Chapter

Residual Cardiovascular Risk Factors in Dyslipidemia

Van Si Nguyen, Xuan Truong Tran, Thanh Duy Vo and Quang Truong Le

Abstract

Cardiovascular disease poses a major challenge for the 21st century. Although good control of blood pressure and type 2 diabetes and reducing low-density lipoprotein-cholesterol levels can improve cardiovascular outcomes, a substantial residual risk remains existed after treatment in most patient populations. Recently, many efforts have been directed at finding the important role of low high-density-lipoprotein cholesterol, high triglycerides, especially triglyceride-rich lipoproteins and lipoprotein (a) in the metabolism of atherosclerotic plaque formation Therefore, based on the recent evidence, identification and treatment of these risk factors may play a role in optimizing therapeutic strategy, particularly in high risk subjects along with conventional treatment. In clinical practice, adequate attention should be paid when screening and managing residual cardiovascular risk factors in dyslipidemia in term of individualized approach. The ongoing trials will give more answers to elucidate this important area.

Keywords: cardiovascular disease, dyslipidemia, residual risk factors, hypertriglyceridemia, low HDL-C, lipoprotein (a)

1. Introduction

Risk factors for cardiovascular disease (CVD) are specific lifestyles, behaviors and a set of conditions that increase likelihood of CVD. An individual may have more than one cardiovascular (CV) risk factors. In fact, CV risk factors often appear coherently. The more risk factors, the greater the risk of CVD. However, the individual with increased risk does not necessarily develop cardiovascular diseases.

A number of factors have been linked to an increased risk of cardiovascular disease which can be classified as (1) Unmodifiable risk factors: age (men over 45 years old, women over 55 years old), gender and family history of early CVD (men under 55 years old, women under 65 years old) and (2) Modifiable risk factors: unhealthy diets, high blood pressure, dyslipidemia, smoking, overweight, obesity, pre-diabetes or diabetes, sedentary lifestyle [1–3].

In addition, extended CV risk factors were proposed, including: metabolic syndrome (insulin resistance syndrome, syndrome X) including triglyceridemia, chronic kidney disease (CKD) with reduced glomerular filtration rate [15–59 ml/min/1.73 m^2], chronic inflammatory conditions (rheumatic disease, HIV), early menopause (< 40 years), history of eclampsia, high-risk ethnicity (South Asian), elevated lipoprotein (a) [Lp(a)] ≥ 50 mg/dL (≥ 125 nmol/L) or elevated apolipoprotein B

(ApoB) ≥ 130 mg/dL, C-reactive protein (CRP) ≥ 2 mg/L and ankle-brachial index <0.9 [4].

Residual CV risk factor is defined as the risk of CV events that persists despite achieving treatment goals for low-density lipoprotein cholesterol (LDL-C), blood pressure and blood glucose as recommended by current evidence-based guidelines [5, 6]. Residual CV risk factors include LDL-C > 100 mg/dL, high-sensitive C-reactive protein (hsCRP) > 2 mg/l, triglyceride (TG) > 200 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, Lp(a) > 50 mg/dL [7]. The origin of residual CV risk factors in dyslipidemia is based on atherogenic dyslipidemia characterized by elevated TG and triglyceride-rich lipoproteins (TRLs), decreased HDL-C, and qualitative changes of lipoprotein particles [8–10].

2. Epidemiology

Most large studies extending over the last 25 years suggested that the leading cause of atherosclerotic cardiovascular disease (ASCVD) is high LDL-C levels and this has been widely recognized and accepted [9, 11]. Furthermore, there is also growing evidence that increased levels of LDL-C and other ApoB containers, including very low density lipoprotein cholesterol (VLDL-C), intermediate density lipoprotein cholesterol (IDL-C) and Lp(a), are directly related to the progression of ASCVD [12, 13]. In 2010, a multicenter study analyzing data from 26 randomized clinical trials in 2009 demonstrated that statins are effective in lowering LDL-C blood levels and controlling blood glucose levels. LDL-C at the recommended level is beneficial in reducing atherosclerotic CV events and CV mortality [14].

