused by polygenic effect of multiple genes influencing both VLDL production and removal. So far rare mutations in 6 genes (LPL, APO C2, APO A5, LMF1, GPIHBP1, and GPD1) with monogenic effect have been recognized. They lead from mild up to very severe elevation of serum TGs due to the disruption of the chylomicron removal pathways. Extremely high TGs occur in patients who are homozygous or compound heterozygotes for mutations of the LPL and in the other genes linked to catabolism of TGs rich lipoproteins. Gain of function mutation in APO C-III leading to high Apo C-III levels can also cause severely elevated plasma TGs.[35] Apo C-III exerts its atherogenic action by attenuating lipolysis of TG-rich particles through LPL inhibition that results in increased circulating levels of VLDL and chylomicrons.[36] Elevated levels of Apo C-III are present in patients with very high plasma TGs and have been causally associated with metabolic syndrome and insulin resistance.[37]

Apo A-V also plays a role in stabilizing the lipoprotein–enzyme complex thereby enhancing lipolysis. Therefore, defective or absent Apo A-V can result in reduced efficiency of LPL-mediated lipolysis and, subsequently increased number of TG-rich particles. A number of genes involved in TGs metabolism do have a pleiotropic nature and are also Apo B genes, so the metabolism of TG-rich particles and Apo B lipoprotein particles is closely related. For example, PCSK9 markedly increases intestinal TGs-rich Apo B containing particles production through mechanisms mediated in part by transcriptional effects on Apo B, microsomal TG transfer protein, and lipogenic genes and in part by posttranscriptional effects on the LDL receptor and microsomal TG transfer protein.

Genome-wide association studies (GWAS) of patients with elevated TGs revealed that common variants in Apo A-V, glucokinase regulator (GCKR) which plays an important roles in the regulation of glucokinase (GK) activity and the metabolism of glucose and lipids, LPL and Apo B genes were associated with the elevated TGs at genome-wide significance and rare variants in these four genes explained 1.1% of total variation in patients with elevated TGs.[38]

WHY ARE ELEVATED TRIGLYCERIDE-RICH LIPOPROTEINS A RISK FACTOR FOR CARDIOVASCULAR DISEASE?

Severely elevated TGs, defined by the 2014 National Lipid Association guidelines as a TGs level of ≥500 mg/dL (≥5.6 mmol/L), are not only connected with higher CVD risk but are a well-established risk factor for acute pancreatitis which can be a life-threatening disease.[39][40] Moderately elevated TGs are supposed to be a risk factor for CVD as well, even in patients treated effectively with statins to reduce LDL-C.[41][42] This has been confirmed in a most recent study the results of which have shown that despite well controlled LDL-C levels with statins,

https://doi.org/10.4070/kcj.2018.0343

CVD events were greater among patients with diabetes and elevated TGs levels. Since in this study the patients were controlled for all other cardiometabolic risk factors, it might be concluded that the difference in TGs levels contributed to the excess CVD risk observed in patients with elevated TGs.[43]

Epidemiological studies

The traditional view has been that, while elevated concentration of TG-rich particles may be associated with increased CVD risk, the association is weakened when adjustment is made for other risk factors, particularly HDL-C.[44] Indeed, elevated TGs are often accompanied with low HDL-C levels. Many studies have looked whether elevated TGs and/or decreased HDL-C are responsible for increasing the risk of CVD. For instance, one of them was published most recently indicating that 25% of 1,720 apparently healthy 50-year-old men with the highest TG/HDL-C plasma concentration ratio developed more CVD over the next 40 years, compared with those not meeting the point which was the highest quartile >1.8 mmol/L.[45] However, even after the adjustment for HDL-C, elevated TGs remained a risk factor for CVD and it was established that TGs levels and small dense LDL particles could be caused by two different genetic loci in FHTG.[46] Issues regarding the relevance of HDL-C concentration for CVD have been raised and today most authors consider not the low concentration but the disturbed functionality of HDL particles are important for CVD. Nevertheless, firm validated data for HDL particles functionality are still lacking.[23] The nature of the association between elevated plasma levels of TG-rich particles and CVD remains still to a certain extent controversial and the understanding was for long time that if TGs are at all associated with CVD, the relationship is clearly not a linear one as it is with total cholesterol or LDL-C. Elevated levels of TGs-rich particles are commonly associated with diabetes and/or metabolic syndrome.[47] The general view was that correlation with these and other risk factors including low HDL-C, smoking, overweight/obesity and hypertension could explain the association with CVD, apart from elevated LDL-C levels. This was and still is a problem because many authors have attributed the effects of co called "atherogenic dyslipidemia" characterized by elevated TGs, low HDL-C and increased number of small dense LDL particles primarily to other lipid components and not so much to elevated plasma levels of TG-rich particles.[23]

