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Lipoprotein(a) and cardiovascular disease: current state and future directions for an enigmatic lipoprotein

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1. ABSTRACT

Lipoprotein (a) (Lp (a)) is a complex polymorphic lipoprotein. Although structurally similar to low-density lipoprotein, Lp(a) has a glycoprotein, apolipoprotein(a) (apo(a)), attached to the apolipoprotein B-100 component. Several unique properties of Lp(a) can be attributed to the presence of apo(a). Several decades of research has improved our understanding of the structure, biochemistry, and pathophysiology of Lp(a) associated diseases. Genetic, epidemiological, and translational data indicate that elevated Lp(a) levels are likely in the causal pathway for atherosclerotic cardiovascular diseases as well as calcification of the aortic valves. The "Lp(a) hypothesis," unlike the "LDL hypothesis," has not been tested in clinical trials yet. Currently, the management of elevated Lp(a) is directed at lowering low-density lipoprotein cholesterol levels. Developing therapies include antisense oligonucleotides which inhibit the synthesis of apo(a). This review discusses the current state of literature on pathophysiological and clinical aspects of Lp(a), including its role in coronary heart disease, stroke, aortic valve stenosis, and other vascular diseases. Current and emerging therapies aimed at treatment for elevated Lp(a) levels are also discussed.

2. INTRODUCTION

Lipoprotein (a) (Lp (a)) is one of the most complicated and polymorphic lipoproteins. Although first reported in 1963 (1-3), research on Lp(a) did not

gain much attention until 1987, when the *LPA* gene coding for apolipoprotein(a) (apo(a)) was cloned and sequenced by a group led by Richard Lawn (4,5). Apo(a) is the primary protein that accounts for the difference between low-density lipoprotein (LDL) and Lp(a) particles. Another era of heightened interest in Lp(a) followed in 2009, when robust evidence from Mendelian randomization studies6 and large cohort studies showed the association of Lp(a) with cardiovascular disease (CVD) events (7,8).

Although five decades of research have improved our understanding of the structure, biochemistry, and pathophysiological aspects of Lp(a) and its association with CVD risk, Lp(a) remains a puzzle that the scientific community has not fully decoded. Below, we aim to review the current state of the literature regarding the association of Lp(a) with CVD and therapies that lower Lp(a), and discuss future directions of therapies in development.

3. STRUCTURE AND METABOLISM

Lp(a) contains a lipoprotein moiety that is similar to LDL in regards to the lipid concentration as well as the presence of the protein apoB-100. The Lp(a) particle has an exclusive glycoprotein, apo(a), which is attached to the apoB-100 by a single disulfide bond (9). Hence the Lp(a) particle contains apo(a) and apoB-100 in a 1:1 molar ratio (10). Apo(a) is synthesized primarily in the liver; however, its assembly site is unconfirmed and could be within the hepatocyte, the space of Disse, or the plasma component (11).

3.1. The apo(a) chain contains five cysteine-rich domains known as “kringles.”

McLean *et al.* reported marked similarities between the sequence of apo(a) and the serine protease zymogen plasminogen (an inactive version of plasmin, a major enzyme involved in the cascade of fibrinolysis) (4). The apo(a) kringle IV–like sequences are grouped into 10 types depending on the amino acid sequence (KIV1 to KIV10) (12). All KIV kringle types are typically present in a single molecule of apo(a) except KIV2, which is present in variable number of identically repeated copies usually ranging from 3 to more than 40 (10). In general, apo(a) isoform size is inversely related to Lp(a) concentration in most populations (13).

The presence of apo(a) gives unique synthetic and catabolic properties to Lp(a). Given the structural similarity of apo(a) to plasminogen, Lp(a) hinders fibrinolysis by competing with plasminogen binding to molecules and cells. As a result, plasminogen activation, plasmin generation, and fibrinolysis are impaired (14,15). Lp(a) can also bind to macrophages via a high-affinity receptor that promotes foam cell formation and the deposition of cholesterol in atherosclerotic plaques (16). Because of its combined prothrombotic and proatherogenic properties, Lp(a) may influence CVD development, progression, and events through multiple mechanisms, as described in subsequent sections.

