

Review Article

Lipoprotein(a): A Promising Marker for Residual Cardiovascular Risk Assessment

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Atherosclerotic cardiovascular diseases (CVD) are still the leading cause of morbidity and mortality worldwide, although optimal medical therapy has been prescribed for primary and secondary preventions. Residual cardiovascular risk for some population groups is still considerably high although target low density lipoprotein-cholesterol (LDL-C) level has been achieved. During the past few decades, compelling pieces of evidence from clinical trials and meta-analyses consistently illustrate that lipoprotein(a) (Lp(a)) is a significant risk factor for atherosclerosis and CVD due to its proatherogenic and prothrombotic features. However, the lack of effective medication for Lp(a) reduction significantly hampers randomized, prospective, and controlled trials conducting. Based on previous findings, for patients with LDL-C in normal range, Lp(a) may be a useful marker for identifying and evaluating the residual cardiovascular risk, and aggressively lowering LDL-C level than current guidelines' recommendation may be reasonable for patients with particularly high Lp(a) level.

1. Introduction

Atherosclerotic cardiovascular diseases (CVD), in terms of coronary heart disease (CHD), ischemic stroke, and peripheral artery disease, are still the leading cause of morbidity and mortality worldwide, although optimal medical therapy has been prescribed for primary and secondary preventions. According to previous epidemiological studies and meta-analyses [1–7], plasma level of low density lipoprotein-cholesterol (LDL-C) is causally associated with atherosclerosis and CVD, and plasma LDL-C level diminished by hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statins), which leads to incident CVD reduction and further supports the notion that LDL-C plays an important role on atherosclerosis initiation and progression. In line with the outcomes of published clinical trials, American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC) guidelines have recommended a target plasma LDL-C level, based on cardiovascular risk stratification, for each individual. However, some researchers observed that the residual

cardiovascular risk for some population groups was still considerably high although target LDL-C level has been achieved [8–11] and other risk factors, including lipoprotein(a) (Lp(a)), have been identified to be responsible for these phenomena.

During the past few decades, compelling pieces of evidence from clinical trials and meta-analyses consistently illustrate that Lp(a) is a significant risk factor for atherosclerosis and its manifestations, CHD and ischemic stroke [12–15]. Accordingly, Lp(a) is composed of two key components, named LDL particle and apolipoprotein (Apo(a)), and the assembly of Lp(a) may be both the intracellular and extracellular [16, 17]. Contrary to LDL-C, Lp(a) catabolism is less dependent on LDL-C receptor, and statins have a modest effect on Lp(a) regulation [16]. Substantial studies consistently show that plasma Lp(a) level is predominantly dependent on the isoform size variability of Apo(a) in terms of small isoform size of Apo(a) which results in higher Lp(a) level and vice versa [18–21]. And previous epidemiological studies also firmly demonstrate that, with Lp(a) elevation, the risk for cardiovascular risk is significantly increased [22–24]. For example, Kardys et al. observed that Lp(a) was associated

with a higher 1-year risk of cardiovascular events, with an adjusted hazard ratio (HR) of 3.1 (95% confidence interval (CI): 1.1–8.6) for the highest versus the lowest tertile [22]. In another study conducted by Momiyama and colleagues [23], they found out that Lp(a) levels were associated with aortic atherosclerosis as well as coronary atherosclerosis. Therefore, recently, some specialists of lipidology recommend that for patients with established CHD with a history of recurrent events despite appropriate therapy, Lp(a) should be taken into account for future risk stratification [25]. The European specialists of lipidology also recommend screening of elevated Lp(a) in patients with intermediate or high CVD risks [26]. Moreover, some studies also indicate that the Apo(a) isoform may also play an important and independent role on cardiovascular outcomes [21, 27].

Taken together, combined with the state-of-the-art clinical trials published previously and the advancements with regard to the understanding of Lp(a) biological effects on cardiovascular system, our current literature is going to systematically review the following aspects of Lp(a): structural and metabolic characteristics, pathophysiological roles, polymorphisms of Apo(a) gene and related clinical epidemiological studies, and potential approaches in modulating Lp(a), so as to present insights, if any, to future clinical and basic researches.