Still, evidence for a role of TGs as an independent risk factor accumulated during last 30 years.[48] An early meta-analysis of 6 studies reported univariable relative risks (RRs) for CHD of 1.32 and 1.76 per 1 mmol/L increase in TGs for men and women respectively. These RRs attenuated on multivariable adjustment to 1.14 and 1.37, but remained statistically significant.[49] A much larger meta-analysis involving a total of 10,158 incident CHD cases from 262,525 participants in 29 studies showed that moderately strong associations exist between TGs concentrations and CHD risk.[50] However, there were studies which reported loss of statistical significance after correction for other risk factors such as diabetes, body mass index, glucose, hypertension, and smoking. In spite of this, the results of these studies also suggested that even slightly elevated TGs levels are associated with a higher risk of recurrence of CVD events in statin-treated patients and should be considered a useful marker of risk.[51]

An analysis based upon the Chinese Multi-provincial Cohort Study in which 30,378 participants were followed for 15 years showed that higher TGs predicted CHD and lower HDL-C predicted ischemic stroke only in patients with low LDL-C levels.[52] This implies that active management of disturbed other lipid fractions, including TGs, is of particular importance in those subjects who do not have simultaneously also elevated LDL-C.

https://doi.org/10.4070/kcj.2018.0343

Accumulating evidence from epidemiological and genetic evidence supporting elevated plasma levels of remnant particles, or TG-rich lipoproteins as an additional cause of CVD has driven in recent years renewed interest in this type of dyslipidemia.[53] Therefore, today it is generally considered that elevated levels of TGs-rich lipoproteins, associated with atherogenic dyslipidemia, are one of the major contributors to lipid-related CVD risk.[1][47][54]

This was confirmed by an analysis based upon a very large cohort of 86,476 Korean subjects who had undergone a general health checkup at Asan Medical Center between January 2007 and June 2011 and in which CVD events and death were gathered from the nationwide health insurance claims database and death certificates using International Classification of Diseases-10 codes. The results of this survey suggest that elevated TGs are indeed independently associated with an increased risk for CVD, for major CVD events, major ischemic heart disease events, and overall CVD events even after adjustment for multiple risk factors including HDL-C. This was especially so in non-obese, normotensive, or non-diabetic subjects.[55] At about the same time the results of Circulatory Risk in Communities Study also showed that non-fasting TGs are predictive of risk of ischemic CVD in Japanese subjects of both sexes.[56] These results are similar to the results obtained on European populations showing that high TGs, even in subjects with favorable HDL-C levels, may identify a subset of subjects who have an increased risk for CVD.[57] It has also been shown that in patients with proven CHD, higher TGs are independently associated with increased 22-year all-cause mortality. Even in patients with relatively low TGs of 100 to 149 mg/dL (up to 1.13–up to 1.7 mmol/L), the increased risk for death could be detected than in patients with higher TGs levels. Above this, differently from what was considered for several decades, the 22-year mortality risk for patients with severely elevated TGs was significantly increased by 68% when compared with patients with low-normal TGs (<100 mg/dL or up to 1.13 mmol/L).[40]

Nevertheless, the results of Emerging Risk Factors Collaboration meta-analysis suggested that the association between TGs and CVD risk was abolished when adjustment was made for HDL-C, non-HDL-C and other lipids.[58] The results of this study were the main reason why for a number of years TGs were not much investigated as the possible causative risk factor of CVD and their role was quite neglected. On the other hand, more recent data from the same group were totally different – they strongly favor the causal association between TG-mediated pathways and CHD.[59] A meta-analysis of 17 prospective studies with 2,900 CHD endpoints revealed that an increment of 1 mmol/L in fasting TG levels was associated with a 14% increase in CVD risk.[49]

An important study published 2 years ago was the first one to show that lower plasma levels of TGs were associated with plaque regression across broad categories of CVD risk.[60]