The mechanisms underlying Lp(a) catabolism are not clear. Although plasminogen receptor, LDL receptor (LDL-R), and scavenger receptor B1 have all been described in the clearance pathway of Lp(a), their exact role is not fully understood (17). Cain *et al.* postulated that apo(a) is the primary ligand that mediates Lp(a) uptake and plasma clearance18. Lp(a) is primarily cleared by the liver, with the kidneys playing a minor role (18,19).

4. PHYSIOLOGICAL FUNCTION

Lp(a) may play a role in wound healing (20,21). Lp(a) has been postulated to facilitate this process by inhibition of fibrinolysis through kringle-mediated binding to fibrin and by transportation of cholesterol to sites of injury for cell proliferation during tissue repair (20). This hypothesis suggests that high Lp(a) concentrations could lead to decreased risk of bleeding, and epidemiological data support this hypothesis. In a prospective cohort study in 10,494 Japanese individuals, the highest versus the lowest tertile of Lp(a) was associated with a hazard ratio (HR) of 0.34 (95% confidence interval (CI) 0.15–0.76) for the risk of cerebral hemorrhage in men and HR of 0.44 (95% CI 0.21–0.96) for women (22). However, the antifibrinolytic and lipid transport functions of Lp(a) may also contribute to the observed relation between Lp(a) level and CVD risk as described below.

5. ASSOCIATION WITH CARDIOVASCULAR DISEASES

5.1. Coronary heart disease or ischemic stroke

Elevated Lp(a) is one of the leading inherited dyslipidemias in patients with premature coronary heart disease (CHD) (23). Initially, retrospective case–control studies evaluated the association of elevated Lp(a) levels and CHD among patients with existing CHD (24). However, given the risk of bias with case–control design, a causal role of Lp(a) in the pathogenesis of CHD could not be established. In the past two decades, epidemiological and Mendelian randomization studies have suggested a causal role of Lp(a) with incident CHD.

A large epidemiological study, led by John Danesh in the Emerging Risk Factors Collaboration, assessed the relationship of Lp(a) concentration with the risk of major vascular and nonvascular outcomes. This study involved data from 126,634 participants

in 36 prospective studies. The risk ratio for CHD after adjustment for age and sex was 1.16 (95% CI 1.11–1.22) per 1–standard deviation (SD) increase in Lp(a) (equivalent to 3.5-fold higher than usual Lp(a) concentration of 1.25 mg/dL) and 1.13 (95% CI 1.09–1.18) in models adjusted for CVD risk factors and traditional lipids (7). A number of large epidemiologic studies (25,26) and several meta-analyses (7,27,28) have demonstrated this significant association of Lp(a) with incident CHD.

In 2009, Kamstrup *et al.* used a Mendelian randomization approach to assess the causal association of Lp(a) with CVD. This study included data from the Copenhagen City Heart Study (CCHS; a prospective general population study with 16 years of follow-up), the Copenhagen General Population Study (CGPS; a cross-sectional general population study in more than 29,000 individuals), and the Copenhagen Ischemic Heart Disease Study (a case–control study in 2461 individuals). Results showed that genetically elevated Lp(a) levels were associated with increased risk of myocardial infarction (MI) (6). The HR for MI was 1.22 (95% CI 1.09–1.37) per doubling of Lp(a) level between the first and fourth KIV2 quartiles (6–30 vs 41–99 KIV2 repeats, respectively) (6). In the same year, Clarke *et al.* identified two *LPA* variants that were strongly associated both with increased levels of Lp(a) and increased risk of CHD8. Odds ratios (ORs) for CHD were 1.70 (95% CI 1.49–1.95) for the common variant (rs10455872) and 1.92 (95% CI 1.48–1.49) for a second, independent variant (rs3798220). Since genetic studies are usually free of regression dilution bias, confounding, or reverse causation (21), these studies strengthen the argument that Lp(a) levels may be causal in their association with CHD.