However, studies in recent years have revealed that control of plasma LDL-C concentrations is not the only goal of reducing the risk of CVD [15]. Based on the results of their study, Cannon et al. demonstrated an ongoing risk of major CV events after treatment with high doses of atorvastatin or pravastatin. The data signified that up to 26.3% in the atorvastatin-treated group and 22.4% in the pravastatin-treated group experienced a major CV event or death [16]. This evidence suggests that the goal of reducing the risk of CVD requires control not only of blood LDL-C levels but also of residual CV risk factors in other dyslipidemia, including TG and TRLs, HDL-C and Lp(a) [9].

3. Residual risk factors in dyslipidemia

3.1 Pathogenesis of atherosclerosis

Atherosclerosis is a complex phenomenon that is involved by a number of factors. Firstly, when the vascular endothelial cell layer is injured, the synthesis of nitrite oxide (NO), a chemical that protects blood vessels, is reduced, while the production of oxidants rises [17, 18]. Infiltration of ApoBs including remnants of chylomicron, VLDL-C, IDL-C, LDL-C and Lp(a) into the endothelial layer. The ApoBs that are retained in the vessel wall oxidize, triggering a cascade of biological events that result in an inflammatory response [19, 20]. Furthermore, platelets are stimulated to cause chronic vascular inflammation which leads to leukocyte recruitment [21, 22]. Monocytes and neutrophils penetrate the endothelial layer into the arterial wall. Macrophages that have been differentiated from monocytes amplify lipid absorption and produce foam cells, which play a key role in the formation and instability of atherosclerotic plaques. T lymphocytes, mastocytes, and other inflammatory cells penetrate the lesion and help to continue the noxious inflammatory

response [20–24]. This process is also maintained and enhanced through signaling pathways such as MCP-1, M-CFS, GM-CFS [25–27]. As a result, the plaque ruptures and leads to clinical manifestations for example, myocardial infarction or stroke.

3.2 Hypertriglyceridemia and related markers

The function of TG in the etiology of atherosclerosis has garnered limited attention in recent years, with most studies focusing on the benefits of raising HDL-C. Contemporary clinical and genetic evidence, on the other hand, suggests that TG, especially TRLs, and apoprotein C3, play essential roles in the etiology of atherosclerosis. Therefore, TG and TRLs are getting increasing attention and are becoming one of the therapeutic targets for lowering the risk of ASCVD [28].

TG is the main component in the structure of the TRL group including VLDL-C and chylomicrons which are synthesized in the liver and small intestine, respectively [29, 30]. The metabolism of TG and TRLs has the involvement of lipoprotein lipase (LPL) which is capable of activating the hydrolysis of the TG component in the core of TRLs into fatty acids. As a result, residual VLDL-C and residual chylomicrons are formed, which contain less TG and more cholesterol than normal TRLs [29, 31]. A portion of VLDL-C residues and residual chylomicrons are captured in the liver and neutralized by hepatic bile. The remainder is metabolized again by LPL or hepatic lipase enzymes, forming cholesterol-rich LDL-C [29, 30]. The residual LDL-C, VLDL-C, and residual chylomicrons are all cholesterol-rich lipoproteins and are classified as non-HDL [29, 32]. As with LDL-C, residual VLDL-C and chyplomicron molecules can be engulfed by macrophages in the vascular wall, which contributes to vascular inflammation and progression of atheromal. However, unlike LDL-C, the residual VLDL-C and chylomicron molecules do not require oxidation when participating in the process of atherosclerosis [29, 30]. Many factors impact the metabolism of TG and TRLs, with LPL playing a major role. The activity of the LPL enzyme has a direct effect on the concentration of TG and TRLs in the blood; for example, increasing LPL activity lowers TG and TRL concentrations while increasing VLDL-C molecules and residual chylomicrons, and vice versa (**Figure 1**).