On the other side, recently there is an increased interest in triglyceride-rich lipoprotein cholesterol (TRL-C). So in a post-hoc analysis from TNT trial it has been shown that increased TRL-C levels were associated with an increased CVD risk and provided evidence for the CVD benefit of lipid-lowering with statins among CHD patients with high TRL-C.[61] Also, it has been shown that increased levels of remnant-like particle cholesterol (RLP-C) and triglycerides in low-density lipoprotein (LDL-TG) were predictive of CVD and associated with Apo E variants. These authors have concluded that LDL-TG may represent a marker of dysfunctional remnant lipoprotein metabolism associated with increased CVD risk.[62]

https://doi.org/10.4070/kcj.2018.0343

Genetic studies

A support for a causative role of TG-rich lipoproteins in CVD arises from genetic studies. These studies equally indicate that remnant particles, which represent the partially degraded products of TG-rich lipoprotein particles (i.e. chylomicrons and VLDL), play a key role in the pathophysiology of atherosclerotic CVD.[59][63-65]

Genetic studies have showed already several years ago that elevated TGs are causal factor for CVD.[64] A Mendelian randomization study published a year later (which is a method of using measured variation in genes of known function to examine the causal effect of a modifiable exposure on disease in non-experimental studies), based on data from the Copenhagen City Heart Study found that individuals with genetically confirmed reduction in non-fasting plasma TGs had reduced all-cause mortality.[66] The idea of this study was to test whether low concentrations of non-fasting TGs were associated with reduced all-cause mortality in observational analyses (n=13,957) and whether genetic variants in the TG-degrading enzyme LPL, resulting in reduced nonfasting TGs and remnant cholesterol, were associated with reduced all-cause mortality (n=10,208). Indeed, a plethora of epidemiological evidence exists (some of them were mentioned earlier in this text), demonstrating that both fasting and nonfasting TGs levels are significant predictors of CVD events, even in individuals who have already achieved recommended LDL-C levels with lipid-lowering therapy.[67][68]

The results of another Mendelian randomization study using multiple instrumental variables supported a causal effect of TG-rich particles on CHD risk as well, but a causal role for low HDL-C, though possible, remained less certain.[65]

In the DiscovEHR human genetics study performed on 42,930 subjects of mainly European ancestry, carriers of the E40K variant of ANGPTL4, which is known to be associated with reduced plasma TGs levels and CHD risk, had 13% lower TGs levels than non-carriers. Carriers of E40K and other inactivating mutations in ANGPTL4 had also a 19% lower risk of CHD than did non-carriers suggesting that lower CHD risk is hinted with gene variants linked to lower TGs.[69] Another analysis of 72,868 patients with CHD and 120,770 controls who did not have CHD also showed decreased TGs levels and increased CHD protection in those with vs. without ANGPTL4 mutations.[70] The results of both of these studies also suggested that TGs might play a causal role in the CHD.

LIFESTYLE INTERVENTIONS

Elevated number of plasma TG-rich particles can be reduced by lifestyle interventions much more effectively than elevated LDL-C. The main interventions include reducing excessive body weight, and there are many studies suggesting that weight loss is one of the most important and effective approach to lower the elevated TGs, no matter which method was used to achieve it.[71][72] Crucial is also diet. In diet it is important to reduce the intake of mono- and disaccharides and total abstinence or reducing to minimum alcohol intake.[73] Of course, reducing the amount of carbohydrates, especially sucrose and/or high-fructose corn syrup is very important. Fructose consumption causes hepatic de novo lipogenesis and elevated TGs levels.[74] Although high fructose intake is not advisable for patients with elevated number of TG-rich particles in plasma, surprisingly a recently published meta-analysis showed that high intake of fruit but not vegetables is inversely associated with elevated levels of TGs.[75]

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Higher risk for CHD with increasing sugar-sweetened beverages consumption has been clearly proven but is often forgotten when giving advices to the patients or healthy individuals.[76][77] The explanation might be that high fructose corn syrup, a sweetener used to flavor soft drinks (much more commonly used for this purpose in the US and some other parts of the world than in Europe), increases dietary glycemic load and serum TGs levels, and may increase insulin resistance.[78] However, low-calorie beverages are associated with lower free sugar intake without affecting the intake of other macronutrients or negatively impacting cardiometabolic risk factors.[79] Physical activity (PA) is also essential in decreasing the number of TG-rich particles.[80] For instance Personal Activity Intelligence (PAI), a personalized metric of PA tracking could help in estimating the effects of PA. In a study performed on 3,133 patients with CVD obtaining a weekly PAI score of at least 100 was associated with lower mortality risk from CVD and all causes in individuals with CVD regardless of whether the current PA recommendations were met.[81] On the other hand, it has been shown that prolonged sitting contributes to CVD risk while intermittent resistance activity can mitigate this detrimental effect of prolonged unbroken sitting in overweight and obese adults.[82] Some authors suggest that appropriately tailored exercise regimen for every CVD risk patient should be planed and exercise prescription given to patients with CVD risk factors, including elevated plasma TG-rich particles.[83]