Recently, in the Biomarkers for Cardiovascular Risk Assessment in Europe project, the authors analyzed 56,804 participants from seven prospective population-based cohorts across Europe (maximum follow-up of 24 years) (29). In this large dataset with a homogenous Lp(a) measurement method, there were regional differences within the European population in the Lp(a) levels. Elevated Lp(a) was shown to confer an increased risk for major coronary events (MCE: definite, possible, definite or possible acute MI, coronary death, unstable angina pectoris, and cardiac revascularization) and CVD events (first fatal or nonfatal CHD event or likely cerebral infarction, coronary death, unstable angina pectoris, cardiac revascularization, ischemic stroke, and unclassifiable death). In analyses adjusted for age, sex, and CVD risk factors, individuals with Lp(a) levels above the 90th percentile had the highest risk for future MCE, with an HR of 1.49 (95% CI 1.29–1.73). Individuals with Lp(a) level ≥90th percentile (corresponding to levels ≥43.5 mg/dL) had the highest MCE risk (HR of 1.31 (95% CI 1.15–1.50)) as well as CVD events with HR of 1.44 (95% 1.25-1.65) (29).

Lp(a) concentrations are variable in different ethnicities and regions (29). African American individuals have higher Lp(a) levels than Caucasians. However, a recent study showed that the risk of incident CVD events (CHD or ischemic stroke) conferred by Lp(a) concentration was similar in Caucasians and African Americans (30). Quintile analyses of a cohort of 3467 African Americans and 9851 Caucasians showed a graded risk for incident CVD; HR of 1.35 (95% CI 1.06–1.74) for African Americans and 1.27 (95% CI 1.10–1.47) for Caucasians with Lp(a) levels in the highest vs lowest quintile. Similar results were obtained when comparing incident CHD or ischemic stroke as the outcome.

Other studies have tested the association between small apo(a) isoforms and CHD risk due to their conformational differences compared with the larger isoforms (30). A study by Emanuele *et al.* suggested that patients with acute MI had a higher percentage of small apo(a) isoforms (31). Lp(a) particles with small apo(a) isoforms (hence, high Lp(a) concentrations) have also been shown to inhibit fibrinolysis (32). Another reason small isoforms may be more atherogenic is their enhanced ability to inhibit fibrinolysis (33).

The association between Lp(a) and CVD events is not only limited to the Caucasian and African American populations. Recently, in a Mendelian randomization study in 9015 cases and 8629 controls from the Pakistan Risk of Myocardial Infarction Study (PROMIS) study, Saleheen *et al.* showed that smaller apo(a) isoform size and increased Lp(a) concentration were both independently associated with CHD (34). In this population, the OR for MI was 1.10 (95% CI 1.05–1.14; p<0·0001) per 1-SD increment in Lp(a) concentration (data adjusted for *LPA* KIV2 repeats and conventional lipids). Genome-wide analysis revealed a common variant (rs2457564) associated with small apo(a) isoform size but not with Lp(a) concentration and another variant (rs3777392) associated with Lp(a) concentrations but not apo(a) isoform size. The OR for MI was 1.27 (95% CI 1.07–1.50; p=0·007) per 1-SD increment in Lp (a) concentration due to rs3777392 and 0.96 (95% CI 0.94–0.98; p<0.001) per 1-SD increment in apo(a) protein isoform size due to rs2457564 in the cohort.

5.2. Heart Failure

In a recently published study, Kamstrup and Nordestgaard combined data from the CCHS and CGPS cohorts and evaluated the association between elevated Lp(a) levels and heart failure (HF) in a total of 98,097 Danish individuals followed up in

1976–2013 (35). The results of this study showed that Lp(a) levels were associated with incident HF risk. The observed multivariable-adjusted HRs for HF were 1.10 (95% CI 0.97–1.25) for the 34th–66th percentiles of Lp(a) (8–19 mg/dL), 1.24 (95% CI 1.08–1.42) for the 67th–90th percentiles of Lp(a) (20–67 mg/dL), 1.57 (95% CI 1.32–1.87) for the 91st–99th percentiles of Lp(a) (68–153 mg/dL), and 1.79 (95% CI 1.18–2.73) for levels >99th percentile (>153 mg/dL) versus less than the 34th percentile (Lp(a) levels <8 mg/dL) (p<0.001). The equivalent population-attributable risk was determined to be 9%. Furthermore, genetic analyses showed a relative risk of 1.18 (95% CI 1.04–1.34) per 10-fold higher Lp(a) levels (which was equivalent to observational HR of 1.22 (95%CI 1.11–1.35) for HF (35). Mediational analyses showed that 47% of the increased risk for HF secondary to elevated Lp(a) levels was mediated through MI and 21% through aortic stenosis, with 37% remaining unexplained. The authors postulated that high levels of Lp(a) may lead to increased arterial stiffness, including noncompliance of the aorta resulting in HF not explained by development of MI or aortic stenosis (35).

