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LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (G DE BACKER, SECTION EDITOR)

Lp(a): Addressing a Target for Cardiovascular Disease Prevention

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Abstract

Purpose of Review To review the current recommendations for lipoprotein(a) (Lp(a)) screening, the evidence behind the thresholds for increased cardiovascular disease (CVD) risk, and the available data supporting Lp(a) lowering.

Recent Findings Lp(a) is almost entirely genetically determined and has an independent causal association with CVD. Measurement of Lp(a) is challenging given the structural heterogeneity of apolipoprotein a (apo(a)), for which isoform-insensitive immunoassays should be used. Current guidelines do not recommend treatment to lower Lp(a) but rather focus on intensified preventive measures including low-density lipoprotein cholesterol (LDL-C) lowering in patients with high Lp(a). Evidence suggests that levels higher than 50 mg/dL (125 nmol/L) identify significantly increased CVD risk. Mendelian randomization studies suggest that in order to have a clinically significant reduction in coronary heart disease, Lp(a) levels should be reduced by at least 60–70 mg/dL to attain a significant benefit. Ongoing studies of targeted therapy with antisense oligonucleotides (ASO) have shown promising reductions in Lp(a) up to 80%, but a cardiovascular outcomes trial is needed.

Summary There is unquestionably an increased risk for CVD in patients with elevated Lp(a); however, measurement assay issues and the lack of Lp(a)-targeted therapies with proven outcome reduction limit the clinical utility of this important risk factor. Available evidence suggesting specific thresholds for clinically significant CVD risk are based on European or Caucasian populations, not accounting for important racial differences. Novel Lp(a)-targeted emerging therapies may need to account for an expected reduction of at least 60–70 mg/dL to achieve a clinically significant benefit.

Keywords Lipoprotein(a) · Cardiovascular disease · Prevention · Lipids

Introduction

Despite considerable progress since the discovery of lipoprotein(a) (Lp(a)) more than 60 years ago, there remain important unknowns regarding its clinical utility for reducing cardiovascular disease (CVD) [1]. Lp(a) is a low-density lipoprotein (LDL)–like particle with an apolipoprotein-B100 (apo-B100) covalently bound by a disulfide bond to apolipoprotein a (apo(a)). Evidence for an independent association with CVD risk extends to epidemiologic, Mendelian randomization, and genome-wide association studies [2–5]. The proposed mechanistic link is mediated via atherogenesis due to intimal deposition of Lp(a) [6]. In addition, apo(a) is structurally similar to plasminogen but lacks fibrinolytic activity, resulting in a potential net pro-thrombotic effect by competing with plasminogen [7, 8, 9•].

Lp(a) is almost entirely genetically determined by the *LPA* gene and is not particularly susceptible to diet or environmental factors [10, 11]. Despite compelling data linking elevations in Lp(a) with increased CVD risk, it is not routinely measured in clinical practice for several reasons including measurement issues and a lack of outcomes studies.

Measurement poses a challenge given the structural heterogeneity of apo(a). The *LPA* gene encodes apo(a), which is a protein that contains repeating kringle IV (KIV) domains similar to the structure of plasminogen [12]. Among the KIV subtypes in apo(a), KIV_2 exhibits high variability in the frequency of repeats based on the *LPA* alleles (Fig. 1). Fewer KIV_2 repeats result in a smaller apo(a) and subsequently

