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Update on Lipoprotein(a) as a Cardiovascular Risk Factor and Mediator

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Abstract Recent genetic studies have put the spotlight back onto lipoprotein(a) [Lp(a)] as a causal risk factor for coronary heart disease. However, there remain significant gaps in our knowledge with respect to how the Lp(a) particle is assembled, the route of its catabolism, and the mechanism(s) of Lp(a) pathogenicity. It has long been speculated that the effects of Lp(a) in the vasculature can be attributed to both its low-density lipoprotein moiety and the unique apolipoprotein(a) component, which is strikingly similar to the kringle-containing fibrinolytic zymogen plasminogen. However, the ability of Lp(a) to modulate either purely thrombotic or purely atherothrombotic processes in vivo remains unclear. The presence of oxidized phospholipid on Lp(a) may underlie many of the proatherosclerotic effects of Lp(a) that have been identified both in cell models and in animal models, and provides a possible avenue for identifying therapeutics aimed at mitigating the effects of Lp(a) in the vasculature. However, the beneficial effects of targeted Lp(a) therapeutics, designed to either lower Lp(a) concentrations or interfere with its effects, on cardiovascular outcomes remains to be determined.

Keywords Lipoprotein(a) · Apolipoprotein(a) · LDL · Cardiovascular disease · Coronary heart disease · Atherosclerosis · Inflammation · Thrombosis · Fibrinolysis · Oxidized phospholipids · Clinical chemistry · Risk factors · Niacin · Genetics · Mendelian randomization

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Introduction

Emerging clinical and epidemiological evidence strongly supports elevated plasma lipoprotein(a) [Lp(a)] concentrations as an independent risk factor for cardiovascular diseases [1•]. First, new approaches and insights from the field of genetics have implicated Lp(a) as a causative agent in the atherothrombotic process [2•]. Second, although manifold potential pathogenic mechanisms for Lp(a) are still considered to underlie the harmful effects of Lp(a), evidence is beginning to emerge that the modification of Lp(a) by oxidized phospholipids may be a common denominator [3•]. Finally, several approaches to lower plasma Lp(a) concentrations may soon lead to studies that address the proposition that decreasing plasma Lp(a) concentrations can prevent cardiovascular events [4•]. This review aims to summarize the most recent data with respect to each of these developments.

Modulation of Lp(a) Synthesis, Assembly, and Clearance

Properties of Lp(a) and Apolipoprotein(a)

Lp(a) is a unique lipoprotein particle whose biological function and metabolic role remain unknown. Lp(a) consists of a lipoprotein moiety essentially indistinguishable from low-density lipoprotein (LDL) [5] to which the signature glycoprotein apolipoprotein(a) [apo(a)] is covalently linked (see Fig. 1). It is apo(a) that appears to confer the unique properties of Lp(a), including its remarkable heterogeneity in size and plasma concentrations, its very different metabolism, and the multiple ways by which it may promote atherosclerosis and thrombosis [6•].

Apo(a) is evolutionarily related to the serine protease zymogen plasminogen [7], and this homology underlies many of the potentially harmful properties of Lp(a) [8]. Plasminogen is