WHICH DRUGS ARE USED TODAY TO DECREASE THE PLASMA CONCENTRATION OF TRIGLYCERIDE-RICH PARTICLES?

While statins are without any doubt effective in lowering elevated LDL-C, evidence from the VOYAGER analysis discussed in Landmark study, show that even with high-dose, high-intensity statin therapy, about 50% of patients with elevated TGs do not reach desirable levels of TGs (<1.7 mmol/L or up to 150 mg/dL).[84] This is quite comprehensible since statins are the drugs which are primarily used to lower elevated LDL-C. It is well known that their effects on lowering elevated TGs are more than modest. However, it has been shown that atorvastatin can significantly lower levels of TG-rich remnant lipoproteins and favorably change LDL particle size (from small dense particles to larger, less atherogenic) when TGs levels are high (Karlson). In spite of all this, a recent meta-analysis showed that statins significantly decrease Apo C-III levels which would indicate a more important role of statins in decreasing elevated plasma levels of TG-rich particles.[85]

On the other hand, fibrates are the drugs of choice for elevated TGs. Their lipid-modifying effects are mediated primarily via interaction with PPARα.[23] The results of monotherapy with fibrates (Helsinki Heart Study), or more precisely with gemfibrozil, which according to its structure is not a fibrate but has a TGs-lowering effect like fibrates, indicated a reduction in nonfatal MI and revascularization, with no effect on stroke or CV death. However, the results of this trial could not prove neither morbidity nor mortality reduction.[86] In FIELD study fenofibrate did not significantly reduce the risk of the primary outcome of coronary events - CHD death or non-fatal MI but it did reduce total cardiovascular (CV) events, mainly due to fewer non-fatal MI and revascularisations.[87] A most recent substudy of FIELD showed that fenofibrate was not associated with improved carotid IMT in adults with T2D when compared with placebo, despite a statistically significant improvement in all lipid parameters, including TGs at 4 months and 2 years.[88] In Veterans Affairs HDL Intervention Trial (VA-HIT), which

https://doi.org/10.4070/kcj.2018.0343

was, as the name says, primarily directed towards increasing HDL-C with gemfibrozil, during the treatment only the increase in HDL-C, but not the decrease of TGs levels, significantly predicted a lower risk of CHD events by multivariable analysis.[89] These results were subsequently confirmed by a meta-analysis published several years later.[90]

Neither the Bezafibrate Infarction Prevention (BIP) study, the large randomized outcomes study dealing with secondary prevention, could prove any significant benefit with bezafibrate in high risk patients for the primary outcome which was a composite of fatal and nonfatal MI plus sudden death.[91]

However, a most recently published meta-analysis which included 13 trials and 16,112 patients showed with a moderate level of evidence a protective effect of the fibrates compared with placebo as regards a compound objective of non-fatal stroke, non-fatal myocardial infarction, and CVD death.[92]

Although fibrates stimulate FA oxidation, suppress FA and TGs synthesis, and reduce plasma TGs or TG-rich lipoprotein levels,[93] different studies showed inconsistent results regarding the effects of PPARα agonists on glucose metabolism.[94][95]

Fibrates are almost never used as monotherapy for CVD prevention but are most often combined with statins. This is stressed in the most recently published position paper in which such a combination is recommended for patients who have elevated TGs plus low HDL-C.[96] The benefit of combination treatment with fenofibrate plus simvastatin in the Action to Control Cardiovascular Risk in Diabetes (ACCORD)[97] lipid study was limited to the subgroup of patients with atherogenic dyslipidemia (elevated TGs and low plasma concentration of HDL-C).[98] Both fibrates and statins are associated with an increased risk of myopathy.[99] However, unlike statin therapy which is not associated with a significant alteration of plasma homocysteine levels, fenofibrate increases the homocysteine levels.[100] Therefore, it could be expected that the risk should be particularly increased when they are co-administered, especially if the doses of a statin are very high. However, in the ACCORD trial, as in other published studies, combination of fenofibrate and simvastatin did not increase the incidence of myopathy, myozitis or rhabdomyolysis.[97] Nevertheless, gemfibrozil should not be combined with statins since the risk of myopathy in this combination is 15-fold higher because it increases exposure to and reduces the renal clearance of statins by inhibiting their glucuronidation.