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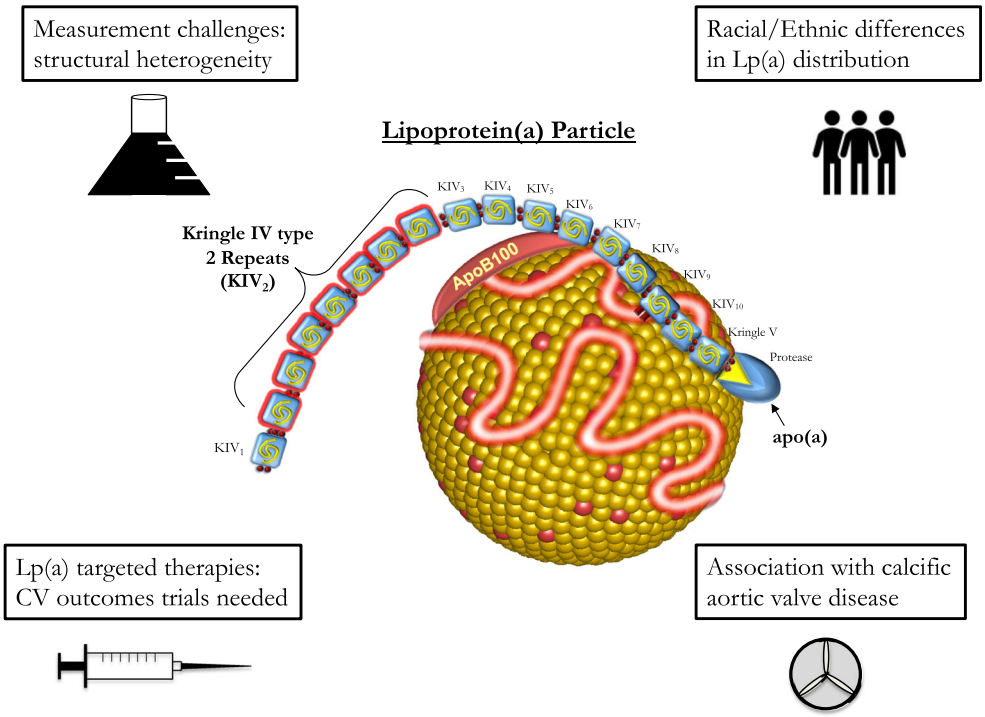

Fig. 1 Lp(a) diagram showing apo-B100 and the variable KIV_2 repeats that apo(a) contains. Important future directions in Lp(a) are also included. (Adapted by permission from Springer Nature from: Joshi PH, et al. *Current Treatment Options in Cardiovascular Medicine* 2010, 12(4): 396–407) [13]

higher levels of Lp(a) [14, 15]. Antibody assays are susceptible to cross-reactivity with multiple KIV_2 repeats, resulting in overestimation or underestimation among patients with large or small isoforms, respectively [16–18]. Ideally, apo(a) isoform–insensitive immunoassays should be used [9•, 17, 19, 20]. It has been proposed that standardized Lp(a) assays should report values in apo(a) particle concentrations (nmol/L), as mass assays (mg/dL) are more susceptible to the previously described limitations [21]. A conversion factor of ~2–2.5 from mg/dL to nmol/L has been previously suggested, although this is also susceptible to apo(a) heterogeneity [21].

A primary limitation in incorporating Lp(a) measurement and treatment into clinical practice is the lack of outcomes studies due to a lack of Lp(a)-targeted therapies. Outcomes trials are anticipated in the near future and will be pivotal to understanding the clinical utility of Lp(a) [9•, 21]. This review synthesizes the current recommendations regarding Lp(a) screening and the evidence supporting specific thresholds for increased CVD risk. Recent data supporting Lp(a) lowering to prevent CVD and future directions are also presented.

Current Lp(a) Guideline Recommendations: a Screening Tool

Recent international guidelines differ slightly in recommendations surrounding the clinical use of Lp(a) (Table 1). None of the guidelines recommend treatment to lower Lp(a) directly due to insufficient data showing an outcomes benefit. The primary differences center around patient selection for Lp(a) screening and the Lp(a) threshold that identifies higher risk.

The 2018 American Heart Association/American College of Cardiology (AHA/ACC) multi-society cholesterol treatment guideline recommends Lp(a) as a risk enhancer in adults between the ages of 40 and 75 years for primary prevention [22]. In patients without prior CVD who are indicated for, but uncertain about statin initiation, an Lp(a) cholesterol ≥ 50 mg/dL (or Lp(a) ≥ 125 nmol/L for molar assays) favors starting statin therapy (class I recommendation). However, limited guidance is given as to when Lp(a) should be measured, with a relative indication to measure it if there is a family history of premature atherosclerotic cardiovascular disease (ASCVD) or a personal history of ASCVD not explained by major risk factors [18, 22]. Women may derive less benefit from Lp(a) measurement; a specific mention is made for women with hypercholesterolemia (total cholesterol > 220 mg/dL) in whom Lp(a) may render only a minimal improvement in risk prediction based on an analysis from the Women's Health Study, the Women's Health Initiative, and the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial [23].