The reduction in TG and TRLs metabolism leads to less cholesterol-rich lipoprotein concentrations and is expected to reduce the risk of atherosclerosis. However, intensive genetic and molecular biology studies of TG, TRLs and LPL all showed conflicting results. The first observational studies in the field of genetics related to TG, TRLs and LPL found that mutations that decrease TRLs metabolism were associated with atherosclerosis and coronary artery disease, whereas mutations TRLs metabolism enhancer had the opposite effect. Several mutations directly in the LPL enzyme associated with CVD risk have been observed including Gly188Glu, Asp91Asn and Asn291Ser substitution mutations. In which, the Gly188Glu substitution mutation in LPL can increase the risk of coronary heart disease 5 times higher than those without the mutation [33]. ApoC-II and ApoA-V loss-of-function mutations, both have been conveyed to increase blood TG, increase the risk of myocardial infarction and coronary artery disease, while mutations in the APOC3 gene - the gene that codes for Apo C-III - such as the RX 9 mutation and some other rare mutations give the opposite result [29, 34]. Most recently, ANGPTL4 mutations have appeared to reduce TG levels and reduced the risk of coronary artery disease. When conducting whole-chromosome studies on single-nucleotide polymorphisms (SNPs), susceptibility loci in the genomic regions encoding ApoC-III, ApoA-V, ANGPTL3, and ANGPTL4 were revealed to be associated with ASCVD, which lays the foundation for gene therapy to improve CV risk. In addition, there are

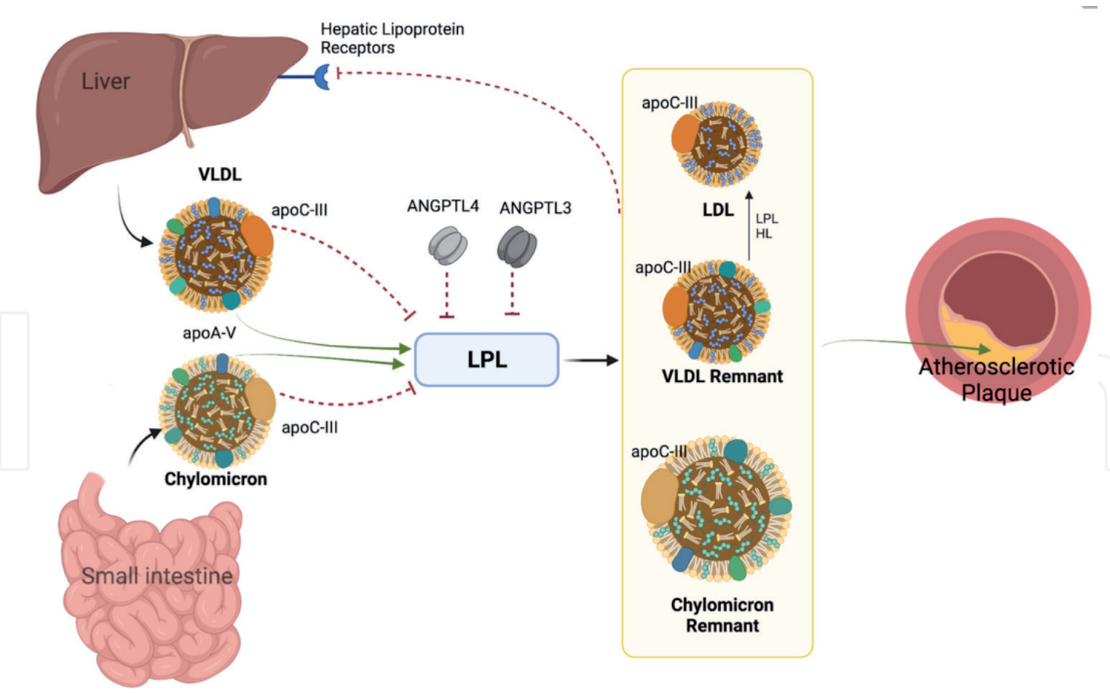

Figure 1.
The center role of LDL-C and TRLs in the formation of atherosclerotic plaque. ANGPTL = angiopoietin like protein, HL = hepatic lipase, LPL = lipoprotein lipase.

many other genetic studies with similar results regarding the role of TG in vascular events [29].

Due to the inverse correlation of HDL-C and TG, most of the previous epidemiological studies intimated the association between increased TG and atherosclerosis, which was explained by the lowering effect of HDL-C. However, there are studies that refute this view and provide strong evidence that TG is an independent factor affecting the risk of CV events. Furthermore, there appears to be a positive correlation between serum TG levels and mortality risk, even when adjusted for HDL-C and other factors [29].