Omega-3 fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], and docosapentaenoic acid) decrease TGs levels when applied in doses of 2–4 g/day. It has to be mentioned that omega-3 fatty acids can decrease Apo C-III which can be one of the mechanisms to achieve this.[101] However CVD outcome studies with omega-3 fatty acids have produced inconsistent results. A meta-analysis including data from 63,030 patients from 20 clinical trials demonstrated that treatment with omega-3 fatty acids did not have an impact on a composite CVD end point or total mortality but was associated with a significantly decreased rate of vascular death.[102] Most recently published results of the ASCEND study performed on 15,480 patients with diabetes but without evidence of CVD who received 1,000 mg capsules containing either omega-3 fatty acids or matching placebo (olive oil) daily could not find any significant difference in the risk of serious CVD events between those who were assigned to receive omega-3 fatty acid supplementation and those who were assigned to receive placebo.[103] Similar results were obtained in a most recent Cochrane systematic review

https://doi.org/10.4070/kcj.2018.0343

which was the most extensive systematic assessment of effects of omega-3 fats on CVD to date. Moderate- and high-quality evidence suggests that increasing EPA and DHA has little or no effect on CVD mortality nor does it reduce the risk for CVD events, deaths from CHD, strokes, or cardiac arrhythmias (evidence mainly from supplement trials). This analysis encompassed findings of 79 studies involving more than 112,000 subjects. Low-quality evidence suggests that alpha linolenic acid (ALA) may slightly reduce CVD event risk, CHD mortality and arrhythmia.[104]

The results of ongoing Statin Residual Risk Reduction With Epanova (a mix of omega-3 FFAs, not requiring co-ingestion with food, which can lower TGs by up to 31%) in STatin Residual Risk Reduction with EpaNova in HiGh Cardiovascular Risk PatienTs with Hypertriglyceridemia (STRENGTH) trial which is evaluating the treatment with EPA plus DHA will provide some more answers concerning the effects on TGs and CVD outcomes in patients with high CVD risk.[105]

Prescription icosapent ethyl (IPE, Vascepa) is a high-purity EPA agent which lowers TGs levels but does not increase LDL-C levels which some of the prescription EPA and DHA preparations do.[106][107] Therefore the results of ongoing REDUCE-IT trial are eagerly awaited. This is a phase 3b randomized, double-blinded, placebo-controlled trial with IPE vs. placebo and its main objective is to evaluate whether treatment with IPE could reduce ischemic events in statin-treated patients with high TGs at elevated CVD risk.[108] Most recently a structurally engineered new more potent form of omega-3 fatty acids – icosabutate, seems to be promising in lowering TGs since it reduced TGs for 27.0%,[109] but there are no data on possible CVD prevention benefit of this substance so far.

WHAT DO THE GUIDELINES AND POSITION PAPERS SAY?

The most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the assessment of CVD risk do not mention TGs at all.[110] The guidelines point out also, which has been already mentioned earlier in the text, that severely elevated TGs such as >1,000 mg/dL (up to 11 mmol/L) which is generally associated with genetic disorders of TGs metabolism or according to the 2014 National Lipid Association guidelines even TGs level of ≥500 mg/dL (≥5.6 mmol/L), which are often exacerbated by secondary causes, are an important risk factor for acute pancreatitis. Other relatively recently published guidelines, such as European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemias and European guidelines on CVD prevention in clinical practice (version 2012), do not include TGs in CVD risk estimation neither they recommend any specific target value for treatment of elevated TGs levels. However, they suggest that those with a TGs level of >1.7 mmol/L (or >150 mg/dL) should be considered as increased risk.[7][111] The reason is, among others, because elevated TGs are very often associated with decreased HDL-C, but also with increased number of very atherogenic small dense LDL-particles so it is difficult to discriminate which of these lipid parameters is really an important and independent CVD risk factor. This is probably the main reason why the guidelines do not mention elevated TG-rich particles as an independent CVD risk factor.[112]