2. Structural Characteristics of Lp(a)

Lp(a) is a recent evolutionary arrival and was firstly discovered by Berg more than 50 years ago [28]. Lp(a) is only expressed in human, old world nonhuman primates (such as rhesus and baboon), and European hedgehog but not in the commonly used animal models such as rat, mice, and rabbits [16]. After being identified, a series of studies were conducted to further elucidate the characteristics of Lp(a). It has been well recognized that Lp(a) is composed of two main components, named low density lipoprotein (LDL) and Apo(a). These two moieties are covalently tethered by a disulfide bond, which is established between Apo(a) and apolipoprotein B-100 (ApoB-100) motif of lipid core (see Figure 1) [16, 29]. Similar to LDL-C, each Lp(a) is equipped with one molecule of ApoB-100, which is predominantly responsible for the proatherosclerotic feature of Lp(a). Another important motif, Apo(a), is a glycosylated-rich moiety, and the gene sequence of Apo(a) is highly homologous with that of plasminogen (see Figure 1) [30, 31]. Apolipoprotein(a) gene (*LPA*) locates on chromosome 6q23 and is flanked by plasminogen gene [32]. Accordingly, Apo(a) cDNA contains an inactive protease domain, 1 Kringle V, and 10 types of Kringle IV [33, 34], while the cDNA of plasminogen contains Kringles I to V as well as an active form of protease domain, which is critical for endogenous fibrinolysis [35]. Combined with Kringle V, the inactive protease domain of Apo(a) is structurally similar to the corresponding part of plasminogen (Kringle V plus active protease) while cannot be activated by tissue plasminogen activator and urokinase plasminogen activator [36]. Therefore, when thrombotic event occurs, Lp(a) could interfere with plasminogen activation through a competitive mechanism, which finally leads to

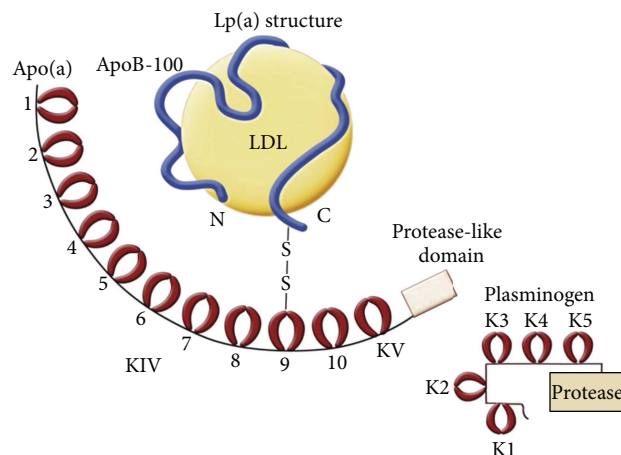


FIGURE 1: Delineation of structural characteristics of Lp(a) and similarity between Lp(a) and plasminogen. (Adapted from [16].)

thrombosis formation, artery occlusion, and tissue perfusion impairment. Kringle IV is the most mysterious and important domain of Apo(a). Kringle IV comprises 10 domains, named types 1 to 10. KIV-1 and KIV-(3-10) are single copy domains, while KIV-2 is a multiple copy domain (3 to 50) which leads to Apo(a) molecular weight quite variable (approximately ranging from 300 kDa to 800 kDa) [37]. Kringles of Apo(a) are enriched with cysteines and arrayed tandemly like a loop by three disulfide bonds. In brief, each Kringle has its unique binding site for specific substrate wherein special function is related to. For example, the only unpaired cysteine of KIV-9 is special for binding with cysteine of ApoB-100 through a disulfide bond [38]. Furthermore, KIV-9 is found to be related to smooth muscle cells proliferation and migration in an *in vitro* study, and KIV-(6-7) mediates the process of foam cells formation. KIV-(7-8) is significant for Lp(a) formation, which is believed to be due to the weak lysine binding sites (LBS) among these Kringles [39]. In conjunction with Kringle V, KIV-(9-10) is potential to inhibit angiogenesis. By virtue of unique LBS within Kringles, the capacity of Lp(a) attaching to and retaining in vessel walls is significantly enhanced. Finally, KIV-2, the most critical motif of Apo(a), is not only associated with isoform size heterogeneity of Apo(a) but also determines the synthetic rate, plasma level, and biological function of Lp(a) [34, 40].