The 2016 European Society of Cardiology (ESC) guidelines recommend a more comprehensive group for Lp(a) screening. The ESC guideline suggests measurement in patients with premature CVD, a family history of either premature CVD or elevated Lp(a), familial hypercholesterolemia, recurrent CVD despite optimal lipid-lowering treatment, or > 5% 10-year risk of fatal CVD [24]. Similar to the AHA/ACC guidelines, Lp(a) > 50 mg/dL is considered a significant

Table 1 Guideline recommendations for Lp (a)

	Screening recommendations	Target or cut-off value
USA	- Family history of premature ASCVD*	50 mg/dL
	- Personal history of ASCVD not explained by major risk factors	
	- Useful in adults 40–75 years of age without diabetes mellitus and intermediate risk for ASCVD: 7.5–19.9% 10-year risk per the PCE	
	- Can be considered in women with hypercholesterolemia	
Europe	- Premature CVD**	50 mg/dL (80th percentile)
	- Family history of premature CVD**	
	- Family history of elevated Lp (a)	
	- Recurrent CVD despite optimal therapy with lipid-lowering agent	
	- ≥ 5% 10-year risk of fatal CVD according per SCORE	
Canada	- Patients with intermediate CV risk per the modified Framingham Risk Score: 10–19% risk of CHD at 10 years	30 mg/dL
	- Family history of premature CAD***	

*Premature CVD defined as < 55 years in males and < 65 years in females

**Premature CVD defined as < 55 years in males and < 60 years in females

***Premature CVD defined as < 55 years in first-degree male relatives and < 65 years in first-degree female relatives

CVD risk factor [19, 24]. For patients with high Lp(a), the recommendation is to intensify treatment of modifiable risk factors such as LDL-C [24]. However, it is important to note that even at low LDL-C levels, elevated Lp(a) remains a significant risk factor [25–27].

The 2016 Canadian guidelines for the management of dyslipidemia give a moderate-quality evidence recommendation that Lp(a) be assessed in patients with a family history of premature coronary artery disease (CAD) and subjects with intermediate CVD risk per the modified Framingham Risk Score (10–19% risk of coronary heart disease at 10 years) with the intention to aid in the decision of statin therapy [28]. In contrast to both the ACC/AHA and ESC guidelines, Lp(a) level > 30 mg/dL (~ 75 nmol/L) is recommended as the threshold for increased CVD risk, based on the Copenhagen City Heart Study, and the Emerging Risk Factors Collaboration [2, 28, 29].

Lp(a) Threshold: 30 vs. 50 mg/dL

While Lp(a) is an independent predictor of CVD, the recommendations for a specific cut-off value for risk-stratifying purposes and clinical decision-making have differed [22, 24, 28]. The AHA/ACC and ESC guidelines suggest a threshold of 50 mg/dL while the Canadian guidelines recommend 30 mg/dL.

Historically, an Lp(a) threshold above 30 mg/dL was associated with increased CVD risk [30]. In the Copenhagen City Heart Study, a prospective cohort study evaluating risk factors for incident MI, a stepwise increase in risk for CHD was seen with increasing Lp(a) population percentiles [29]. A statistically significant increase in risk was seen at Lp(a) levels greater than 30 mg/dL, corresponding to ~ 70th percentile value for the study cohort [29]. An extensive meta-analysis of prospective studies with data on Lp(a) and subsequent major vascular morbidity and/or cause-specific mortality through 2009 was conducted by the Emerging Risk Factors Collaboration [2]. The curvilinear risk for non-fatal MI and coronary death associated with Lp(a) started markedly increasing at 24 mg/dL, although it was not until a level of approximately 48 mg/dL that the ratio was clearly statistically significant. A subsequent study of data from the Copenhagen City Heart Study showed re-classification improvement for CHD risk among patients at intermediate risk with an Lp(a) > 47 mg/dL(corresponding to the 80th percentile), further supporting current guideline recommendations using 50 mg/dL for risk stratification purposes [3, 22, 24]. An analysis of the JUPITER trial showed significantly increased risk for a composite CVD endpoint including MI, stroke, hospitalization for unstable angina, arterial revascularization, or CVD death when Lp(a) > 50 mg/dL [25].