However, more recently, in an analysis of the biracial ARIC study, Lp(a) levels were not associated with HF hospitalization when individuals with prevalent and incident MI were excluded from the analyses (36). The association between Lp(a) levels and incident HF hospitalizations was not significant (HR 1.07, 95%CI (0.91–1.27)) when comparing quintile 5 vs. quintile 1 of Lp(a). Whether Lp(a) functions as an independent mechanism leading to the development of HF or whether the association between Lp(a) level and HF is mediated by interim development of CHD remains to be seen.

5.3. Aortic Stenosis

The first observation of the association between high Lp(a) levels and aortic valve sclerosis was made in 1995 (37). In the recent past, high plasma Lp(a) concentrations have been shown to correlate strongly with aortic stenosis (38-40). In the CCHS and CGPS cohort (combined n=77,860), an incremental risk associated with aortic stenosis was noted across percentile increases in Lp(a) levels. HRs of 2.0 (95% CI 1.2–3.4) for 90th–95th percentile of Lp(a) levels (65–90 mg/dL) and 2.9 (95% CI 1.8–4.9) for Lp(a) levels greater than the 95th percentile (>90 mg/dL), versus levels less than the 22nd percentile (<5 mg/dL; p-trend <0.001) was observed in this population (41).

Thanassoulis *et al.* showed that *LPA* single nucleotide polymorphism (SNP) rs10455872, which carries a high risk for MI and CHD, reached significance in a genome-wide analysis and was the strongest genetic causal risk factor for aortic stenosis and calcifications of the aortic valve across multiethnic groups (42). In this prospective analysis, the association of *LPA* genotype with incidence of aortic stenosis was robust; HR per allele of *LPA* gene was 1.68 (95% CI 1.32–2.15). Other studies have since confirmed the strong association between Lp(a) levels and aortic valve calcifications, aortic stenosis, and progression of aortic stenosis across different racial groups (41,43).

6. PATHOGENICITY IN CARDIOVASCULAR DISEASES

Despite the abundance of studies that have assessed potential mechanisms by which elevated Lp(a) levels may increase CVD risk, the role of Lp(a) in the development and progression of CVD still continues to be explored. The currently hypothesized mechanisms are several and are summarized in Table 1.

Lp(a) and apo(a) have been found within the intima of human arteries and vein grafts of reoperated coronary artery bypass patients (44-46). Similarly, arterial samples from monkeys, rabbits, and mice have shown intimal aggregates of Lp(a) particles and apo(a), either when injected with human Lp(a) or after transgenic modifications with human Lp(a) (47-49).

The entry of Lp(a) particles into the intimal lining of arteries depends on the Lp(a) concentration in the plasma, Lp(a) particle size, blood pressure, and arterial permeability (50). Typically, LDL particle influx into the intima is 15-fold higher than that of Lp(a) in most individuals, and *in vivo* studies have shown that the rates of removal of both lipoprotein particles is similar (51). Lp(a) can be oxidized, degraded, and/or aggregated (44), and once it is oxidized, it is more readily taken up by macrophage scavenger receptors (52) and preferentially trapped in the arterial wall compared to LDL particles.

Interestingly, Lp(a) particles have also been shown to have a preferential arterial sequestration than LDL in the event of an intimal injury. In rabbit models, Lp(a) particles were shown to accumulate approximately 2- to 3-fold more in the intima following balloon injury than LDL (45). One explanation may be that the balloon injury in the arteries could expose the arterial intima directly to the blood flow, perpetuating formation of a blood clot. This may attract Lp(a) particles as they bind to fibrin, thus leading to higher Lp(a) levels (21) in the intima. High Lp(a) concentrations, or small apo(a) sizes, have been associated with the formation of dense fibrin clots or reduced clot permeability and prolonged clot lysis time both in healthy individuals and in individuals with previous MI (53).

