Review article

Evidence-based assessment of lipoprotein(a) as a risk biomarker for cardiovascular diseases – some answers and still many questions

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Abstract

The present article is aimed to outline the current state of knowledge regarding the effects of lipoprotein(a) (Lp(a)) on cardiovascular disease (CVD) risk by summarizing the recent results of studies, meta-analyses and systematic reviews. The literature supports the predictive value of Lp(a) on CVD outcomes, although the effect size is modest. Lp(a) would also appear to have an effect on cerebrovascular outcomes, with the effect appearing even smaller than that for CVD outcomes. Consideration of apolipoprotein apolipoprotein(a) (apo (a)) isoforms and *LPA* genetics in relation to the simple assessment of Lp(a) concentration may enhance improving clinical practice in vascular medicine. We also describe recent advances in Lp(a) research (including therapies) and highlight areas where further research is needed such as the measurement of Lp(a) and its involvement in additional pathophysiological processes.

Keywords: apo(a), cardiovascular disease, cerebrovascular disease, coronary heart disease, Lp(a), LPA, stroke

Introduction

A variety of lipids and lipoproteins are involved in the development of vascular pathologies [1-8]. The role of lipoprotein(a) (Lp(a)) on health and disease has long been of interest [9]. Lp(a) is a unique and still enigmatic lipoprotein particle, composed by a covalent association mediated by a single disulphide bridge between apolipoprotein B_{100} ($ApoB_{100}$; the main protein moiety of low-density lipoprotein (LDL)) and apolipoprotein(a) (apo(a), a hydrophilic glycoprotein) [10-14] **(Figure 1)**. Apo(a) has a high degree of structural homology with plasminogen and can hence antagonize both *in vivo* and *in vitro* activity of the patter enzyme [15]. Due to its similarity with LDL and the structural homology with plasminogen, Lp(a) plays an atherothrombotic action [13].

Although the definitive metabolism of Lp(a) remains to be completely defined, biological evidence seemingly attests that apo(a) is secreted by the liver, rapidly associated with $apoB_{100}$ in the circulation, whereas its catabolism pathway is then mainly sustained by the liver (*via* the hepatic scavenger receptor class B type I and LDL receptor), spleen and kidney [13, 16]. Intriguingly, a large part of the circulating Lp(a) level is heritable, with its genetic components located in the *LPA* gene responsible for the encoding of apo(a) [17-22]. However, Lp(a) concentrations are also dependent on the rate of hepatic apo(a) and $apoB_{100}$ secretion [23]. A recent study showed that free apo(a) has a plasma residence time of approximately 11 days compared to only 4 days when the protein is bound to $apoB_{100}$ within the Lp(a) particle, thus supporting the concept of an individual metabolism for these components [24].

Studies of Lp(a) have led to the increasing recognition of its role as a risk biomarker causally associated with vascular pathologies [10, 25]. However, circulating Lp(a) concentrations above 50 mg/dL but less than 200 mg/dL are found in <1% of the general population [11]. A greater understanding of the pathophysiological roles of Lp(a) may lead to clinical measurements of Lp(a) as part of risk prediction and management of cardiovascular disease (CVD). However,

the heritable nature of Lp(a) concentrations would raise questions about who should be screened for and at what age. Lp(a) is modulated by several drugs and presents an interesting therapeutic target [26]. In this review, we aim to summarize and share current knowledge regarding the relationship between Lp(a) and vascular diseases, and to describe other interesting features of this intriguing lipoprotein particle. To date, there have been numerous review papers on the implications of Lp(a) for vascular medicine. We based the present paper on the meta-analyses, which were conducted on this topic, thus ensuring that our discussion reflects the highest quality available evidence.

Lp(a) and cardio- and cerebrovascular disease: an updated summary of evidence

A search of PubMed/Medline was performed to discover all the papers written in an English-language and published before January 15, 2016. The title terms 'lipoprotein (a)' or 'Lp (a)' and 'meta-analysis' or 'meta analysis' or 'metaanalysis' or 'systematic review' or 'study' or 'trial' were used. From the results, we selected high-quality and relevant meta-analyses for inclusion and discussion in this review. We supplemented these with other high-quality papers to expand the scope our work to other aspects of Lp(a) in health and disease.