With a few other CVD not caused by atherosclerosis, TG also showed a similar association. One study found that increase levels of TG and residual cholesterol molecules (total cholesterol minus LDL-C and HDL-C) were risks of aortic stenosis [35].

3.2.1 Treatment of hypertriglyceridemia

Because of the harmful effects of TG on the cardiovascular system, strategies to control TG levels were rapidly investigated to contribute to the control of CV risk in general population. Several epidemiological studies have indicated a reduction in the risk of CV events in subjects regularly consuming fish or foods rich in omega-3 fatty acid (EPA), which has been proved to reduce TG level [36–38]. However, studies testing natural EPA in subjects with ASCVD or heart failure or at high CV risk such as the ORIGIN study and most recently the STRENGTH study have showed no beneficial effect [39, 40]. Similarly, most trials of TG-lowering therapies have failed to improve CV risk. Until 2019, the REDUCE IT trial – a multicenter, double-blind, randomized, placebo-controlled study – was performed in statin-treated diabetic patients with CVD or other CV risk factors having TG levels between 135 and 499 mg/dl (1.52 to 5.63 mmol/L) and blood LDL-C levels between 41 and 100 mg/dl (1.06 to 2.59). mmol/L). There were one group treated with icosapent ethyl - a synthetic derivative of EPA with TG-lowering effects - and a placebo group. The results

concluded that in patients with elevated TG, the use of icosapent ethyl reduced significantly CV events [41]. In addition to TG-reducing effect, the CV benefits of icosapent ethyl are also attributed to its effects on the main mechanisms underlying the progression of atherosclerosis, such as reduced inflammation and anti-oxidation, which stabilize and even regress atherosclerotic plaques [42]. Up to now, icosapent ethyl is considered a potential drug to help eliminate the residual CV risk caused by hypertriglyceridemia (**Figure 2**).

Research on the effects of fibrates which is a potent TG-lowering agent on CVD was also conducted quite early. In 1975, clofibrate in combination with niacin showed no significant benefit in reducing the risk of CVD [43]. However, VA-HIT study compared the gemfibrozil-treated group with the placebo group in patients with blood HDL-C levels <40 mg/dL and blood LDL-C levels <140 mg/dL showed effects on lipid parameters: HDL-C levels increased by 6%, total cholesterol decreased by 4% and TG decreased by 31% compared to the placebo group. In addition, VA-HIT also uncovered that gemfibrozil reduced the risk of mortality from major vascular events such as coronary artery disease, myocardial infarction, and stroke by 24% [44]. However, in 2010, ACCORD trial on combination of fenofibrate and statin in type 2 diabetes showed no favorable results [45]. A multicenter meta-analysis examinining data from 18 studies of fibrates during 1950–2010 to further assess their impact on CVD revealed fibrates decreased the risk of major CV events by 10% and coronary events by 13% but did not lower the overall risk of stroke or mortality rate [46]. With these results, there is practically no clear evidence that fibrates are beneficial in improving the risk of CVD or vascular events.

Novel therapies of hypertriglyceridemia are being applied to achieve maximum efficacy while minimizing undesirable side effects. For example, AKCEA-APOCIII-LRx is targeted on inhibiting the synthesis of Apo C-III by hindering the mRNA that translates it. In healthy volunteers, clinical trials of the treatment revealed a reduction in the risk of CV events in the treated group, as well as acceptable tolerability [47].

Residual lipoprotein cholesterol (RLP-C) which has close relation with TG level has also recently been demonstrated to be a residual CV risk factor even in those