3. Metabolism of Lp(a)

Accordingly, Apo(a) is synthesized in the liver, and the assembly of Apo(a) and LDL may be either intracellular and extracellular as supported by published basic research papers [41, 42]. Basically, the process of Lp(a) assembly primarily includes two steps [43]. In the first place, establishing two noncovalent couples between KIV-7 of Apo(a) and Lysine680/690 of ApoB-100 and KIV-8 of Apo(a) and Lysine4372 of ApoB-100 and then followed by the formation of a specific disulfide bond between Apo(a) and ApoB-100 [44]. The plasma Lp(a) level is modestly regulated by life style modification and medication therapy, whereas it

is significantly dependent on the isoform size of Apo(a), which is determined by the copy number of KIV-2 [16]. An inverse relationship was also identified between the isoform size of Apo(a) and plasma Lp(a) level, and the underlying mechanism is at least partially because (1) the biosynthetic time for small isoform size of Apo(a) is significantly less than that for the large one [45] and (2) large isoform size of Apo(a) is more prone to be degraded than small one [16]. Other factors in regulating *LPA* gene expression are also considered accountable for the Apo(a) biogenesis [46, 47]. For example, in the transcriptional level, other sequences related to Apo(a) encoding gene may enhance or diminish Apo(a) cDNA transcription as well as mRNA stability [19, 48, 49]. Preceding Apo(a) release from liver, posttranslational modification of Apo(a), in terms of three disulfide bonds formation and N-linked glycan addition in endoplasmic reticulum, is also significantly associated with the rate of Lp(a) assembly [50]. Boffelli reported that estrogen was negatively associated with plasma Lp(a) level in women, which was believed to be due to the negative effect of estrogen on Apo(a) promoter activity [46]. Moreover, many enhancer regions between *LPA* and plasminogen genes were also identified to be responsible for Apo(a) expression [51, 52]. For example, a regulatory region within *LPA* and plasminogen genes (accurately 20 Kb upstream of *LPA* gene) significantly increases the promoter activity of *LPA* gene thereby enhancing Apo(a) expression [52].

Nevertheless, compared to Lp(a) synthesis, biological catabolism plays a relative modest role on plasma level of Lp(a) [16]. The underlying mechanism through which Lp(a) is removed from circulating system is still not fully understood yet, neither is the site. Lp(a) can be either cleared as wholeness from circulating system or cleaved into LDL and Apo(a) for further degradation [16]. Currently, at least three general pathways have been identified responsible for Lp(a) and its components catabolism [16, 50]. In the first place, Lp(a) can be recognized by LDL receptor and undergo degradation similar to LDL-C. The significance of this process may be less important for Lp(a) than that for LDL-C [53, 54], because it was reported that only 10–25% of Lp(a) clearance from blood takes place via LDL-C receptor [55, 56]. Lp(a) can also be recognized and taken up by fibroblasts, hepatocytes, and macrophages via VLDL receptor [57]. Secondly, Lp(a) can be cleaved into LDL and Apo(a). Knowingly, LDL is abundantly removed from circulating system by its receptor with high affinity. With regard to Apo(a) degradation, the weakness bond of LBS between KIV-4 and KIV-5 is critical for proteolytic enzymes (like neutrophil elastase and metalloproteinase) to cleave Apo(a) into small pieces thereby excreted to urine [50, 58]. Kronenberg and colleagues previously observed an arterial-venous gradient of Lp(a) level after the blood flowed through renal circulating system [59], which suggested that renal secretion might be one of the important approaches for Lp(a) clearance. This finding was further substantiated by other studies in which plasma Lp(a) level in patients with renal dysfunction was significantly increased [60, 61]. Intriguingly, Apo(a) fragment was found in urine, and the volume of Apo(a) in urine was reduced in patients with renal dysfunction, further indicating that kidney was

crucial for Apo(a) excretion and catabolism [62, 63]. Last but not the least, Lp(a) and Apo(a) fragments are able to deposit in the vascular wall and exert multiple adverse effects on endothelial cells [57, 64, 65]. Many research papers showed that the volumes of Lp(a) and Apo(a) within the plaque were in proportion to the plasma levels of Lp(a) and Apo(a). Moreover, in comparison with large isoform size of Apo(a), small isoform size seems to have a higher propensity to retain in vessel walls [27, 66]. Typically, Lp(a) and Apo(a) bind to vessel walls predominantly through the coupling of LBS sites of the Kringles with the vessels component such as fibrinogen, fibrin, fibronectin, and laminin [16]. Notably, the affinity of Lp(a) and Apo(a) to bind to extracellular matrix of vessels is higher than that of LDL-C, which may partially explain the previous epidemiological findings that Lp(a) contributed to atherosclerosis and CVD progression was independent of LDL-C [16, 67].