The relationship between Lp(a) and CVD outcomes has been confirmed by at least three meta-analyses [27-29] (**Table 1**). An earlier meta-analysis (published in 1998) also suggested that Lp(a) is a risk marker for CVD [30]. The statistical methods of the meta-analysis were identical with those used in more recent studies; accordingly, this paper was not included here. Although all the three papers used prospective studies in the meta-analysis [27-29], this presented some difficulties as the outcomes of trials could not be divided into fatal and nonfatal events, or the study populations could not be divided into primary and secondary prevention groups. One meta-

analysis reported a significant prognostic value of Lp(a) on coronary heart disease (CHD) events by comparing the frequency of CHD deaths or myocardial infarction (MI) in patients with high and low baseline levels of Lp(a) [27]. The relative risk (RR) associated with high Lp(a) in the entire population was 1.6 (95% CI, 1.4 to 1.8; p<0.00001). In a subpopulation of patients with previous coronary disease the relative risk was 1.3 (95% CI, 1.1 to 1.6; p<0.001) [27]. A subsequent study reported a significant prognostic value of Lp(a) on CHD events (RR, 1.13 and 95% CI, 1.09 to 1.18 per 3.5-fold higher usual Lp(a) concentration, i.e., per 1 standard deviation) [28]. A more recent study has reported a significant prognostic value of Lp(a) on CHD events (RR of the entire population, 1.57 and 95% CI, 1.41 to 1.75, p < 0.001; RR of a subpopulation with previous coronary disease, 2.37 and 95% CI, 1.41 to 3.97, p=0.001) [29]. More recently, a review paper summarizing population-based studies has also described a continuous positive association between Lp(a) and the risk of CVD events [31]. Thus, a prognostic value of elevated Lp(a) on CHD events has been repeatedly confirmed, although the magnitude of the effect appears to be globally modest.

The predictive value of Lp(a) on CHD events in a population with a previous history of coronary disease shows great variability between the first study (RR of a population with previous coronary disease, 1.30, that is lower compared to that of an entire population) [27] and the recent study (RR of a population with previous coronary disease, 2.37, which is higher compared to that of an entire population) [29]. Further work is needed to resolve this discrepancy. Additionally, a review paper pointed out that in the presence of a high level of LDL, the association between Lp(a) and risk of CVD events was enhanced [31]. This also warrants further investigation.

The relationship between Lp(a) concentrations and cerebrovascular outcomes has been determined in at least three meta-analyses [28, 29, 32], with both fatal and nonfatal events as outcomes. The first paper reported a significantly high Lp(a) level and a more frequent existence of elevated Lp(a) concentrations ≥30 mg/dL (odds ratio [OR], 2.39; 95% CI, 1.57 to 3.63) in patients with stroke than in those without (this used case-control studies) [32]. Including prospective studies, a significantly greater number of stroke events was observed in the highest tertile of Lp(a) distribution than in the lowest tertile (RR, 1.22; 95% CI, 1.04 to 1.43) [32]. A subsequent article described a significant prognostic value of Lp(a) on ischemic stroke events (RR, 1.1 and 95% CI, 1.02 to 1.18 per 3.5-fold higher usual Lp(a) concentration (i.e., per 1 standard deviation)) [28]. On the other hand, another study reported no apparent prognostic value of Lp(a) on stroke (RR, 1.10 and 95% CI, 0.97 to 1.25; p=0.14) [29]. Thus, a prognostic value of Lp(a) on cerebrovascular (stroke) events is suggestively confirmed, but still inconsistent (**Table 1**).

Importantly, the magnitude of the prognostic value of Lp(a) on stroke events appeared to be low compared to that of Lp(a) on CVD events. This might be at least in part attributable to the more complicated pathogenetic mechanisms related to the development of stroke compared to those involved in CHD. Similar differences have been also observed by comparing the effect of blood pressure lowering [33] as well as the effect of LDL-cholesterol reduction (especially in secondary prevention patients) [34] on stroke versus the other CVD outcomes. Therefore, the effect of Lp(a) on stroke events [35, 36] is still hard to establish. On the other hand, in a more recent meta-analysis, including 20 trials and totaling 90,904 subjects and 5029 stroke events, an increased Lp(a) concentration has been reported to be an independent risk factor for ischemic stroke (OR, 1.41 and 95% CI, 1.26 to 1.57 for case-control studies; RR, 1.29 and 95% CI, 1.06 to 1.58 for

prospective studies), mainly pertinent for young patients (≤55 years of age) who suffered from stroke [37].