Furthermore, the oxidized phospholipids (OxPL) component of Lp(a), present in the lipid

Table 1. Associated mechanisms for the proinflammatory, prothrombotic and proatherogenic features of lipoprotein(a) molecule

Features	Effect
Proinflammatory	• Increases interleukin-8 expression • Increases phospholipid oxidation • Increases monocyte cytokine release • Increases chemotaxis • Increases transmigration of monocytes
Proatherogenic	• Increases smooth muscle cell proliferation • Increases proteoglycan matrix binding • Increases foam cell formation • Increases necrotic core and calcification of atherosclerotic lesion • Upregulates adhesion molecules
Prothrombotic	• Increases endothelial cell PAI-1 expression • Increases TFPI activity • Increases platelet aggregation • Decreases plasminogen activation • Decreases fibrin degradation

PAI-1= Plasminogen activator inhibitor-1; TFPI=Tissue factor pathway inhibitor

phase of Lp(a) or found covalently bound to apo(a), is proinflammatory. Studies have shown that the OxPL on Lp(a) upregulate inflammatory genes (54), and induce the expression of interleukin-8 in macrophage cell lines (55).

An *in vivo* study showed increased arterial inflammation (detected by increased accumulation of 18-fluorodeoxyglucose) in the carotid arteries and aorta of subjects with increased levels of Lp(a) (108mg/dL (50-195mg/dL); n=30) (56). A higher production of proinflammatory cytokines by these individuals' macrophages upon stimulation and a greater capacity for endothelial penetration of monocytes were also demonstrated in this study. These proinflammatory effects rescinded by inactivating OxPL with a specific antibody or via the use of recombinant apo(a) lacking OxPL (56). These findings suggest that the proinflammatory effects of elevated Lp(a) were predominantly mediated by the OxPL on Lp(a).

Glycation of lipoprotein(a) particle is another mechanism by which Lp(a) may enhance the atherosclerotic process. Glycated Lp(a) (gly-Lp(a)) has been shown to enhance the production of plasminogen-activator inhibitor-1 and to increase the synthesis of tissue plasminogen activator in the arterial and venous endothelial cells. This process is carried out more readily by the gly-Lp(a) compared to the glycated LDL particles (57). Similar to glycated LDL, gly-Lp(a) is also more susceptible to oxidative modification compared to its unmodified form (57).

7. CONTROVERSIES IN Lp(a) MEASUREMENT

The highly heterogeneous nature of apo(a), in particular variations in KIV2, has been the primary challenge in the development of immunoassays to measure Lp(a) in the plasma and serum. Besides the variations in KIV2 already described, variable glycosylation occurs in the core of the KIV motifs as well as the sequences linking the kringles (58).

At the present time, several difficulties in the standardization of Lp(a) measurements are due to different analytical methods. Some of these obstacles include assignment of uniform target value to the assay calibrators, assessment of Lp(a) mass (typically mg/dL) versus particle number (nmol/L), and an absence of implemented guidelines for validation of methodical approaches (59). Lp(a) levels measured as mg/dL usually include apoB-100, apo(a), cholesterol, cholesteryl esters, phospholipids, triglycerides, and carbohydrates attached to apo(a), whereas Lp(a) levels when measured as nmol/L are typically the number of apo(a) (and therefore Lp(a)) particles (60). Lp(a) concentration is not affected by the fasting state (61). A conversion factor of 2.8 (5) for small isoforms and 1.8 (5) for large isoforms, with a mean of 2.4 nmol/L for every 1 mg/dL, was recommended in the past (62). More recently, Marcovina *et al.* have demonstrated that this conversion factor is dependent on appropriate calibrations and if not properly followed, may alter the correct Lp(a) values (59).

The temperature and length of storage of samples can also impact Lp(a) measurements. Marcovina *et al.*, showed that the measurement results are similar between fresh samples and samples frozen at −70°C with the Lp(a) values stable for 3–4 days after thawing (59). However, subsequently there is approximately a 30% decrease in the levels of Lp(a) predominantly in the samples with an elevated Lp(a). No such difference in Lp(a) levels was found in samples stored at 4°C for up to 6 days. However, samples stored at -20°C have shown the greatest

sample dependent Lp(a) decrease even when blood samples were analyzed right after thawing (59). Although the potential variation in Lp(a) levels due to sample storage conditions can be quite impactful, the currently available literature on this topic is limited.