4. Pathophysiological Effects of Lp(a) and Its Moieties on CVD

The pathophysiological effects of Lp(a) on atherosclerotic CVD can be broadly categorized into two aspects, named proatherogenesis and prothrombosis or antifibrinolysis. Similar to LDL-C, cholesterol-enriched lipid core in Lp(a) plays a crucial role in atherogenesis and progression. Importantly, in recent years, many clinical and basic studies observed that, besides LDL, another molecule named oxidized phospholipid (OxPL), binding to ApoB-100 (OxPL/ApoB-100), is also quite critical in mediating adverse effects of Lp(a) on vascular system [68]. OxPL/ApoB is an inflammatory and oxidative compound which leads the atherogenic capacity of Lp(a) to significantly increase [69, 70]. Strong association between OxPL/ApoB and plasma Lp(a) level was also observed ($R = 0.86$, $P < 0.0001$) [68]. Furthermore, as reported by Tsimikas et al. [70], the strength of this relationship was dependent on Apo(a) isoform size, in terms of large isoform size that corresponds to weaker association, and vice versa. A series of epidemiological studies also consistently revealed that OxPL/ApoB elevation not only was related to the initiation and progression of CVD but also contributed to the recurrence of CVD and mortality [68, 71–73]. And the underlying mechanisms can be generally ascribed to the following aspects such as amplifying oxidative stress, inducing endothelial cells necrosis, promoting monocytes, macrophages migration, and foam cells formation, and expanding necrotic lipid core [68]. As a consequence, OxPL/ApoB-enriched LDL is considered significantly responsible for the adverse effects of Lp(a) on cardiovascular system.

Intriguingly, other than OxPL, another important enzyme, named lipoprotein associated-phospholipase A2 (Lp-PLA₂), has also been identified noncovalently coupled with ApoB-100. The roles of Lp-PLA₂ on cardiovascular system have also drawn many attentions from scientific society in the past decade. Lp-PLA₂ is a key enzyme which is mainly responsible for platelet active factor (PAF) catabolism. As it is well known, PAF is a potent proinflammatory factor and is associated with atherosclerotic plaque formation

and progression [74]. Many early basic research papers showed that, in comparison with control group, Lp-PLA₂ overexpression was beneficial for ameliorating inflammatory reaction and oxidative distress in vessel walls [75–78]. Nevertheless, upon metabolizing oxidative LDL (oxLDL) and other phospholipids such as OxPL, two important and potent proinflammatory factors, named oxidized fatty acid (ox-FAs) and lysophosphatidylcholine (lyso-PC), are abundantly generated [79, 80]. A large number of basic research papers and epidemiological studies consistently indicated that the adverse effects of Lp-PLA₂ on cardiovascular system significantly surpassed the so-called cardioprotective benefits of Lp-PLA₂ [81, 82]. Basically, apart from metabolizing PAF and oxLDL, Lp-PLA₂ is also capable of degrading OxPL/ApoB-100, which is considered at least partially responsible for the cardio-protective effects of Lp(a). For example, in the Bruneck study [66], the authors noted a J-shaped-curve relationship between plasma level of Lp(a) with the incidence of CVD, indicating that at an appropriate plasma level of Lp(a), although the exact value currently is still little known, it may be useful and helpful to degrade OxPL/ApoB-100 and oxLDL within atherosclerotic plaque so as to reduce cardiovascular events. In retrospect, this finding was also indirectly illustrated by the previous 4S study [83], in which the most significant benefits of simvastatin therapy were derived from the second but not the first quartile of plasma Lp(a) level. To our best knowledge, the underlying mechanisms with regard to the cardio-protective effect of Lp(a) may be related to the degradation OxPL/ApoB-100 of by Lp-PLA₂. Unfortunately, there is still no randomized, prospective, and controlled trial to document the aforementioned intriguing findings. Because of the complicated and dual effects of Lp-PLA₂ on vascular system [84, 85], to our knowledge, prespecifying an appropriate range for plasma Lp(a) level is very useful, helpful, and critical for clinical practices in terms of better stratifying cardiovascular risk and carrying out more appropriate therapy, especially to those whose LDL-C is within target level. Knowingly, Lp-PLA₂ activity is also influenced by the isoform size of Apo(a), where an inverse correlation is observed [86, 87], suggesting that the association between Lp-PLA₂ and Lp(a) may also partially be determined genetically. This finding may, at least partially, also explain the discrepancies of CVD outcomes among different ethnic populations with comparable plasma Lp(a) levels.