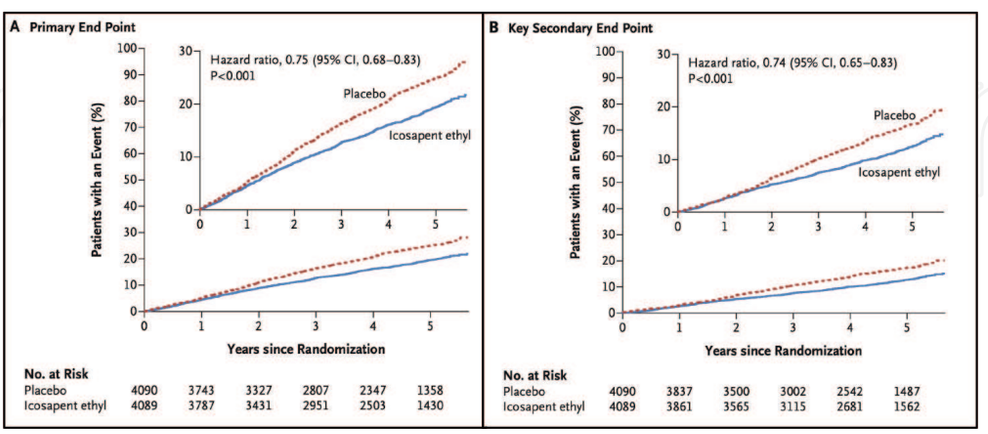

Figure 2.
(A) The Kaplan–Meier event curves for the primary end point of CV events without death. There was a statistically significant difference in primary CV events in the icosapent ethyl group (17.2%) compared with the placebo group (22%), corresponding to an absolute between-group difference of 4.8 percentage points, hazard ratio, 0.75 (95% CI, 0.68–0.83) P < 0.001, NNT = 21 over a median follow-up of 4.9 years. (B) The Kaplan–Meier event curves for the secondary end point of CV events without death. There was a statistically significant difference in secondary CV events in the icosapent ethyl group (17.2%) compared with the placebo group (22%), corresponding to an absolute between-group difference of 3.6 percentage points, hazard ratio, 0.74 (95% CI, 0.65–0.83) P < 0.001, NNT = 28 over a median follow-up of 4.9 years. NNT = number needed to treat, Cl = confidence interval. Reproduced with permission from Deepak L. Bhatt, M.D., 2019 [41].

with good LDL-C control. Elevated blood levels of RLP-C have been proved to predict coronary and other CV events [35, 48]. This is a new direction that need investigating in order to enhance the accuracy of assessing residual CV risk. In addition, more RLP-C intervention trials are required to demonstate the effect in CVD prophylaxis.

3.3 Low HDL-C

Research on the role of TG and TRLs in atherosclerotic disease are progressively providing conclusive evidence while trials to raise blood HDL-C levels have so far failed to show significant clinical benefit. This augments the possibility that the previously established causal link between higher HDL-C and a lower risk of vascular events is attributable to a comparable reduction in TG as HDL-C rises. The function of HDL-C in atherosclerosis-related CVD is still debatable nowadays.

There are several factors that contribute to HDL-C to protect blood vessels from atherosclerosis. The HDL-C molecule is responsible for cholesterol transfer from organs and peripheral blood vessels to the liver for biliary elimination. HDL-C also diminishes immune cell adherence and increases vasodilating process as well as inhibits platelet aggregation via prostacyclin. Prostacyclin modulation, in turn, aids in the breakdown of fibrin and thrombolysis in couple with decreasing inflammatory mediators and restoring vascular endothelial cell function. In addition, HDL-C is an inherent antioxidant involved in the preservation of blood vessels from oxidative damage [8, 49].

It is evident that HDL-C can prevent blood vessels from atherosclerosis. However, the role of HDL-C in lowering the overall risk of cardiovascular disease remains unknown. While epidemiological studies linked HDL-C to a lower risk of atherosclerotic CV events [50, 51], genetic study found that HDL-C had no effect on CV event risk [52, 53]. Indeed, when delving into a few gene mutations related to Scavenger receptor class B type 1 (SR-BI) and Cholesteryl ester transfer protein (CEPT) receptors - two components involved in HDL-C metabolism, these ones affect CV events differently. The pathway of HDL-C metabolism in the human body has the participation of SR-BI and CEPT receptors. When these two factors lose their function, the concentration of HDL-C in the blood will increase [54–56]. Studies in individuals with anomalies in the gene that cause loss of SR-BI receptor function have showed an increase in HDL-C levels but also an increased risk of CV events [55]. Nevertheless, studies of mutations that reduce function of CEPT showed irrelevant outcome. With the Ile405Val substitution alteration on CEPT, it is concluded that there was a decrease in CEPT activity and an increase in HDL-C regarding gender, but further an increased risk of ischemic heart disease in women but not in men [56]. Despite that, studies with other gene mutations such as TaqIB, I405V and -629C > A have clarified a reduced risk of coronary heart disease [57]. In 2009, a genetic study in different loci of the gene coding for CEPT, gave an explaination for this heterogeneity. There was an inverse association between HDL-C and the risk of cardiovascular events as a result of mutations; however, there are other alterations that do not demonstrate this correlation [8]. With achievements in functional decoding of HDL-C in terms of genes, researchers and clinical practitioners would assume the role of HDL-C in ASCVD will soon be clarified and become a state-of-art implement to assist in the treatment, prognosis, and prevention of CVD.