Presently, Denka Seiken reagent assay can provide precise analytical method for Lp(a) measurement. The assay reports Lp(a) concentrations in nmol/L and can be referenced to the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine reference materials (59).

Marcovina *et al.* have implemented a computerized approach to calculate a patient-specific Lp(a) value that corresponds to an individual's racial group. In Caucasian patients, a value of Lp(a) greater than the 75th–80th percentile is suggestive of increased risk of CVD (59). However, for individuals of black or Japanese origin or other ethnicities, no specific cut points have been established. In these cases, clinicians are to exercise their clinical judgment. Hence, at the present time, a common cut point of Lp(a) that is uniform across cohorts of all racial origins is not available.

There remains a need for a standardized in storage condition and Lp(a) measurement technique as well as a uniform cut point across different racial cohorts. This will be essential for optimal interpretation of data from large, multi-center and multi-national clinical trials evaluating the role of Lp(a) in CVD. In the era of novel therapeutic approaches to lower Lp(a), the availability of well-standardized assays that provide comparability of results obtained by different laboratories is indispensable for the selection and classification of individuals at high risk.

8. WHO SHOULD BE SCREENED FOR ELEVATED LP(A) LEVELS?

Screening for Lp(a) levels has been a topic of debate. More than 90% of circulating Lp(a) levels are genetically determined, quantitatively associated with the *LPA* gene, and minimally impacted by diet and environmental factors. Several SNPs associated with the *LPA* gene can influence Lp(a) levels. However, because plasma Lp(a) levels do not fluctuate significantly in an individual (63), for screening purposes, Lp(a) levels may only be checked once in an individual's lifetime, and since currently most labs charge $50–100, measuring Lp(a) level may in fact be cost effective (63).

Because of the lack of clinical trial evidence showing a direct association between Lp(a) reduction and a reduction in CVD events, most current guidelines, including the 2013 American College of Cardiology/American Heart Association treatment guidelines (64), do not recommend universal Lp(a) screening. However, both the National Lipid Association (65) and the European Society of Cardiology/European Atherosclerosis Society (66) recommend Lp(a) measurement for patients with an elevated risk for atherosclerotic CVD (i.e., those individuals with familial hypercholesterolemia, strong family history of CVD and/or elevated Lp(a) levels, personal history of premature CVD, recurrent CVD despite statin treatment, inadequate response to statins, and ≥10% 10-year risk of fatal or nonfatal CHD according to the National Lipid Association guidelines or ≥3% 10-year risk of fatal CVD according to the European guidelines). Currently, both the National Lipid Association and the European Atherosclerosis Society establish Lp(a)≥50 mg/dL (using an isoform-insensitive assay) as a high/lab alert value that requires optimum risk factor control.

Given that there are no direct treatments for Lp(a) lowering as yet (discussed below), Lp(a) measurement should lead to physician–patient discussion. The question that clinicians frequently encounter is why Lp(a) levels should be checked if one is not likely to "do anything specific about it." There are several reasons to measure Lp(a) levels. First, the risk of CHD with elevated Lp(a) levels is well established. Second, recognition of elevated Lp(a) levels may lead to further intensification of primary prevention efforts by more aggressive lowering of LDL-C levels. Third, since Lp(a) is transmitted in an autosomal dominant pattern (67,68) offspring of individuals with elevated Lp(a) could potentially be identified earlier and begin aggressive preventive strategies earlier in life. Lastly, in individuals who are eligible, elevated Lp(a) levels may be an indication to use aspirin therapy.

9. TREATMENT OF ELEVATED Lp(a) LEVELS

Currently no medications that directly lower Lp(a) have been approved for use. In clinical practice, therefore, the primary goal in patients with elevated Lp(a) levels is reduction of LDL-C levels. The effectiveness of this intervention has not been confirmed in randomized clinical trials. In a post-hoc analysis of the Familial Atherosclerosis Treatment Study, elevated Lp(a) levels were associated with progression of coronary atherosclerosis and CHD events only if the LDL-C level was not reduced by more than 10 percent (69).