Notably, due to variable and unique characteristics, the pathophysiological roles of Apo(a) have attracted intensive investigation. Apolipoprotein(a) per se is not only a prothrombotic lipoprotein but also a significant mediator in modulating the process of atherogenesis and progression conferred by Lp(a), oxPL/ApoB-100, and Lp-PLA₂. As mentioned in the structural section, the negative effect of Apo(a) on fibrinolysis is largely due to competitive mechanisms. Moreover, promoting platelets aggregation and increasing plasminogen activator inhibitor expression are also attributable to the prothrombotic effect of Apo(a). In the study conducted by Hervio and coworkers [88], they revealed that compared with large isoform size, small isoform size of

Apo(a) has a higher potential to inhibit endogenous fibrinolysis. In the Bruneck study [66], a strong prothrombotic effect was also found in small isoform size of Apo(a) but not in large isoform size. Overall, the antifibrinolytic and prothrombotic effects are also influenced by its isoform size. In addition, isoform size of Apo(a) is also found significantly associated with the effects of other moieties of Lp(a) and Lp(a) itself. For examples [26, 89], with small isoform size of Apo(a), plasma Lp(a) level, volume of oxPL/ApoB-100, and Lp-PLA₂ activity are all significantly increased when compared to large isoform size. Some previous, if not all, epidemiological studies showed that with small isoform size of Apo(a), the risk for premature CVD is profoundly increased, which is independent of LDL-C and other traditional risk factors [27, 90, 91]. In a recent published meta-analysis including 40 studies [89], when compared with KIV-2 repeats > 22 (corresponding to Apo(a) molecular weight ≥ 640 Kda), KIV-2 repeats ≤ 22 results in an increased CVD risk of 2.08 (95% CI: 1.67–2.58). In a study conducted by Kamstrup et al. [92], they revealed that when compared with the highest quartile of KIV-2 repeats (41–99), the lowest quartile of KIV-2 repeats (6–30) was responsible for a higher Lp(a) level as well as cardiovascular events. Taken together, based on previous findings, it is reasonable to make a conclusion that increased plasma Lp(a) level is a significant and independent predictor for incident CVD and mortality, which is profoundly enhanced by coupling with small isoform size of Apo(a) or with small copynumber of KIV-2 repeats.

5. Effects of Apo(a) Gene Polymorphism on CVD and Related Epidemiological Studies

Interestingly, compared to LDL-C, which is highly modifiable by lipid lowering drugs and lifestyle change, plasma Lp(a) level is predominantly determined by its encoding gene (*LPA*), which locates on chromosome 6q23, and the underlying mechanism is largely due to the copy-number variation of KIV-2 [48, 65]. Isoform size variability of Apo(a), determined by KIV-2 copy-number, was reported to be responsible for 40% to 70% of interindividual variation of plasma level of Lp(a) [20]. Other than KIV-2 copy-number variation, copy variation of pentanucleotide repeats (TTTTA) in the promoter area and C/T polymorphism in the coding area were also associated with plasma Lp(a) level [16]. In the past decades, some single nucleotide polymorphisms (SNPs) of Apo(a) gene associated with copy-number variability of KIV-2 have been identified [27, 93–96]. Nonetheless, after adjusting for other variables, only a minority of these SNPs have been documented to contribute to the elevated plasma Lp(a) level and increased risk for incident CVD. Accordingly, rs3798220 and rs10455872 may be the most intensively investigated variants [17, 97]. For example, in the study conducted by Luke and colleagues [98], they observed that compared with noncarriers, carriers of the variant rs3798220 have both increased 5-fold higher median plasma Lp(a) level and an adjusted odds ratio for severe CHD of 3.14. In the Cardiovascular Health study [99], rs3798220 was also observed associated with incidence of myocardial infarction in Caucasian. Interestingly, in the Women's Health Study [27], after a 9.9-year followup, aspirin seemed to render

benefits to the carrier of rs3798220 in the healthy Caucasian women, in which cardiovascular risks were reduced more than 2-fold when compared with control group. Another common variant rs10455872 was concomitantly identified to be strongly correlated with both increased plasma Lp(a) level and an odds ratio for CHD of 1.70. Lower copy number of KIV-2 and small isoform size of Apo(a) were considered attributing to these findings [95]. In a prospective study [100], rs10455872 SNP was found associated with incident CHD, and in case-control studies [95, 101], a relationship between rs10455872 SNP and incident CHD and myocardial infarction was also observed. In our recent study (paper has been recently accepted by *Journal of Lipids in Health and Disease*) in investigating the relationship between 3 variants (rs3798220, rs10455872, and rs6415984), plasma Lp(a) level, and future cardiovascular risk in Chinese Han populations with previously documented CHD, we observed that only the variant of rs6415084 was associated with plasma Lp(a) level and no correlation was found between these 3 SNPs with future cardiovascular risk. To our knowledge, these discrepancies among different studies may be at least partially due to the differences of ethnic background, the prevalence of minor allele of SNPs, and the different clinical protocols.