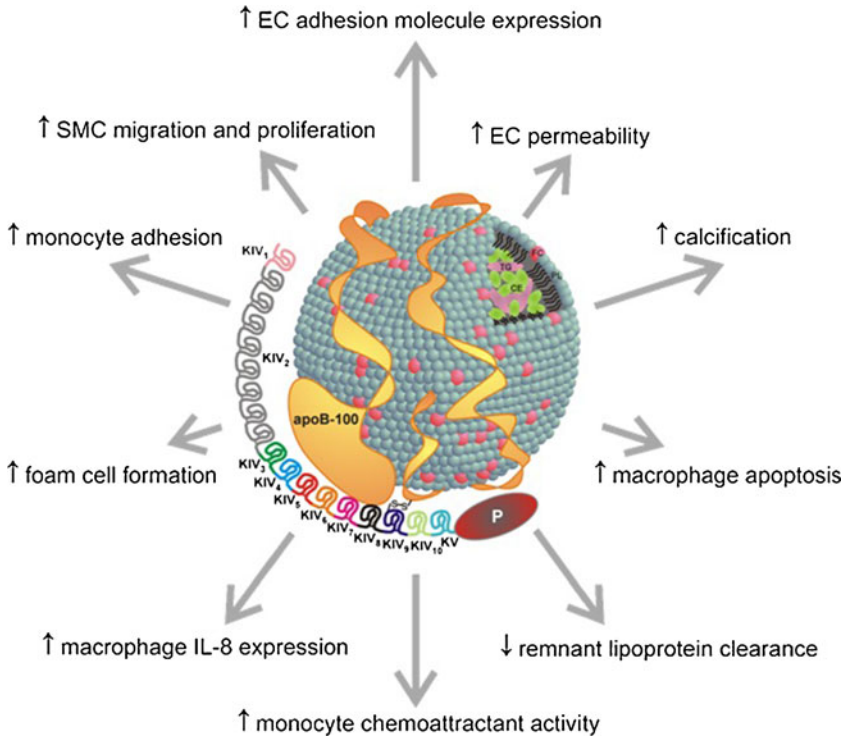

Fig. 1 Structure of lipoprotein(a) [Lp(a)] and its manifold potential pathogenic mechanisms. Lp(a) consists of a lipoprotein moiety identical to low-density lipoprotein, consisting of a core of cholesteryl esters (*CE*) and triglycerides (*TG*), an outer shell of phospholipids (*PL*) and free, unesterified, cholesterol (*FC*), and a single molecule of apolipoprotein B-100 (*apoB-100*). Apolipoprotein(a) is covalently linked to apoB-100 through a single disulfide bond, and consists of ten types of plasminogen kringle (*KIV*)-like sequences (KIV_1–KIV_{10}), a kringle V (*KV*)-like domain, and an inactive protease-like domain (*P*). KIV_2 is present in different numbers of repeated copies in different apoliprotein(a) isoforms. A large number of mechanisms by which Lp(a) could promote the initiation and progression of atherosclerosis have been described in the literature, as indicated (reviewed in [1•, 2•, 3•, 6•, 9]). *EC* endothelial cell, *SMC* smooth muscle cell

composed of an amino-terminal "tail" domain that participates in maintaining the "closed" tertiary structure of native plasminogen, five different domains known as kringles, and a trypsin-like protease domain that is activated by tissue-type or urokinase-type plasminogen activators. Kringles are tri-looped structural domains containing three invariant disulfide bonds and are found in a variety of proteases involved in coagulation and fibrinolysis, where they appear to mediate protein–protein interactions. Apo(a) lacks domains homologous to the plasminogen tail domain or kringles I–III. Instead, apo(a) contains multiple copies of sequences homologous to kringle IV of plasminogen, followed by single copies of a kringle V-like domain and the protease domain (see Fig. 1) [7]. The apo(a) protease domain is catalytically inert and cannot be cleaved by plasminogen activators [9]. There are ten types of kringle IV domains in apo(a), which differ in amino acid sequence; nine of these (kringle IV types 1 and 3–10) are present in a single copy, whereas kringle IV type 2 (KIV_2) is present in differing numbers of repeated copies (as few as three to more than 30; see Fig. 1) [10–12]. The differing numbers of KIV_2 copies are specified by the different alleles of *LPA*—the gene encoding apo(a)—present in the population and accounts for the marked size heterogeneity of Lp(a). *LPA* allele size is an important determinant of plasma Lp(a) concentrations as there is a general inverse correlation between *LPA* allele size and plasma Lp(a) concentrations [13]. This correlation can largely be explained by the less efficient post-translational processing and secretion of large apo(a) isoforms by hepatocytes, where apo(a) is synthesized [14].

Plasma Lp(a) concentrations differ widely—over 1,000-fold—in the population, and most of this variation (up to 90 %) is attributable to the *LPA* gene itself [2•]. Although *LPA* allele size plays a significant part in this variation (up to 60 % of the total), other sequence variations within *LPA* also contribute, as do certain nongenetic factors [2•, 15].

Modulation of *LPA* Gene Expression

Although plasma Lp(a) concentrations are largely resistant to dietary and drug interventions, several nongenetic modulators of *LPA* gene transcription have been identified. These findings have important implications for the development of therapies aimed at lowering plasma Lp(a) concentrations.