9.1. Nicotinic Acid

Nicotinic acid (2–4 grams/day), or niacin, may reduce Lp(a) levels by as much as 38% (70,71). In addition, niacin lowers LDL-C, apoB-100, small dense LDL, and triglycerides, and raises high-density

lipoprotein cholesterol levels. However, given the lack of CVD benefit with niacin in the recently concluded AIM-HIGH72 and HPS-THRIVE73 clinical trials, the role of niacin in ASCVD risk reduction is questionable. Since both AIM-HIGH and HPS2-THRIVE enrolled CVD patients without regard to baseline Lp(a), it remains unknown whether the use of niacin in patients with primary Lp(a) elevation would be of benefit.

9.2. Statins

Statins are not generally associated with reductions in Lp(a) levels. In theory, statins do not affect Lp(a) levels because the LDL-R is not known to have a role in Lp(a) clearance (except postulated at very low levels of LDL-C; see below in PCSK9 Inhibitors section). However, an assessment of published reports suggests that statins may raise Lp(a) by 10–20%, as evaluated by pre- and post-statin Lp(a) levels in individual patients (60). In a recent analysis in 3,896 patients in whom Lp(a) and oxidized phospholipids on apoB-100 (OxPL-apoB) were measured before and after statin therapy (atorvastatin, pravastatin, rosuvastatin, pitavastatin, or simvastatin/ezetimibe), per-patient Lp(a) level increased by a mean of 11% (and up to 50%), and OxPL-apoB increased by a mean of 24%74. Therefore, the role of statin therapy in patients with elevated Lp(a) is to lower LDL-C, since lowering LDL-C levels in patients with elevated Lp(a) could be beneficial as discussed above.

9.3. Aspirin

In the Women's Health Initiative, carriers of rs3798220, a minor variant of *LPA,* had elevated Lp(a) levels and increased CVD risk (HR 2.11, 95% CI 1.39–2.52) compared with noncarriers, and over a period of 9.9 years of follow up, the carriers benefited more from use of aspirin therapy than noncarriers (75). With the use of aspirin, CVD risk was reduced by more than 50% (HR 0.44, 95% CI 0.20–0.94) in carriers but was not significantly reduced in noncarriers, and the interaction between carrier status and aspirin use was statistically significant (75). The benefit of aspirin therapy in individuals with elevated Lp(a) levels could likely be due to its antiplatelet effect given the prothrombotic properties of Lp(a).

Interestingly, Akaike *et al.* showed that in 37 Japanese patients with high Lp(a) concentrations (>30 mg/dL), aspirin lowered serum Lp(a) concentrations to approximately 80% of the baseline values (76). The authors proposed that the observed lowering of Lp(a) with aspirin could be secondary to the preferential action of aspirin in reducing *LPA* gene transcription rather than suppressing secretory processing of mature apo(a), independent of cyclooxygenase-176 (77). To our knowledge, these findings have not been replicated thus far.

9.4. PCSK9 inhibitors

The recently developed proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a novel class of drugs for the treatment of dyslipidemias. PCSK9 inhibitors have been shown to reduce LDL-C levels by 50–60% in addition to statin therapy (78). Evolocumab was associated with reduction in CVD events in the recently published outcomes trial (79). A very encouraging finding in trials of PCSK9 inhibitors has been the reduction of Lp(a) by approximately 30% (78,80). Although the exact mechanism by which PCSK9 inhibitors lower Lp(a) levels is not known, it has been hypothesized that at extremely low levels of LDL-C (which can be obtained with PCSK9 inhibition), LDL-R may be involved in the clearance of Lp(a).

Currently, PCSK9 inhibitors are not approved for treatment of elevated Lp(a) levels and are only indicated for LDL-C lowering in patients with specific indications of ASCVD and/or familial hypercholesterolemia (81,82).

9.5. Lipoprotein apheresis

Lipoprotein apheresis (LA), a therapy involving selective or nonselective removal of plasma constituents including lipoproteins in an extracorporeal fashion, has been approved for treatment of patients with various forms of severe hypercholesterolemias (83). Currently, this is the only therapy that directly reduces Lp(a) levels by 50% (84). Patients with stable CHD as well as elevated Lp(a) levels (>50 mg/dL; mean 103 mg/dL) and within-range LDL-C levels on statin therapy were shown to have regression of coronary atherosclerosis (assessed by quantitative coronary angiography) after weekly Lp(a)-specific apheresis for at least 18 months (85). Lp(a) level was reduced by a mean of 73%, to a mean level of 29 mg/dL.