Since the role of HDL-C is uncertain, the use of the HDL-C measurement in clinical practice has been limited up until present. Due to the extreme prior belief that HDL-C is a favorable factor for lowering CVD risk, HDL-C was added to

SCORE – the CV risk assessment model – to create SCORE – HDL-C in European Society of Cardiology recommendations for the treatment of dyslipidemia [58, 59]. A study published in 2015 evaluated the predictive capacity of two models, SCORE - HDL-C and SCORE, and found that while the SCORE - HDL-C did not enhance CV mortality prognosis, it did lower the sensitivity of finding persons at high risk of CVD in the population [60].

3.3.1 Treatment of low HDL-C

Niacin is a medication that raises HDL-C levels and has been examined extensively in clinical studies. Its efficacy in controlling dyslipidemia and lowering the risk of cardiovascular disease is not well established. In a 1975 study comparing the CV merits of niacin, clofibrate, and placebo, treatment with a high dose of 3000 mg/day of moderate-release niacin resulted in a 14% reduction in coronary mortality, and 26% of stroke death [43]. When the research was expanded to include additional possible medicines in the treatment of dyslipidemia, such as estrogens, clofibrate, dextrothyroxine sodium, and niacin, and compared to lactose as a placebo, niacin was found to be encouraging reducing mortality [66]. However, in the AIM-HIGH and HPS2-THRIVE studies, the effects of niacin were only significant on lipid parameters without effect on CV outcomes [61, 62].

CEPT inhibitors came later than niacin and fibrates in terms of development and application. ILLUMINATE, dal-OUTCOMES, ACCELERATE, and REVIEW are among the most notable CEPT inhibitor trials to date. Nonetheless, the results of this medication were similarly unsuccessful due to inconsistencies in genetic research of CEPT. With the exception of the 2017 anacetrapid REVIEW study, which described a reduction in coronary events [63], the majority of the remaining studies suggested that CEPT inhibitors did not improve CVD risk but increased rates of CV mortality or adverse events such as increased CRP levels or increased systolic blood pressure [64–66]. Thus, clinical application studies of drugs that increase HDL-C have not yet provided evidence that HDL-C is beneficial in CVD.

In addition to the genetic aspect mentioned above, another hypothesis about HDL-C levels has been expanded to explicate the incompatible results of studies on HDL-C. When examining at HDL-C levels and mortality in the study population, several studies found a U-shaped relationship between HDL-C levels and overall mortality rates. This is understandable since extremely low or high HDL-C levels increase population mortality [67–69]. In fact, prior HDL-C studies neglected this aspect, requiring more study to more correctly assess HDL- C involvement in ASCVD.

Based on the available evidence, it can be stated that HDL-C modification in clinical practice is currently restricted. Not all HDL-C-increasing medications yield the same outcomes. To better understand the significance of HDL-C, these items must be considered to a greater extent: the threshold concentration of plasma HDL-C and the genetic aspect. It is indeed questionable if increasing HDL-C can assist reducing CV risk.

3.4 Lipoprotein (a)

Lp(a) is made up of an LDL-C molecule covalently bound to an apolipoprotein (a) that is homologous to the coagulation factor plasminogen. It also includes an apolipoprotein B100 as it contains LDL-C. Therefore, Lp(a) has both atherogenic and thrombolytic properties [70, 71]. The ability of Lp(a) to permeate the artery wall has been demonstrated [72]. Lp(a) has been showed to increase thrombus development, inflammatory response, and foam cell production in both laboratory and animal investigations [73].