Work from Kostner's group [16] in Austria discovered that patients with biliary obstructions had very low levels of plasma Lp(a), and that these concentrations rose on surgical

intervention to relieve the obstruction. These findings suggested a potential role for the farnesoid X receptor (FXR), which is activated by bile acids, in suppressing *LPA* transcription. Indeed, transgenic mice harboring the human *LPA* gene on a yeast artificial chromosome showed reduced plasma apo(a) levels in response to common bile duct ligation, whereas this effect was not observed in mice harboring this transgene on a background of FXR gene knockout [16]. Further molecular studies identified sites in the *LPA* promoter that mediate, both directly and indirectly, the effect of bile acids [16, 17]. Elucidation of the pathways by which bile acid activation of FXR suppresses apo(a) expression identifies targets that could be exploited in the design of therapeutics to lower plasma Lp(a) concentrations, although targeting expression of *LPA* alone may prove challenging.

It has been appreciated for a number of years that niacin administration lowers plasma Lp(a) concentrations, in addition to several other effects on the lipid profile [18]. Although the mechanisms underlying this effect have remained a mystery, a recent biochemical study also from Kostner's group [19] indicates that the effect of niacin may be mediated at the level of *LPA* gene transcription. Niacin was shown to decrease *LPA* messenger RNA levels both in transgenic *LPA*-YAC mice and in primary hepatocytes and hepatoma cell lines. Analysis of the *LPA* promoter revealed the presence of several cyclic AMP response elements, accounting for the ability of niacin, which decreases cyclic AMP levels in the cell, to suppress *LPA* transcription. However, the negative results of two large clinical trials of niacin (see later) might suggest that this agent is not a promising strategy for lowering the risk for cardiovascular disease attributable to elevated Lp(a) concentrations [20, 21].

Site of Lp(a) Assembly

The dogma in the Lp(a) field for several decades has been that Lp(a) is assembled extracellularly, perhaps on the surface of hepatocytes, from apo(a) and an apolipoprotein B (apoB)-100-containing lipoprotein. The basis for this was (1) the lack of observation of covalently linked apo(a) and apoB-100 intracellularly [22] (except for one study, which used a truncated, nonphysiological, and highly over expressed form of recombinant apo(a) [23]), (2) the observation that Lp(a) assembly can proceed spontaneously outside the cell [22, 24], and (3) the existence of a secreted oxidase-type enzyme that catalyzes specific disulfide bond formation between apo(a) and apoB-100 [25]. A major missing piece of this puzzle has been the identity of the apoB-100-containing lipoprotein that couples to apo(a) to form the nascent Lp(a) particle. A recent study using an in vivo stable-isotope kinetic approach threatens to topple this dogma [26•]. It was found that the apoB associated with Lp(a) has production kinetics very different from that of apoB associated with either LDL or very low density lipoprotein (VLDL); Frischmann et al. [26•] took this as evidence that Lp(a) assembly must occur intracellularly. It may be more accurate to state that the results in fact suggest that Lp(a) arises from a specific and distinct pool of apoB; this may be consistent with intracellular assembly, but also with assembly directly on the surface of hepatocytes or in the space of Disse [26•]. Intracellular assembly of Lp(a) from a physiological isoform or direct observation of an Lp(a)-targeted apoB population has never been observed, although Frischmann et al. [26•] correctly point out that the existing cell models may not faithfully represent human hepatocytes in situ. Clearly, additional work is required to reconcile the existing data. These advances will likewise be crucial for the development of therapeutics aimed at inhibition of Lp(a) biosynthesis and/or assembly.