A relatively low level of understanding among both physicians and the general public of the importance of elevated TGs and decreased HDL-C as CVD risk factors has been pointed out as one of the reasons for inadequate treatment of so called 'residual' CVD risk. Namely,

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'residual' CVD risk is partially attributed exactly to elevated plasma TG-rich particles and low HDL-C.[113][114] This is despite the fact that several important position papers were published in the last 10 years.[23][47][114][115]

The guidelines do not mention neither the importance of elevated TGs and/or low HDL-C in the ethiopathogenesis of microvascular changes. This is in spite of the fact that it has been shown that not only macrovascular changes causing CVD but also microvascular changes are associated with higher levels of TGs and decreased HDL-C, particularly in patients with T2D who have good control of LDL-C. These results implicate the role of elevated TGs and low HDL-C in diabetic nephropathy and retinopathy as well.[116]

The burden of elevated plasma levels of TGs as an important CVD risk factor is highlighted by the fact that 34.7% of patients with CVD have elevated TGs.[117] A number of recently published review papers and editorials suggest also that therapeutic targeting of TG-rich particles could possibly provide further benefit in reducing CVD risk and events, apart from LDL-C lowering.[115][118]

NOVEL POSSIBILITIES FOR ANTI-ATHEROSCLEROTIC THERAPY BY LOWERING TRIGLYCERIDE

Since it has been proven that carriers of mutations disrupting Apo C-III function presented 40% lower risk for CHD compared to non-carriers,[119] Apo C-III is considered as a new target for lowering TGs.[119] Namely, as stated earlier, Apo C-III has a critical role in regulating clearance of TGs-rich lipoproteins but also exerting its direct atherogenic effect of provoking pro-inflammatory responses in vascular cells, including monocytes and endothelial cells,[35] although these effects have been questioned by some authors.

Volanesorsen is a second generation antisense oligonucleotid (ASO) that acts to reduce the levels of Apo C-III messenger RNA. By acting through ribonuclease H1, volanesorsen induces the degradation of the target mRNA and thus inhibits the production of the Apo C-III. As already explained, this glycoprotein plays a regulative role on lipoprotein metabolism and SNPs in the Apo C-III gene are emerging as a cause of severely elevated TGs. A recent meta-analysis found evidence that 2 SNPs in Apo C-III are associated with increased CHD risk. In specific two polymorphisms, SstI and T-455C, increased the odds for CHD development by up to 48 and 77%, respectively.[120] The production of Apo C-III is suppressed by the ribonuclease H1-mediated degradation of the target mRNA.[121] In a randomized, double-blind, placebo controlled, dose-ranging phase II study this drug as monotherapy lowered of Apo C-III which was followed by significant reductions in TGs levels by 31.3 to 70.9%.[122] No drug-drug interactions were noted because of different mechanism of action and drug metabolism. Apart from TGs reduction, HDL-C increased, and VLDL-C decreased in a dose-dependent manner. All these promising effects were accompanied by a good safety profile. In another study volanesorsen was when compared with placebo associated with around 80% (82.3±11.7%, 81.3±15.7%, and 80.8±13.6%) reduction in Apo C-III-Apo B100, Apo C-III-Lp(a) and Apo C-III-Apo A-I lipoproteins respectively after 92 days of follow-up.[123] In the most recently published ReFOCUS study volanesorsen during a median of 222 days also significantly improved the quality of life of patients by reducing the number of symptoms per patient across physical, emotional, and cognitive domains but also steatorrhea, pancreatic pain, and constant worry about an attack of abdominal pain and/or acute pancreatitis.[124]

https://doi.org/10.4070/kcj.2018.0343

This is important because patients with FHTG experience multiple physical, emotional, and cognitive symptoms on a daily to monthly basis. For example, according to the most recent analysis, 40% were admitted to the hospital in the past year, lifetime mean of 13 episodes occurred in the 40% of patients with acute pancreatitis due to this disease, more than 90% patients found managing fat intake to be difficult, and 53% experienced symptoms despite adherence to their diets.[125] There is a number of ongoing studies with volanesorsen (APPROACH, COMPASS, etc.).[126]