While the risk for CVD progressively rises with higher Lp(a) levels, it is between 24 and 50 mg/dL that a significant increase is seen. Given that Lp(a) distribution is skewed towards higher levels, 50 mg/dL appears to be a reasonable threshold to identify significantly increased CVD risk. However, most of the prior studies were done in European or Caucasian populations, and significant racial variation exists such that higher median values have been found in black and South Asian populations, with potentially differing thresholds for increased CVD risk [21, 31–33]. For instance, data from black participants of the Atherosclerosis Risk in Communities (ARIC) Study showed that CVD risk increased when Lp(a) > 72 mg/dL [32]. The combination of ethnic variability, previously described methodological considerations for measurement, and lack of assay standardization makes it challenging to identify a specific threshold to apply to clinical

practice. The risk is consistently skewed towards the highest quartile or quintile of a population and so future studies may be best analyzed by the population value that is represented by the 75th or 80th percentile for a given group by a given assay.

The Magnitude of Lp(a) Lowering to Reduce CVD

The principal clinical knowledge gaps for Lp(a) are whether direct reduction, and by how much, will lead to reductions in CVD risk. The primary limitation for this issue has been a lack of Lp(a)-targeted therapies that do not also impact other lipoproteins, primarily LDL. For example, while PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitors lower Lp(a) more so than statins do, their effects on outcomes cannot be easily disentangled from their direct actions on LDL-C reduction. With the advent of an antisense oligonucleotide directed at apo(a) synthesis, an outcomes trial is planned [34].

Until direct Lp(a) reductions are tested in a randomized, controlled cardiovascular outcomes trial, Mendelian randomization studies can be informative, especially given the strong genetic influence on Lp(a) levels [35]. By using genetic variants associated with lifelong Lp(a) concentrations, different levels of exposure can be evaluated. Inheriting an Lp(a) allele associated with lower concentrations would be analogous to randomly assigning a subject to an Lp(a)-lowering drug, whereas inheriting the an allele associated with high concentrations would correspond to randomization to the placebo group [35]. Two recent studies have evaluated the association of Lp(a) variants and coronary heart disease (CHD) with the intention to estimate the magnitude of Lp(a) reduction needed for future clinical trials [36•, 37]. Both studies estimated the absolute Lp(a) reduction that would equate to an LDL-C reduction of ~ 39 mg/dL (or 1 mmol/L) by statin therapy which produces a 22% reduction in CHD events based on the Cholesterol Treatment Trialist Collaboration [38].

Each study investigated the association of *LPA* gene variants with risk for coronary disease [36•, 37]. The first analysis developed an LPA genetic score based on 43 genetic variants and after adjustments for variants that accounted for LDL-C lowering, the authors estimated that a reduction of ~ 101 mg/dL in Lp(a) would be necessary to achieve the same CHD risk reduction as an ~ 39 mg/dL in LDL-C [36•]. A second analysis found that a 27-variant score performed similarly to the previously developed 43-variant score [37]. In this analysis, the authors found that an Lp(a) reduction of ~ 66 mg/dL would be necessary to achieve the same CHD risk reduction as an LDL-C reduction of ~ 39 mg/dL [37].

Taken together, the two Mendelian randomization studies suggest large amounts of Lp(a) reduction would be required for a clinically meaningful reduction in CVD events. Differences in the specific value estimated can be attributed to differences in median values for Lp(a) and variability in the assays used.

In addition to the Mendelian randomization studies, secondary analyses of trials of therapeutic agents with an effect on Lp(a) are helpful. While statins are widely used as the first-line agent for LDL-C reduction to improve ASCVD risk, they do not lower Lp(a) [25, 39, 40]. Niacin has been found to reduce Lp(a) levels by ~ 20–30%, although in combination with statins, niacin has not been shown to reduce CVD events [41, 42].