Lp(a) Clearance and Catabolism

The route of clearance of Lp(a) is also an unresolved area replete with controversy. It is clear that differences in plasma Lp(a) concentration primarily are a function of differences in the rate of synthesis, not of the rate of clearance [27]. Yet, the receptors in the liver that clear Lp(a) from the circulation remain undefined. In vivo evidence in human subjects homozygous for familial hypercholesterolemia strongly suggests against a role for the LDL receptor (LDL-R) in Lp(a) catabolism [28]. Indeed, this finding is in keeping with the relative resistance of Lp(a) concentrations to the effects of drugs that affect lipid metabolism. In particular, statins, which increase the number of hepatic LDL-Rs, have been very well studied, and various reports have shown that different statins can increase, decrease, or have no effect on plasma Lp(a) concentrations (reviewed in [29]). Although a recent meta-analysis of randomized trials (3,540 patients) showed that atorvastatin does indeed decrease plasma Lp(a) concentrations (although to what extent was not presented) [30], data from the large Collaborative Atorvastatin Diabetes Study (CARDS) (1,156 patients) showed no effect of atorvastatin [31]. Interestingly, this same report (also using additional statin trials) showed a strong contribution of Lp(a) to the genetic determinants of response of LDL cholesterol (LDL-C) to atorvastatin. A single-nucleotide polymorphism (SNP) in *LPA* emerged from a genome-wide association study of the LDL-C response to this statin, an effect that was entirely accounted for by the association of this SNP with plasma Lp(a) concentrations [31]. Since Lp(a) was resistant to atorvastatin, the patients with high Lp(a) appeared to be comparatively resistant to the therapy as Lp(a) cholesterol could account for as much as 20 % of their apparent LDL-C.

A very interesting recent report demonstrated that infusion of a monoclonal antibody against proprotein convertase subtilisin/kexin 9 (PCSK9) into healthy human volunteers decreases plasma Lp(a) concentrations by 25-30 % [32•].

PCSK9 is an enzyme that normally functions to decrease the number of LDL-Rs on the cell surface by promoting shunting of the receptor to degradative pathways during recycling inside the cell [33]. The idea that PCSK9 might target receptors other than the LDL-R is an emerging one, with LDL-R-related protein 1, VLDL receptor, and apolipoprotein E receptor 2 being identified as candidates [34, 35]; further analysis of this phenomenon may thus address three key questions: (1) whether the LDL-R is truly involved in Lp(a) catabolism; (2) what the receptor or receptors that mediate Lp(a) catabolism are; and (3) whether PCSK9 can indeed operate through receptors other than the LDL-R.

A recent study examined relationships between plasma Lp(a) concentration [both Lp(a) particle number (Lp(a)-P) and Lp(a) cholesterol] and markers of triglyceride and high-density lipoprotein (HDL) metabolism [36]. At low concentrations of triglycerides, Lp(a)-P and Lp(a) cholesterol were highly related, but at elevated concentrations of triglycerides the relationship between these parameters was much weakened, surprisingly, and Lp(a)-P was related more to parameters of HDL lipidation, VLDL, and triglycerides. The mechanistic basis for these findings could not be explained by the approach used in this study, and it is not clear that the non-Lp(a) lipid parameters influence Lp(a) synthesis or catabolism. Yet, there are certainly elements in the literature that may be germane, including the ability of certain modulators of lipid metabolism to, at times unexpectedly, modulate plasma Lp(a) concentrations, as described in the following section.

Therapeutic Modulation of Lp(a)

For elevated plasma Lp(a) concentrations to graduate from "emerging" to "established" cardiovascular risk factor status, one key criterion is demonstration that lowering plasma Lp(a) concentrations leads to a reduction in indices of cardiovascular disease such as events. However, there is as yet no therapy that lowers plasma Lp(a) concentrations in the absence of other salutary effects on the lipid profile. In addition, it is not known if some of these therapies may be more effective in patients with elevated plasma Lp(a) concentrations.

Niacin

Niacin (nicotinic acid) has long been known to favorably influence concentrations of LDL-C, triglycerides, and HDL cholesterol (HDL-C), through a variety of mechanisms [37]. Niacin is also able to substantially decrease plasma Lp(a) concentrations [38]. One mechanism for this may involve the effect on *LPA* gene transcription, as outlined earlier. Niacin also inhibits apoB secretion by inhibiting triglyceride synthesis, thus promoting intracellular degradation of apoB during synthesis [39]. It will be interesting to determine if the presumptive Lp(a)-specific pool of apoB (see earlier) is similarly modulated by niacin. Although niacin can lower plasma Lp(a) concentrations by as much as 40 %, not all studies have reported an effect of niacin on plasma Lp(a) concentrations and not all patients exhibit a decrease [18].