It was also hypothesized that the predictive role of Lp(a) on CVD and stroke events might be associated with inflammation. The role of inflammation or normal food intake in predicting CHD was assessed in 34,829 Danish participants included in the Copenhagen City Heart Study and the Copenhagen General Population Study [38]. This study showed that increased levels of C-reactive protein (CRP) were minimally associated with increased Lp(a) concentrations, and the Lp(a) value was not significantly modified by normal food intake [38]. A multidirectional Mendelian randomization approach including 100,578 Danish individuals then proved no association between plasma Lp(a) concentrations and low-grade inflammation, despite the causal association with increased risk of myocardial infarction and aortic valve stenosis [39].

Evidence is being accumulated in terms of the role of Lp(a) on CVD risk. All above issues would deserve further investigation to finally establish the prognostic value of Lp(a) on cardio- and cerebro-vascular outcomes.

Lp(a) and cardiometabolic and vascular disease: a unique insight

In recent years, additional meta-analyses and systematic reviews focused on the clinical significance of Lp(a) for vascular diseases have been published (**Table 2**). First, a meta-analysis which included population-based observational studies has examined the relationship between apo(a) and cardio- and cerebrovascular disease risk [40]. Apo(a) is a heritable modulator of Lp(a) effects and smaller apo(a) isoforms have been convincingly shown to be associated with higher Lp(a) levels [15, 17-22]. A significant association between smaller apo(a) isoforms and CHD events compared with larger apo(a) isoforms was described by Erqou et al (RR, 2.08; 95% CI, 1.67 to

2.58) [40]. A significant association was also appreciated between smaller apo(a) isoforms and ischemic stroke events compared with larger apo(a) isoforms (RR, 2.14; 95% CI, 1.85 to 2.97) [40]. The impact of apo(a) on CHD events might be related to Lp(a) concentrations. However, few studies included in this meta-analysis adjusted the data for Lp(a) values for exploring the relationship between apo(a) and outcomes [40].

Two different meta-analyses, involving case-control studies, investigated the role of Lp(a) in non-CVD pathologies [41, 42]. One article explored the relationship between Lp(a) and venous thrombembolism (VTE). It has been reported that a significant association may exist between increased Lp(a) levels (i.e., >30 mg/dL) and VTE (OR, 1.87; 95% CI, 1.51 to 2.30) [41]. The influence of Lp(a) on arterial pathologies is well-documented, but this article described new insights into the role of Lp(a) in venous pathologies. Another meta-analysis investigated the relationship between CVD risk based on Lp(a) levels and polycystic ovary syndrome (PCOS) [42]. It was reported that women with PCOS had significantly higher Lp(a) levels than controls (standardized mean difference, 0.81; 95% CI, 0.58 to 1.04) [42]. Notably, it is hence reasonable to put forward an hypothesis that the cardiometabolic propensity in PCOS may be partly caused by Lp(a).

Here, we would add the finding from a recent study (although it was not the meta-analysis and systematic review), the Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study (CGPS), has also shown that there is a causal association between increased Lp(a) concentrations, corresponding *LPA* risk genotypes, and increased risk of heart failure [43]. The association was partially mediated by myocardial infarction and aortic valve stenosis [43].

Finally, a systematic review comprising 6 observational studies, described the relationship between Lp(a) and familiar hypercholesterolemia (FH) in children [44]. No apparent relationship

between Lp(a) and FH in children was noticed [44]. The levels of Lp(a) were found to be higher in FH children, but this association remains controversial [45, 46]. The management of FH in childhood is commonplace to prevent adverse cardiovascular effects [47, 48]. To date, the levels of Lp(a) have been poorly described in FH children, since only a few studies comprising a small number of patients have addressed this association. Therefore, the need of further studies has been proposed although the data were negative [47] (**Table 2**).

Update on therapies for modulating Lp(a)

Apheresis is the most effective technique to reduce circulating Lp(a) concentrations up to 75% from the baseline levels [49]. Lp(a) is quite refractory to both drug intervention and lifestyle [49, 50]. Currently, therapeutic apheresis is recommended by most lipid and atherosclerosis societies only in cases of severe FH [51]. The HEART-UK and the German Committee of Physicians and Health Insurance Funds also recommended apheresis for individuals with progressive CHD and plasma Lp(a) concentrations higher than 60 mg/dL [52, 53]. However, plasma Lp(a) concentrations generally returned to baseline levels only two weeks after apheresis (which is compatible with the biological half-life of this enigmatic lipoprotein paticle), thus limiting the potential benefits of this technique, as well as reducing the quality of life of these patients [52, 54].