Similar to the Mendelian randomization studies, an analysis from the HPS2-Thrive randomized clinical trial of niacin-laropiprant combination vs placebo in statin-treated patients suggested large reductions of ~ 80 nmol/L (~ 40%) in Lp(a) would be required to have significant clinical benefit [43]. Furthermore, the issue is likely more complex as the percent reduction in Lp(a) varied strongly with the number of KIV domains in the predominant apo(a) isoform, suggesting that Lp(a)-lowering therapies should account for apo(a) isoform size [43].

A secondary analysis of the AIM-HIGH trial of niacin vs placebo in addition to background statin therapy showed that although a higher response was seen in patients in the highest Lp(a) percentiles, this did not result in a difference of event rates between the placebo and treatment groups, perhaps due to low baseline Lp(a) values in the study [26]. The clinical utility of niacin has dwindled in the current era due to the null overall results in HPS2-Thrive and AIM-HIGH. Given overall 20–30% reduction in Lp(a), niacin may be useful as add-on therapy to other Lp(a)-lowering agents in those patients at high CVD risk due to very high Lp(a).

PCSK9 inhibitors also reduce Lp(a) by 20–30% [44, 45]. At 48 weeks, evolucumab reduced Lp(a) by a median of 27% and at 24 weeks, alirocumab similarly reduced Lp(a) by up to 29%. In a large placebo-controlled outcomes trial of evolocumab added to maximally tolerated statin therapy, individuals randomized to the placebo arm and in the highest quartile of Lp(a) were at the highest risk of CHD, independent of LDL-C levels. Furthermore, those with Lp(a) > median achieved a 23% relative risk reduction in CHD which trended towards a higher benefit than those with Lp(a) < median (7% relative risk reduction) [46•]. Similar findings were suggested in a preliminary presentation of a large cardiovascular outcomes trial of alirocumab (not yet published) [47]. The estimated absolute reductions in Lp(a) from PCSK9 inhibitor trials to have a clinically significant impact on CHD are likely lower than those of the previously discussed Mendelian randomization studies perhaps due to the inclusion of a secondary prevention population exclusively in the PCSK9 inhibitor trials [36•, 37, 46•].

The Mendelian randomization and PCSK9 inhibitor studies strongly support the need for therapies directed specifically at Lp(a). A current therapy in development, AKCEA-

APO(a))-L_{RX}, focuses on inhibiting apo(a) synthesis by antisense oligonucleotides (ASO) and has shown Lp(a) reductions up to 80% with absolute reductions up to 75 mg/dL (not yet published) [34, 48]. A phase 3 cardiovascular outcomes trial is anticipated and will help to address critical questions that remain regarding the clinical utility of Lp(a).

Conclusions and Future Directions with Lp(a)

Beyond the well-described associations with ASCVD, epidemiologic and genetic studies have shown an association between Lp(a) and aortic stenosis [49–51]. This was further supported by data from the CHARGE study that showed Lp(a) to be a causal risk factor for calcific aortic valve stenosis, with up to a 60% increase in risk associated with each 10-fold increase in Lp(a) [52, 53]. Further work has suggested faster rates of progression of aortic stenosis associated with higher levels of Lp(a) [54]. The emerging link between Lp(a) and aortic stenosis is an important area of ongoing research.

As highlighted in this review, there are several clinical questions that are left to be addressed with Lp(a) to ultimately optimize its clinical utility (Fig. 1). A key issue that remains unaddressed is the need for assay standardization. Along with standardized measurement, epidemiological studies from non-Caucasian/European cohorts will help to better establish thresholds for CVD risk. While Lp(a) is becoming a well-recognized marker of increased CVD risk, the most important remaining question regarding the clinical utility of Lp(a) is whether or not targeted Lp(a) reduction results in improved outcomes. With novel therapies emerging, the future holds promise.

Compliance with Ethical Standards

Conflict of Interest Nestor Vasquez declares that he has no conflict of interest. Parag H. Joshi reports grant support from the AHA, Novo Nordisk, GlaxoSmithKline, Sanofi/Regeneron, AstraZeneca, and Pfizer; and personal fees from Regeneron and Bayer; and equity interest in the Global Genomics Group.

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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