Niacin is probably the most recognized means to therapeutically lower plasma Lp(a) concentrations. In fact, the European Atherosclerosis Society Consensus Panel has recommended that patients at intermediate or high risk of cardiovascular disease be screened for plasma Lp(a) concentration, and that reduction of a patient's Lp(a) level to under 50 mg/dL with the use of niacin should be a treatment priority after management of lipoprotein cholesterol [40]. A major side effect of niacin that has stood in the way of its wide use has been flushing. However, sustained-release niacin formulations and antiflushing adjunct therapy have promised to decrease this side effect. Unfortunately, two large trials of niacin using these respective approaches (AIM-HIGH and HPS2-THRIVE) have both failed to show a cardiovascular benefit of niacin treatment over treatment with a statin (with or without ezetimibe) alone [20, 21]. Although this would seem to mark the end of the road for niacin as a treatment of elevated Lp(a) concentrations, it should be noted that the effects of niacin were not examined as a function of initial plasma Lp(a) concentration. In addition, although Lp(a) concentrations in AIM-HIGH decreased by 25 % with niacin treatment [20], the analogous data from HPS2-THRIVE have yet to be presented.

Cholesteryl Ester Transfer Protein Inhibitors

Modulation of HDL-C levels as a way to prevent cardiovascular disease has been a long-standing target of drug development [41, 42]. Phase III trials of two cholesteryl ester transfer protein inhibitors, torcetrapib and dalcetrapib, have been halted prematurely because of safety and futility, respectively, even though both were successful at raising HDL-C levels [43, 44]. Two other compounds, anacetrapib and evacetrapib, have been developed that are more potent than dalcetrapib while lacking the off-target effects on blood pressure of torcetrapib [45–47]. Anacetrapib has been demonstrated to markedly (by 36 %) lower plasma Lp(a) concentrations [45]. The mechanism by which this occurs remain unknown, but investigation of this effect will likely yield new insights into Lp(a) production and/or catabolism and the role of triglycerides and HDL in these processes.

Mipomersin

Mipomersin is an antisense oligonucleotide directed against apoB. In addition to lowering LDL-C concentrations, mipomersin also lowers plasma Lp(a) concentrations by 40–50 % [48•]. These findings suggest that a specific pool of apoB directed towards Lp(a) assembly is synthesized in

hepatocytes and may couple with apo(a) prior to becoming incorporated into the circulating apoB pool.

Apheresis

Removal of apoB-containing lipoproteins by lipid apheresis is a very effective technique for the treatment of familial hypercholesterolemia. Although it is generally not specific for Lp(a), in a recent study that targeted familial hypercholesterolemia patients with elevated Lp(a) concentrations, lipid apheresis reduced plasma Lp(a) concentrations by 73 % and the rate of major adverse coronary events by 87 % [49]. All patients were also taking statins to lower LDL-C concentration; subgroup analysis allowed the investigators to conclude that a major contributor to the reduction of events was the decrease in Lp(a) concentration, rather than the decrease in LDL-C concentration. More recently, a study has been reported in which Lp(a) was selectively removed in CHD patients with normal LDL-C concentration by apheresis [Lp(a) apheresis]; this technique also reduced plasma Lp(a) concentrations by 73 % and yielded significant regression of coronary atherosclerosis as measured by angiographic determination of the percent diameter stenosis and minimum lumen diameter [50•]. This study is thus the first to directly demonstrate that reduction of Lp(a) concentrations (albeit by a relatively invasive technique that is not appropriate for use in the general population) can reverse atherosclerotic disease. These findings provide a clear impetus to investigate the efficacy of Lp(a) lowering in larger populations.

Lp(a) as a Risk Factor for Atherothrombotic Disease

New Insights from Genetics

The strong genetic component underlying elevated plasma Lp(a) concentrations has been recognized for decades. Early studies determined that the *LPA* gene itself was responsible for up to 90 % of the variation in plasma Lp(a) concentrations, and that a large component of this variation resided in differences in the number of KIV_2 repeats in different *LPA* alleles [51]. In fact, the current genetic revolution in appreciating the role of Lp(a) was presaged by the observation in 1992 that individuals who inherited smaller *LPA* alleles were at greater risk of coronary artery disease (CAD) [52]. More contemporary genetic studies, taking advantage of new technologies offering a higher-resolution genetic approach and larger numbers of subjects, have validated this initial result and have thrust Lp(a) once more to prominence.