A well-designed, single-blinded, crossover trial by Khan *et al.* (86) recently evaluated 20 patients with symptomatic stable coronary artery disease and Lp(a) plasma levels >50mg/dL randomized to receive weekly LA or sham apheresis. LA reduced median plasma levels of LDL-C and Lp(a) by >80% and 60%, respectively. After three months on therapy, the primary endpoint of myocardial perfusion reserve showed improvement, increasing by 0.63 (95% CI 0.37–0.89; P <0.0.01) among those randomized to LA therapy. Improvement in the secondary end points of carotid wall volume, carotid distensibility, frequency and intensity of angina pectoris episodes, and quality of life (measured by 6-minute walk test) were also reported (86).

The effect of LA in these studies may have been confounded by the removal of other atherogenic lipoproteins, as LA eliminates any apoB-containing

lipoprotein, including LDL as well as triglyceride-rich lipoproteins and their remnants. Furthermore, fibrinogen (a procoagulant) and proinflammatory molecules like pentraxins can also be removed by LA (83).

For patients with symptomatic CHD and elevated Lp(a), the European Atherosclerosis Society recommends LA as a possible therapy.

10. FUTURE THERAPIES WITH ANTISENSE OLIGONUCLEOTIDES

Emerging therapies aimed at reducing synthesis of Lp(a) in hepatocytes have recently been evaluated. Antisense oligonucleotides (ASOs) targeting apo(a) inhibit apo(a) synthesis; hence, Lp(a) secretion can be inhibited by liver-targeted ASOs (60). Subcutaneously injected ASOs targeting apo(a) enter hepatocytes and then bind to apo(a) mRNA in the nucleus as well as the cytoplasm (if mRNA is present). Enzymatic cleavage of the sense strand by ribonuclease prevents protein synthesis, and the antisense strand can then bind to additional mRNA targets (87). Since the ASO binds specifically to apo(a), the synthesis of very low density lipoprotein (VLDL) by hepatocytes continues, preventing hepatic steatosis.

An ASO specific to apo(a) reduced circulating apo(a) by 86% without affecting apoB in apo(a) transgenic mice88. Optimized ASOs to apo(a) have recently been studied in humans (89). Use of an apo(a)-specific ASO (IONIS-APO(a)LRx) led to dose-dependent mean reductions in Lp(a) levels of 66–92%, as well as reductions in plasma LDL-C levels, proinflammatory OxPL, and inflammatory effects of monocytes (90). In another study of the same agent in 47 healthy volunteers, significant dose-dependent reductions in Lp(a) levels were observed after 1 month: 39.6% with 100mg, 59.0% with 200mg, and 77.8% with 300mg (all $P \leq 0.005$ vs. placebo), and no serious or severe adverse events were reported (91). IONIS-APO(a)-LRx contains an N-acetyl-galactosamine (GalNac3) conjugated molecule designed to be highly and selectively taken up by hepatocytes. A phase 2 clinical trial of this agent is under way to assess the mean reduction of Lp(a), and the safety and tolerability, in patients with established CVD (ClinicalTrials.gov Identifier:NCT03070782).

11. FUTURE DIRECTIONS AND CONCLUSIONS

Great progress has been made in our understanding of Lp(a), but much remains unclear. Because of the observed association of elevated Lp(a) level with increased CVD risk, the potential role of this perplexing lipoprotein in CVD prevention continues to be a focus of research interest. Newer and emerging therapies that provide substantial Lp(a) reduction now offer the opportunity to test the causality of the relation between Lp(a) and CVD. Improved precision in analyzing Lp(a) levels and further standardization of sample collection and storage conditions will be critical in clinical trials of novel therapies aimed at lowering Lp(a). If ongoing and future clinical trials of agents such as PCSK9 inhibitors and ASOs targeting apo(a) report reduction of CVD events with Lp(a) decreases, clinicians will have an additional strategy in prevention of CVD. Perhaps then, we will no longer ask the question, “Why screen for Lp(a) when we cannot do anything about it?”

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