Selective peroxisome proliferator-activated receptor alpha modulators (SPPARMα agents) are other potential targets for TGs lowering. In patients with high TGs and low HDL-C, the first of these agents pemafibrate (K-877) decreased TGs between 30.9% and 42.7%, increased HDL-C, and improved other lipid parameters without increasing adverse effects, as compared to placebo and fenofibrate.[127][128] It seems that pemafibrate also enhances reverse cholesterol transport from macrophages to HDL particles and exerts anti-inflammatory activities thus possibly retarding the progression and even promoting the regression of atherosclerosis.[129][130] Pemafibrate also improves insulin sensitivity by splanchnic glucose uptake from baseline in patients with elevated plasma TGs.[131] In a head-to-head comparison pemafibrate has fewer adverse effects on kidney/liver-related laboratory tests and fewer adverse drug reactions, including those leading to treatment discontinuation, over fenofibrate 200 mg/day.[132] It seems that pemafibrate is approximately 10,000-fold more potent than fenofibrate in vitro, that it has a greater lipid-modifying efficacy at considerably lower doses both in animal models for obesity/T2D and in humans, and is associated with an improved safety/tolerability profile. In addition, pemafibrate 100 μg BID is associated with beneficial changes in markers for liver disease. This suggests that, in addition to improving lipid parameters in people with cardiometabolic diseases, pemafibrate might also be useful for the prevention of NASH/NAFLD.[133] A major outcomes study with pemfibrate in the Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN diabetic patiENTs (PROMINENT) trial on about 10,000 high CVD risk T2D patients with elevated TGs and low HDL-C despite concomitant intensive statin treatment has been recently announced.[134]

The dual PPAR-α/PPAR-δ agonist GFT-505 has shown favorable results in improving atherogenic dyslipidemia and insulin resistance and appears to be a potential candidate not only for decreasing elevated TG-rich particles but even more for the treatment of NAFLD.[135]

Another substance which is promising in reducing extremely high TGs levels is alipogene tiparvovec (AAV1-LPLS447X), a nonreplicating and non-replacing adeno-associated viral vector that delivers copies of the human LPL gene to muscle tissue which accelerates the clearance of TG-rich lipoproteins. This drug has been approved by European Medicines Agency in Europe but only for adult patients diagnosed with familial LPL deficiency and a history of multiple or severe episodes of pancreatitis who have failed dietary therapy. The application is intramuscular and although a causal relationship could not be established and despite the limited number of individuals evaluated, results from a relatively recently published study suggest that treatment with this substance was associated with a lower frequency and severity of pancreatitis events, and a consequent overall reduction in health care resource use up to 6 years post-treatment.[136]

Although gene therapy is a logical therapeutic approach to homozygous familial LPL deficiency for which current therapies are inadequate, two companies have stopped their trials based upon such a treatment. Since rare mutations in APOA5 are associated with

https://doi.org/10.4070/kcj.2018.0343

increased plasma TGs and premature myocardial infarction, Apo A-V supplementation gene therapy might be a prevention option for patients with chronic elevation of TGs who have low plasma Apo A-V due to a proven APOA5 mutation/polymorphism and do not have deleterious mutations/polymorphisms in other genes known to influence plasma TGs. So far there are no published clinical results that could prove this approach.

Pradigastat is a novel diacylglycerol acyltransferase 1 (DGAT1) inhibitor which substantially reduces extremely high TGs levels and seems to be promising in treatment of the rare familial chylomicronemia syndrome (FCS).[137] Since DGAT1 catalyzes the final step in TGs synthesis and is highly expressed in the small intestine enterocytes, where it plays a key role in absorption of dietary fat, DGAT1 inhibition is an attractive strategy to reduce the synthesis and secretion of TGs, and thereby lower plasma TGs. It is important to stress that pradigastat was generally well tolerated in patients with FCS who were on very low fat diet at daily doses up to 40 mg for 3 weeks and they had only mild to moderate gastrointestinal adverse effects like diarrhea, flatulence and abdominal pain. It has to be mentioned that 2 other companies ended their DGAT1 inhibitor programs because of gastrointestinal adverse effects.