Two key articles published in 2009 identified sequence variants in *LPA* associated both with elevated plasma Lp(a) concentrations and with risk of CAD. Using a genome-wide approach, Clarke et al. [53] determined that the *LPA* locus was the strongest candidate locus for CHD among all those examined; two variants, namely, rs3798220 and rs10455872, were identified as mediating this observed relationship. The former SNP represents an isoleucine to methionine substitution at position 4,399 within the apo(a) protease-like domain, whereas the latter is intronic. It is not known whether apo(a) containing either isoleucine or methionine at position 4,399 differs in its properties. However, both of these SNPs were associated with *LPA* allele size and plasma Lp(a) concentrations, suggesting that they may be markers, rather than functional variants [53]. Indeed, it was recently reported that additionally considering these SNPs explained the previous association of four-SNP haplotypes within the *SLC22A3–LPAL2–LPA* locus with CAD [54]. A recent report failed to detect an association of the original four-SNP haplotypes with CAD in a Chinese Han population [55]; it would be interesting to determine if consideration of rs3798220 and rs10455872 would affect this finding and thus imply a different genetic architecture for *LPA* in this population. On the other hand, two studies have shown that carriers of the Met4399 allele respond more favorably to aspirin treatment for prevention of CHD [56, 57]. It remains to be determined if this result is because of an inherent functional difference in the Met4399 variant or because of the elevated Lp(a) concentrations and small isoform sizes in these carriers.

The second key article was the result of a "Mendelian randomization" study which found that small *LPA* allele sizes [which are inherited randomly and which are themselves correlated with elevated plasma Lp(a) concentrations] are associated with CAD risk [58]. The study design therefore allowed the authors to pronounce elevated Lp(a) concentration as a "causal" risk factor for atherosclerosis, as the random inheritance of *LPA* alleles accounts for several potential confounding factors in association studies, including selection bias and reverse causality. The demonstration that elevated Lp(a) concentrations are a causal risk factor was a key milestone, and it helped prompt the European Atherosclerosis Society Consensus Panel recommendations regarding screening for and management of elevated Lp(a) concentrations (see earlier) [40].

What remains a key question is whether small Lp(a) isoforms are more harmful in their own right, i.e., independent of their association with elevated plasma Lp(a) concentrations, by analogy to the situation with rs3798220 (Ile4399Met). In this case, there is direct functional demonstration that smaller Lp(a) isoforms are more harmful (see later). Indeed, several studies have concluded that smaller apo(a) isoforms are independent predictors of vascular risk in multivariate analyses [59, 60]. More recently, a meta-analysis of 40 studies showed that individuals with a small (fewer than 22 kringle IV repeats) isoform are at twofold increased vascular risk [61]. On the other hand, in the genetic studies cited above, the effects of the genetic variants in *LPA* (either KIV_2 repeats or SNPs strongly

associated with isoform size) were eliminated after adjustment for plasma Lp(a) concentrations [53, 58]. Therefore, additional investigations are clearly required in this regard, preferably taking into account "allele-specific" Lp(a) concentrations, as advocated by Berglund's group [62]. On the other hand, from a practical standpoint, it might be argued that a sufficient degree of the excess risk conferred by Lp(a) could be captured clinically by merely measuring plasma Lp(a) concentrations.

Elevated Lp(a) Concentrations as a Risk Factor for Noncoronary Atherosclerosis

The vast majority of the clinical studies on Lp(a) conducted to date have examined CAD, both in terms of events and in terms of surrogate markers. It is reasonable to expect, on the basis of pathophysiological considerations, that elevated plasma Lp(a) concentrations would similarly be a risk factor for atherothrombotic disease in other vessel beds. Indeed, evidence is accumulating that this is in fact the case. Results from the large EPIC-Norfolk prospective population study showed that elevated plasma Lp(a) concentrations were associated not only with CAD outcomes, but also with peripheral artery disease [63]. They were not associated with ischemic stroke (albeit with comparatively few occurrences even in this large cohort), adding to the conflicting literature on this topic. A very recent case–control study of childhood ischemic stroke found that Lp(a) levels were not different between subjects in the case group and subjects in the control group, although when the subjects in the case group were followed as a prospective cohort study, higher Lp(a) concentrations (and smaller isoforms) increased the risk of stroke recurrence [64]. In a genetic study, a series of SNPs and corresponding haplotypes were significant predictors for carotid artery atherosclerotic disease [65]; these SNPs conferred these effects through their influence on Lp(a) concentrations. Another recent study found that increasing Lp(a) concentrations were associated with increasing atherosclerotic plaque scores in the abdominal, but not thoracic, aorta [66]. It is not unreasonable to expect that elevated Lp(a) concentrations will ultimately be found to be associated with most, if not all, forms of atherosclerotic disease. Hence, therapeutic lowering of plasma Lp(a) concentrations may be beneficial with respect to several of these disorders. At the same time, as our understanding of the pathophysiological role of Lp(a) comes into focus, this may provide a rationale in the event that Lp(a) does not turn out to be a risk factor for certain types of atherothrombotic disease.