6. Potential Approaches to Modulate Plasma Lp(a) Level

As it has been intensively discussed, plasma level of Lp(a) is less affected by statins, life style, and dietary than LDL-C [16, 17]; however, some studies showed that nicotinic acid as well as estrogen and/or progestin hormone replacement might be one of the most potential useful approaches to reduce plasma Lp(a) level [102–106]. In the late 1980s, Carlson LA treated hyperlipidemic patients with 4 g nicotinic acid daily [102]. Six weeks later, they observed that Lp(a) was decreased concomitantly with the same percentage reduction of LDL-C when compared with baseline levels, which they speculated to be due to inhibition of ApoB-100 production, a common protein to Lp(a) and LDL-C. In 2010, Bruckert et al. published a meta-analysis regarding the effects of nicotinic acid alone or in combination with lipid lower drugs on the incident CVD [106]. This meta-analysis included 11 studies with more than 5000 participants, and the primary outcomes indicated that nicotinic acid therapy not only reduced the incidence of cardiovascular events but also reversed coronary and carotid atherosclerosis. In line with previous compelling pieces of evidence, the European Society of Atherosclerosis recommended that a patient with increased plasma level of Lp(a) is reasonably considered for nicotinic acid (1–3 g/day) therapy [26]. Accordingly, hormone replacement with estrogen and/or progestin is also potential to decrease plasma Lp(a) level [24, 103, 105]. Furthermore, reduction of incident CVD and mortality rate deriving from Lp(a) reduction with hormone replacement has also confirmed the potential efficacy with this strategy. For example, the study from Shlipak and coworkers revealed that estrogen and progestin therapy contributed to a more favorable outcome on CVD than control group, particularly in participants with initially

higher plasma Lp(a) level [107]. In another study, the authors showed that hormone replacement not only reduced plasma Lp(a) level but also markedly attenuated future CVD risk among women with hormone replacement in comparison with the control group [24]. Other less intensively investigated approaches for Lp(a) reduction involve nonsteroid anti-inflammatory drug aspirin, statins, IL-6 inhibitor, and PCSK9 inhibitor [16, 108]. For example, some researchers reported that interleukin-6 (IL-6) pathway was positively correlated with plasma Lp(a) level and Apo(a) expression in humans and monkey hepatocytes and inhibition of IL-6 pathway may be possible to reduce Lp(a) level [109, 110]. In the Women's Health Study [27], carriers of an Apo(a) variant had elevated Lp(a) and doubled cardiovascular risk in healthy Caucasian women, while aspirin therapy conferred a benefit for cardiovascular outcomes. Statins may reduce Lp(a) level by the means of increasing hepatic clearance of circulating LDL and decreasing Lp(a) assembly. PCSK9 inhibitor may also be useful for lower Lp(a) level via the clearance of LDL particle [111]. Until now, the most robust approach may be blood apheresis, which has been validated to be highly efficient in removing Lp(a) from the circulating system. However, this technique is neither noninvasive nor cheap. Therefore, this strategy seems less practical in clinic [112]. Finally, some previous epidemiological studies suggested that populations with both Lp(a) and LDL-C elevations have a higher cardiovascular risk [66, 90], and these population groups should be given a more intensive lipid lowering drug therapy so as to achieve a lower LDL-C level than those with only Lp(a) elevation. In the future, to our knowledge, exploring a unique medication specific for Lp(a) modulation must be a top priority.

7. Conclusion

With respect to its proatherosclerotic and prothrombotic effects, Lp(a) is believed to be a promising and critical biomarker for cardiovascular risk estimation. Causal relationship between Lp(a) and CVD has been recognized and demonstrated in the past decades. In patients with established CVD and with target LDL-C level achievement, Lp(a) measurement may add additive value for cardiovascular risk stratification.

Conflict of Interests

All authors declare that there is no conflict of interests.

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