Recent data based upon a genome-wide association study which included about 2.5 million SNPs from 3,041 Japanese healthy volunteers indicate that proprotein convertase subtilisin/kexin 7 (PCSK7) may be associated with TGs, and may serve as a candidate for a new drug target to treat elevated TGs.[138] However, so far there is no substance which was tested for this. Another treatment possibility is based upon the fact that fibroblast growth factor 21 (FGF21), an endocrine factor secreted mainly by the liver in response to PPARα activation, can lower TGs. This substance achieves this effect most probably by a dual mechanism, balancing effects in white adipose tissue (predominantly involved in energy storage and mobilization) and brown adipose tissue (involved in non-shivering body thermogenesis).[139] Again, there are no clinical data with this substance so far.

Since ANGPTL3 regulates TGs metabolism in part by inhibiting LPL, loss-of-function variants in the ANGPTL3 gene are associated with decreased plasma levels of TGs, LDL-C, and HDL-C. Therefore, ANGPTL3 is considered an important new potential target for the treatment of lowering TGs and LDL-C and thus prevention of CVD. A monoclonal antibody against ANGPTL3 (REGN1500) called evinacumab was developed and it has been shown in an early phase trial that it can substantially lower elevated TGs levels.[140][141] Also, in a phase I trial, it has been demonstrated that administration of a second-generation antisense oligonucleotide targeting ANGPTL3 (IONIS-ANGPTL3$_{Rx}$) during 6 weeks resulted in a dose-dependent reduction of plasma ANGPTL3 and TGs in healthy individuals.[142] The most recent approach is based upon a CRISPR/Cas mechanism and it is still under development but the initial results are encouraging.[143] Apart from the effect of ANGPTL3 on lipid metabolism, it has been suggested that this substance might have additional anti-atherosclerotic effects, such as an anti-inflammatory, anti-angiogenic, and an increase of macrophage cholesterol efflux. Several years ago antibodies against ANGPTL4 were also shown to interfere with the inactivation of LPL. For ANGPTL4 there are two reported mutations (P251T and R371Q) which are linked to elevated plasma TGs levels.[144] Therefore monoclonal antibodies against ANGPTL4 might also be promising targets for lowering elevated TGs.[145] ANGPTL8 inhibitors might also be promising for lowering elevated TGs but even more for treatment of NAFLD.[146] GPIHBP1 could also be a possible drug development target but there are still no reports dealing with this.

https://doi.org/10.4070/kcj.2018.0343

kcj Korean Circulation Journal

CONCLUSION

Most recent data strongly favor the role of elevated plasma levels of TG-rich particles as an independent risk factor for CVD and there are more and more data that it could be a causal risk factor as well. Results of many large observational, epidemiological, genetic and Mendelian randomization studies support the claims that elevated TGs are associated with increased risk for CVD and indicate that therapeutic targeting of them could possibly provide further benefit in reducing CVD morbidity, events and mortality, apart from LDL-C lowering. At the moment besides lifestyle changes which can be very effective, much more than in lowering elevated LDL-C, fibrates are the drugs of choice for treatment of hypertriglyceridemia. 2–4 mg of omega-3 fatty acids could be added as combined treatment but there is no evidence that this combination alone or on background of statins can reduce CVD morbidity and mortality. There are also some new drugs which might be important in reducing elevated TG-rich particles. Volanesorsen, is an antisense oligonucleotide that inhibits the production of the Apo C-III which is crucial in regulating TGs metabolism because it inhibits LPL and HL activity but also hepatic uptake of TGs-rich particles. Evinacumab is a monoclonal antibody against ANGPTL3 and it seems that it can substantially lower elevated TGs levels because ANGPTL3 also regulates TGs metabolism. Pemafibrate is a selective peroxisome proliferator-activated receptor alpha modulator which also decreases TGs, and improves other lipid parameters without increasing adverse effects, as compared to placebo and fenofibrate. It is important to stress that most probably pemafibrate also enhances reverse cholesterol transport from macrophages to HDL particles and exerts anti-inflammatory activities thus possibly retarding the progression and even promoting the regression of atherosclerosis. Alipogene tiparvovec is a nonreplicating adeno-associated viral vector that delivers copies of the LPL gene to muscle tissue which accelerates the clearance of TG-rich lipoproteins thus decreasing extremely high TGs levels. Pradigastat is a novel diacylglycerol acyltransferase 1 inhibitor which substantially reduces extremely high TGs levels and appears to be promising in treatment of the rare familial chylomicronemia syndrome. Still more evidence is needed to prove beyond any doubt that lowering TG-rich lipoproteins with any of these substances can save lives since CVD outcome studies with all TGs-lowering agents have so far produced inconsistent results.

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