Utility of Lp(a) as a Tool for Improving Prediction

Although the evidence is scant that therapeutic lowering of Lp(a) concentrations (such as by administration of niacin) would be an effective cardiopreventative measure, a more proximal utility of measuring Lp(a) concentrations may be to assist in risk stratification of patients. Measurement of Lp(a) concentrations has long been problematic owing to the absence of an accepted reference standard, nonstandardized assays that suffer from an apo(a) isoform-dependent bias, and lack of agreement on the appropriate cut points and assay units [67]. Many of those issues have been addressed in the past decade, except for the fact that most assays express Lp(a) concentrations in mass units (mg/dL), whereas a molar concentration (i.e., the number of particles per unit volume) is more appropriate [68]. This is because different Lp(a) isoforms possess widely divergent molecular weights. Furthermore, it has become apparent that different ethnic groups have distinct distributions of Lp(a) concentration. For example, sub-Saharan Africans have higher median Lp(a) concentrations and less skewedness to their distribution than Caucasians [13]. Therefore, it is currently recommended that elevated Lp(a) concentration be defined at greater than the 75th percentile (molar concentrations) of a race-specific distribution [68].

Several consensus panels have recommended measurement of Lp(a) concentration in specific groups [40, 69•]. Although screening of the general population is not recommended [most individuals possess Lp(a) concentrations below the concentration which appears to confer risk], those with greater than intermediate risk of CHD according to the Framingham criteria, with existing CHD or recurrent events, or a strong family history of CHD are recommended to be screened. Another population that may be targeted is that in which LDL-C has proven refractory to statin therapy. It is thought that identifying individuals with elevated plasma Lp(a) concentrations would define a population that could benefit from more aggressive management of modifiable risk factors.

Although the efficacy of this approach has not been formally examined, some studies have sought to determine if measuring plasma Lp(a) concentrations in addition to standard lipoprotein analysis might improve prediction of CHD risk [70, 71]. As is the case with other forms of advanced lipoprotein testing such as non-HDL-C and LDL particle number [72], the results have been disappointing, with only a marginal increase, if any, in risk prediction observed [71, 72]. Once again, however, these study designs did not take into consideration what the outcomes might be if a finding of elevated Lp(a) concentration triggered more aggressive management.

Pathophysiological Mechanisms of Lp(a)

A large number of pathophysiological mechanisms for Lp(a) have been proposed (see Fig. 1). These include both proatherogenic and prothrombotic/antifibrinolytic mechanisms, and arise both from the homology of Lp(a) to LDL and plasminogen and from unique properties of apo(a) itself

[8]. As yet, none of the proposed mechanisms have been validated in vivo, which reflects the lack of strong animal models for Lp(a) and the difficulty of modeling several aspects of atherosclerosis in animal models [73].

An alternative means to gain mechanistic insights is to use clinical studies. For instance, it is still not clear whether it is the proatherosclerotic or the prothrombotic/antifibrinolytic effects of Lp(a) that are the more important contributors. Several recent articles have examined this issue. Goldenberg et al. [64] found that elevated plasma Lp(a) concentrations and small apo(a) isoforms increased the risk of recurrent arterial ischemic stroke in children, which presumably lacks an atherosclerotic component. They only partially attributed this link to impaired fibrinolysis on the basis of a weak correlation between Lp(a) concentrations and euglobulin lysis time, although it is debatable whether this assay as implemented by the Goldenberg et al. (lacking tissue plasminogen activator) captures fully the effect of Lp(a) on arterial thrombi [74]. Kamstrup et al. [75•] used a Mendelian randomization approach to determine that genetically elevated Lp(a) concentration (KIV_2 repeat number) is more related to atherosclerotic stenosis than it is to venous thrombosis. Although they concluded that this argues against a role for the prothrombotic/antifibrinolytic mechanisms of Lp(a) in arterial atherothrombotic events, it should be emphasized that venous thrombi have a genesis and composition very different from those of their arterial counterparts. Helgadottir et al. [76•] achieved similar results with analysis of rs3798220 and rs10455872, and also reported that genetically elevated Lp(a) concentration was not associated with ischemic stroke subtypes that are not primarily atherosclerotic in origin. A role for Lp(a) in the thrombogenic phase of CAD remains to be formally ruled out.