Various drugs and nutraceutical interventions have been investigated in experimental and clinical settings as modulators of plasma Lp(a) concentrations. Moreover, few societies have tried to identify the best therapeutic options to reduce Lp(a) concentrations. A target level of Lp(a) below 50 mg/dL, as a feature of global CVD risk, has been recommended by the European Atherosclerosis Society (EAS) Consensus Panel in 2010 [11]. Both the American Heart Association (AHA)/American Stroke Association (ASA) and the European Society of

Atherosclerosis (EAS) guidelines recommended 1-3 grams nicotinic acid (niacin, vitamin B_3) daily for the treatment of increased Lp(a) concentrations [11, 55, 56]. In a randomized, crossover trial of 12-weeks, it has also been reported that extended-release niacin (1-2 grams) daily may be effective to reduce Lp(a) concentrations *via* reducing apo(a) and $apoB_{100}$ production in statin-treated men with type 2 diabetes mellitus [57]. A simvastatin-niacin combination was found to be effective to reduce Lp(a) concentrations up to 21%, but such a reduction was not associated with lower CVD events in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study [58]. Another recent 24-week, prospective, open-label clinical trial evaluated the impact of extended-release (ER) niacin on plasma Lp(a) concentrations in function of apo(a) phenotype [59]. Indeed, high-dose ER niacin decreased plasma Lp(a) concentrations only in male subjects with low-molecular weight apo(a) phenotype [59]. However, different adverse effects have been noticed in clinical practice through increased production of prostaglandin D(2) and E(2) after niacin therapy that limits the widespread use of this drug [60]. Favorable effects of statins on lipid metabolism are well known. Atorvastatin is reported to reduce Lp(a) [61], while in general, plasma Lp(a) concentrations remain unchanged after this therapy, which may help to explain residual CVD risk in general population and FH individuals treated with statins [62, 63]. Fibrates, which are lipid-lowering drugs intracting with the Peroxisome Proliferator Activated Receptor alpha (PPARα), were also proposed as plasma Lp(a)-reducing drugs, but further studies remain warranted [64]. Thyroid mimetics, despite favorable effects through increased expression of hepatic LDL receptor and increasing clearance of LDL in the circulation, were discontinued in 2012 after notable side-effects [65].

Recently, much attention has been paid to several new drugs for modulating lipoproteins. Lomitapide (Juxtapid, Aegerion, Cambridge, MA), an inhibitor of microsomal triglyceride transfer protein (MTP), was shown to reduce plasma Lp(a) concentrations by 17% in hypercholesterolemic patients [66]. A study on individuals with homozygous FH showed a decrease by 15% of plasma Lp(a) concentrations after 26 weeks of lomitapide therapy [67].

There have been also data concerning the role of hormonal drugs on Lp(a) reduction. A recent meta-analysis of 12 RCTs with 1009 participants revealed that tibolone, a synthetic steroid with estrogenic, progestogenic, and weak androgenic actions, was found to be effective to decrease plasma Lp(a) concentrations by over 25% in postmenopausal women [68]. A modest reduction of Lp(a) concentrations has been also observed with aspirin treatment [69]. Cholesteryl ester transfer protein (CETP) inhibitors also decrease plasma LDL-cholesterol and Lp(a) concentrations, but the recent disappointment generated by evacetrapib (October 2015) raised significant doubts over the efficacy of drugs in treating increased plasma Lp(a) concentrations [70]. However, the Defining the Safety of Anacetrapib in Patients at High Risk for Coronary Heart Disease (DEFINE) study showed an essential reduction of Lp(a) by 36.4% after 24-weeks of treatment on 2757 patients recruited from 20 countries using anacetrapib [71].

A dose-dependent reduction of Lp(a) up to 78% was also shown through therapy with a modified antisense oligonucleotide drug [72]. The monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) can reduce Lp(a) [73-75]. Indeed, various trials showed a median reduction of Lp(a) from baseline up to 35% [76]. A pooled analysis of 150 mg every two weeks dosing from phase 2 trials showed the favorable impact of alirocumab on Lp(a) by over 30% [77]. The Program to Reduce LDL and CV Outcomes Following Inhibition of PCSK9 In Different Populations (PROFICIO) showed that evolocumab, another PCSK9 inhibitor (Amgen,

Thousand Oaks, CA), was effective to reduce Lp(a) by 29.5% (in a dose-dependent manner) in four randomized, double-blind phase 2 trials over a 12-week period [78]. Two studies using meta-analysis has shown a 25% reduction of Lp(a) [79] and -0.94 (95%CI, -1.12 to -0.77) of the standard mean difference change in Lp(a) by treatment PCSK9 inhibitors [80]. Furthermore, tocilizumab is a monoclonal antibody targeting the IL-6 receptor, which was found to be effective to decrease Lp(a) concentrations by 30% in rheumatoid arthritis individuals [81]. Another important step in developing a drug which successfully target Lp(a) concentrations might be the inhibition of apo(a) synthesis by fibroblast growth factor 19 (FGF19) and farnesoid X receptor [82, 83].