Many studies prove that Lp(a) is a factor affecting the morbidity and mortality of CVD [74, 75]. The INTERHEART study proclaimed that Lp(a) levels >50 mg/dL increased the risk of myocardial ischemia [76]. The effect of Lp(a) on CV risk was independent of other risk factors, including LDL-C levels [77, 78]. Thus, elevation of blood Lp(a) levels confers a residual CV risk in dyslipidemia, which is similar to the role of TG mentioned above. A large study of LPA genetic variants also showed an independent role for Lp(a) in relation to coronary events, despite low LDL-C levels with statin therapy [79]. To specify the role of Lp(a) in reducing the risk of CVD, a study compared blood levels of Lp(a) with the risk of CVD and LDL-C levels with CVD risk, the results showed that the clinical benefit of lowering Lp(a) was directly proportional to the reduction of Lp(a) levels. Specifically, a 101.5 mg/dL reduction in Lp(a) resulted in a clinically significant reduction in CVD risk similar to a 38.67 mg/dL reduction in LDL-C [80].

Among the factors affecting Lp(a) levels, PCSK9 is one that has been observed in clinical trials to reduce Lp(a) concentration [78]. The role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in influencing Lp(a) levels was also confirmed in a survey of PCSK9 functional-affecting mutants, which explicated that overexpressed function mutations of PCSK9 increased the CV risk while the PCSK9 R46L mutation reduced its function, showing a reduced risk of aortic stenosis and myocardial infarction [81]. The reduction in CV risk is proportional to the level of Lp(a) in the blood as mentioned above. Therefore, PCSK9 inhibitors are a potential agent for reducing the incidence of vascular events through its effect on Lp(a).

3.4.1 Treatment of high lipoprotein (a)

The cornerstone of current potential drug development is the new evidence on the benefits of Lp(a) reduction on the risk of CV events and mortality. Only in the last three years have trials of drugs that reduce Lp(a), such as alirocumab and evolocumab, been conducted. ODYSSEY OUTCOMES was a large trial of alirocumab, the results of which showed that alirocumab reduced the total number of CV events and CV mortality in patients diagnosed with acute coronary syndrome (ACS) [81]. In 2020, the data from the ODYSSEY OUTCOMES trial were reanalyzed to determine the effect of baseline Lp(a) levels and the trend of alirocumab-induced change on Lp(a) and LDL-C, results showed that each 5 mg/dL reduction in Lp(a) was predictive of a 2.5% reduction in CV events. Therefore, Lp(a) should now be considered a therapeutic target, especially after ACS [82]. There was a tremendous advantage when comparing alirocumab or evolocumab with placebo or ezetimibe plus a statin in another trial; however, the benefit difference between the two groups was not significant when comparing the two groups utilizing the combination of ezetimibe and statin [83].

Currently, new therapies that selectively target Lp(a) are being developed. The APO(a)-LRx study is currently ongoing, but preliminary findings indicate that APO(a)-LRx has the potential to reduce Lp(a) levels and their effects by up to 80%, potentially lowering CV risk [84]. In addition, testing a monoclonal antibody that reduces blood Lp(a) levels has demonstrated promising in vitro data [85]. The results of these trials are eagerly awaited.

To date, more persuasive evidence has exhibited that TG and Lp(a) are independent CV risk factors, even with LDL-C, and should be considered as new therapeutic targets in the management of CVD. Meanwhile, the importance of HDL-C has decreased compared to the previous era. However, in-depth studies analyzing genes and blood HDL-C levels are two hypotheses that need to be further studied to clarify the role of HDL-C.