Novel Mechanisms of Lp(a) Action

Role of Oxidized Phospholipids and Phospholipase A_2

Lp(a) has been shown to play a key role as a carrier of oxidized phospholipids, which are damaging molecules with a variety of proatherosclerotic effects [3•]. As such, modification by oxidized phospholipids may be a common denominator in many of the proatherosclerotic mechanisms ascribed to Lp(a), which include proinflammatory effects on endothelial cells and macrophages [8]. Oxidized phospholipids associated with apoB-containing lipoproteins are strongly related to CAD risk [3•]. Oxidized phospholipids were subsequently shown to preferentially associate with Lp(a) compared with other apoB-containing lipoproteins [77], and to accumulate to a greater extent on Lp(a) containing small apo(a) isoforms [78]. It is thought that most of the Lp(a)-associated oxidized phospholipids are covalently linked to apo(a), possibly in the kringle V region [79]. The coronary risk attributable to the oxidized phospholipids on Lp(a) is potentiated at high concentrations of either soluble phospholipase A_2or lipoprotein-associated phospholipase A_2, an enzyme that can liberate the covalently attached oxidized phospholipids [80, 81].

Recent studies have delineated a specific mechanistic link between Lp(a)-associated oxidized phospholipids and the development of advanced, unstable atherosclerotic lesions. The oxidized phospholipids on apo(a) were able to promote macrophage apoptosis through a pathway dependent on Toll-like receptor 2/CD36 [82]. These findings were brought into greater focus by a subsequent immunohistochemistry study in which apo(a), oxidized phospholipids, and macrophage epitopes were found in increasing abundance in vulnerable plaques [83•]. Clearly, the full spectrum of the proatherosclerotic and prothrombotic effects of Lp(a)-associated oxidized phospholipids needs to be discovered, as this modification may prove to be a fruitful target for therapeutic modulation.

Effect of Lp(a) on Calcification

Coronary artery calcification is a parameter that can be measured noninvasively using computed tomography and provides an index of atherosclerotic burden. The relationship between plasma Lp(a) concentrations and coronary artery calcification has been a point of controversy through the years. The is evidence both for [84–86] and against [87, 88] such an association, as well as evidence from a transgenic rabbit expressing apo(a) that Lp(a) can promote this process [89]. Two recent studies detected such an association, albeit either in a dyslipidemic population [90] or in a population with a high degree of preexisting disease [91]. An intriguing genetic study showed that genetically elevated Lp(a) concentrations are a causal risk factor for aortic valve calcification and aortic stenosis [92•]. Although a direct mechanistic link between coronary artery calcification and aortic valve calcification (which is not an atherosclerotic process) remains to be determined, the data speak for the ability of Lp(a) to accumulate in the vessel wall and hence accelerate the calcification process.

Conclusions

Although much recent progress has been made in validating the concept of Lp(a) as a key player in vascular disease and in unlocking the secrets of its pathogenic mechanisms, there are still enormous knowledge gaps that need to be addressed. The foremost challenge is to demonstrate that lowering Lp(a) concentrations ameliorates the risk of cardiovascular events. These studies are currently impaired by the lack of availability of a therapeutic agent, appropriate for widespread use, that specifically lowers Lp(a) levels without affecting the levels of other lipoproteins. An alternative approach would be to

develop a therapeutic that interferes with the harmful effects of Lp(a). The unique structural and functional properties of Lp(a) suggest that a specific agent is a feasible prospect. But first, the appropriate mechanisms to target—among the plethora that have been proposed for Lp(a)—need to be definitively identified. Therefore, there are many basic and clinical research goals related to Lp(a) on the immediate horizon.

Conflict of Interest Michael B. Boffa and Marlys L. Koschinsky declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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