Some dietary supplements have been successfully evaluated for lowering plasma Lp(a) concentrations. A recent meta-analysis has demonstrated that oral L-carnitine significantly reduce Lp(a) concentrations (mean decrease, -8.82 mg/dL; $p<0.001$) [84]. However, these results should be interpreted with caution since oral L-carnitine metabolization generates trimethylamine-N-oxide (TMAO), a product strongly involved in increasing CVD risk and accelerating atherosclerosis [85, 86]. Adding dietary allicin from fresh garlic might be a solution to successfully inhibit the pathway of gut microbiota-dependent TMAO production [87]. On the contrary, another meta-analysis on 6 randomized controlled trials and 151 participants did not show a significant effect of garlic on Lp(a) concentrations (mean reduction, 16.86%; $p=0.12$), despite the inverse association noticed between the changes in plasma concentrations of Lp(a) and duration of supplementation - the significant effect was observed for the supplementation duration >12 weeks (-54.59%; $p<0.001$) [88].

Current perspectives

The role of Lp(a) as an independent risk factor of CVD events, irrespective of other coexisted risk factors, is critical. The knowledge of physicians, and consequently the frequency of measurements, is very limited (which is related to the lack of clear recommendations) [5]. The measurement of Lp(a) also remains problematic [89-92], and its heterogeneity leads to difficulties when comparing the endpoints of the different studies [91]. At present, immunoassays are generally available to measure Lp(a) levels, but when the antibodies for Lp(a) detection recognize the multiply repeated kringle IV-type 2 domain present in the apo(a) moiey, the apo(a) size can strongly impact assay results. Indeed, the composition of Lp(a), which contains apo(a), $apoB_{100}$ and various lipids, is probably the main source of inter-assay viability. Therefore, the levels of Lp(a)-cholesterol, although not commonly assessed in clinical trials, should be seen as a more suitable approach for standardizing (or harmonizing) Lp(a) measurement [89-92]. One proposed solution was that Lp(a) should be expressed in nmol/L of protein, based on the relationship between the total number of Lp(a) particles and apoB [94]. New methods for Lp(a) measurement are currently in development [91, 94].

Consideration of the genetics of Lp(a) is important when using this measurement for CVD risk assessment. Recent studies have suggested that the common variants rs1045587 or rs3798220 at *LPA* locus are significantly associated with increased Lp(a) levels and increased CVD risk [20, 22]. Both carriers of rs10455872 (OR, 1.70; 95% CI, 1.49 to 1.95) and rs3798220 variants (OR, 1.92; 95% CI, 1.48 to 2.49) showed an increased risk of CHD [20]. Similarly, the carriers of rs10455872 (OR, 1.32; 95% CI, 1.22 to 1.42) and rs3798220 variants (OR, 1.34; 95% CI, 1.18 to 1.54) showed an increased risk of coronary artery disease, and the carriers of the variants also showed an increased risk of ischemic stroke (OR, 1.10; 95% CI, 1.02 to 1.18) [22]. On the other hand, rs10455872 variant is more common in Caucasians than in other populations [95].

No apparent relationship between rs3798220 variant and subsequent cardiovascular events was observed in Chinese Han patients with coronary artery disease [96].

The genetic studies might provide further evidence of the role of Lp(a) in the development of cardio- and cerebro-vascular disease. Since genetic determinants are unaffected by environmental factors, the *LPA* genotype-scoring system might be useful to establish a personalized treatment [20, 22]. Future studies should address these aspects in various ethnic and/or diseased populations.