4. Situations for considering residual cardiovascular risk factor intervention

4.1 After achieving LDL-C target

Based on the close association between hypercholesterolemia, especially LDL-C, with the incidence and mortality of ASCVD, the current treatment guidelines mainly focus on on lowering LDL-C levels [9, 11]. However, numerous clinical trials of statins, non-statin LDL-C lowering agents, and combination therapy have shown that the risk of ASCVD persists despite positive LDL-C reduction [14, 86, 87]. Accumulating evidence from epidemiological and genetic studies, as well as randomized clinical trials, suggests that TRLs [29, 41, 88], Lp(a) [77, 79, 82], inflammatory phenomenon [89–91] and thrombosis risk [92–95] are associated with risk of ASCVD in individuals with active LDL-C control and interventions to these factors yield promising results promise in improving the incidence of CV events [96].

Non-HDL-C dyslipidemia plays an important role in the residual risk of CVD. Recent recommendations for the quantification of atherogenic lipoproteins in addition to LDL-C for lipid-lowering strategies have been published [97].

4.2 Post-acute coronary syndrome

Advances in the treatment of ACS over the past few decades have improved the clinical outcomes of CV patients [98, 99]. Despite this, a substantial proportion of individuals continue to experience CV events, even when they are actively treated according to current guidelines [100]. This residual risk may be due to inflammation [90, 101, 102], thrombotic risk [93, 103] and metabolic causes such as TG [88, 104], Lp(a) [82, 105] and with or without HDL-C but has not been effectively addressed by current recommended approaches and is influenced by comorbidities [76, 102].

TG, Lp(a) have been shown to be independent risk factors affecting the risk of major CV events, some studies in subjects with a history of ACS also showed a similar correlation. Furthermore, the data to date suggest that TG and Lp(a) levels are positively correlated with the risk of ASCVD. Therefore, these two factors should be considered as new therapeutic targets to reduce residual CV risk [82, 88, 104, 105].

4.3 Diabetes mellitus

Insulin resistance and type 2 diabetes mellitus are associated with increased production of TRLs, such as VLDL-C and chylomicrons, as well as smaller and denser LDL-C particles (sdLDL-C), which makes LDL-C particles more compressed and therefore more prone to induce atherosclerosis. ApoB-100, the primary lipoproteins in VLDL-C, IDL-C, and sdLDL-C, as well as ApoB-48, the major lipoproteins in chylomicrons, have a significant risk of causing atherosclerosis. Despite effective LDL-C control with statin treatment, severe vascular events such as myocardial infarction, stroke, stable angina, and other vascular events, along with mortality from CV causes, occur substantially more frequently in diabetic patients. This has been shown to be related to TG [88, 104] because hyperglycemia is prevalent in those with type 2 diabetes mellitus [106]. Therefore, elevated TG is an important residual CV risk factor that should be considered in the treatment of diabetes.

In recent years, LDL-C-lowering treatments and other risk factor control strategies have significantly reduced the incidence of CVD, but in patients with type 2 diabetes there is still continue to increase the risk of ASCVD. Based on the evidence

to date, it is suggested that non-LDL-C is a necessary therapeutic target in the prevention of CV events, especially in the TRLs group, in the setting of type 2 diabetes [107]. Furthermore, numerous studies suggest that low HDL-C levels and high TG, particularly TRLs, predict the risk of ASCVD in diabetes 2 which explains how low HDL-C levels impact cholesterol conversion from intravascular atherosclerotic plaque via CETP in TG metabolism. The consequence of all lipid abnormalities in type 2 diabetes is an increased risk of ASCVD. There is strong evidence, both genetic and clinical, that reducing residual TRLs and TG is likely to reduce the risk of CVD in CKD. diabetic patients with 2-insulin resistance [88, 104, 107]. Interventions on ApoC3, ANGPTL3, and ANGTL4 factors are being examined as potential TG- and TRL-lowering treatments and risk reductions in CVD, according to preclinical and human genetic research.

5. Conclusion

Based on the current evidence, the importance of residual CV risk factors in dyslipidemia are undoubtfully obvious. Since the complexity of the pathogenesis of atherosclerosis related to dyslipidemia, the recent interventional studies have shown controversial results. Therefore, identification and treatment of these risk factors is critical to optimizing treatment, particularly in subjects with recurrent vascular events, despite optimal treatment of traditional CV risk factors. In clinical practice, adequate attention should be paid when screening and managing residual CV risk factors in dyslipidemia in individualized approach. The ongoing trials will give more answers to elucidate this important clinical area.

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