The oxidative modification of lipoproteins may be important in the pathophysiology of atherosclerosis [97, 98]. Being a unique lipoprotrein subclass, Lp(a) is relatively easily oxidized. Various phenomena of Lp(a) oxidation and/or oxidative molecules capable of binding to Lp(a) have been observed in vessel walls [99, 100]. Therefore, oxidized-Lp(a) levels might be more suitable markers for the development of cardio- and cerebro-vascular disease. An assay for oxidized-Lp(a) using the sandwich-ELISA method has been recently developed, thus generating an increased interest in oxidized-Lp(a) determination in CVD research [100-103]. The monoclonal antibody obtained using oxidizing agents in this assay was shown to react only with oxidized Lp(a), but not with native Lp(a) and LDL [100.] The antibody detected a specific epitope that appears when the Lp(a) particle has been exposed to oxidative stress [100]. Although Lp(a) is easily oxidized, oxidized-Lp(a) is not well correlated to native Lp(a) level in our experience. Even in low oxidative Lp(a) environment, the mobility of oxidized-Lp(a) is changed, being different from that of native Lp(a) in agarose gel electrophoresis analysis [100]. Additional assays for Lp(a) oxidation are needed [101], as are more studies to address the implication of Lp(a) in vascular pathologies.

In addition to the role of high Lp(a) levels in various vascular diseases, other features of Lp(a) have received attention. In contrast to the pathogenic effects of high Lp(a) levels, low concentrations are also important in vascular medicine [104]. A prospective study suggested a J-curved phenomenon with a slight increase of cardio- and cerebro-vascular outcomes in the group of patients with very low Lp(a) levels and a larger increase in the group of patients with significantly increased Lp(a) levels [104, 105]. The decreased values of Lp(a) have been associated with carotid atherosclerosis [105] and have been proposed as markers of cerebral hemorrhage risk based upon the results of a prospective population-based study [106]. Although the mechanisms of these findings are not sufficiently understood, it is important to explain about the role of Lp(a) on vascular pathophysiology. Low blood lipids might induce angionecrosis and/or reflect impaired nutritional metabolism within the vessels [107], and Lp(a) particles might be involved in these mechanisms. Therefore, excessive lowering of Lp(a) may be seen as a double edged sword, thus reducing the potential beneficial effect of physiological concentrations of this lipoprotein and its metabolites against cancer [108]. Lp(a) particles may also carry the molecules related to vascular dysfunction. Lp(a) can be a transporter through absorption of oxidized lipids in the circulation and vessel walls [109]. An highly increased Lp(a) level induces atherogenic properties with oxidized lipids, while a very low Lp(a) level might show atherogenic properties and a detrimental metabolism of scavenging oxidized lipids.

Some questions remain in relation to the controversial anti-tumor function of Lp(a) [110]. In experimental studies a reduction of tumor cells growth by apo(a) was demonstrated [111, 112]. The degradation of apo(a) inside of Lp(a), produces various size of kringles and this process was associated with anti-angiogenesis and anti-tumor properties [110]. In addition, although the biological mechanisms remain unclear, high Lp(a) levels were repeatedly detected in the very

elderly, suggesting that elevated Lp(a) might be linked with longevity [113]. The putative anti-cancer properties of Lp(a) and its metabolites may at least in part explain the association with longevity, but additional studies are warranted to define the potential beneficial effects exerted by Lp(a) at physiological concentrations. Some studies reported that high Lp(a) levels are predictive markers of CVD outcomes and including mortality, while others reported no apparent relationship between Lp(a) and nonvascular or all-cause mortality **(Table 1)** [28, 29]. It is still unknown if these results are related to the influence of Lp(a) on cancer or longevity. A recent prospective study reported that high levels of Lp(a) are beneficial for cancer- and all-cause mortality [114]. These findings may be increasingly important in the future when CVD events are more susceptible to treatment and the long life-expectancy results in an aging population.

Conclusions

The present paper outlines the current state of knowledge and evidence regarding the effects of Lp(a) on CVD risk by summarizing the results of the available data from meta-analyses and systematic reviews. The literature supports the predictive value of Lp(a) on CVD outcomes, although the effect size is modest. Lp(a) would also appear to have an effect on cerebrovascular (stroke) outcomes, although the effect appears to be smaller than that for CVD outcomes. Consideration of apo(a) isoforms and *LPA* genetics, in relation to circulating Lp(a) concentrations, may enhance improving the clinical practice in vascular medicine. We describe recent advances in Lp(a) research and highlight areas where further study is needed, including the measurement of Lp(a) and its involvement in additional pathophysiological processes.

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Figure legend:

Figure 1. Sketch of Lp(a)

Lp(a): lipoprotein(a), apo(a): apolipoprotein(a), apoB: apolipoprotein B, LDL: low-density lipoprotein