Evidence that elevated lipoprotein(a) (Lp[a]) levels contribute to cardiovascular disease (CVD) and calcific aortic valve stenosis (CAVS) is substantial. Development of isoform-independent assays, in concert with genetic, epidemiological, translational, and pathophysiological insights, have established Lp(a) as an independent, genetic, and likely causal risk factor for CVD and CAVS. These observations are consistent across a broad spectrum of patients, risk factors, and concomitant therapies, including patients with low-density lipoprotein cholesterol <70 mg/dl. Statins tend to increase Lp(a) levels, possibly contributing to the “residual risk” noted in outcomes trials and at the bedside. Recently approved proprotein convertase subtilisin/kexin-type 9 inhibitors and mipomersen lower Lp(a) 20% to 30%, and emerging RNA-targeted therapies lower Lp(a) >80%. These approaches will allow testing of the “Lp(a) hypothesis” in clinical trials. This review summarizes the current landscape of Lp(a), discusses controversies, and reviews emerging therapies to reduce plasma Lp(a) levels to decrease risk of CVD and CAVS. (J Am Coll Cardiol 2017;69:692–711) © 2017 The Author. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
CVD and calcific aortic valve stenosis (CAVS), and the potential of novel therapies to substantially lower Lp(a). This review summarizes the Lp(a) field from a translational and clinical perspective with its relationship with CVD and CAVS.

**HOW IS Lp(a) DIFFERENT FROM LDL AND PLASMINOGEN?**

Lp(a) is composed of an LDL-like particle in which apoB is covalently bound by a single disulfide bond to apolipoprotein(a) (apo(a)), the pathognomonic component of Lp(a) (Figure 1). For unknown etiological and physiological reasons, apo(a) has evolved from the plasminogen gene through duplication and remodeling over the millennia (4). Plasminogen contains 5 kringles (KI to KV) and a protease domain. Plasminogen is a proenzyme, which is converted to the fibrinolytic enzyme plasmin by plasminogen activators, such as urokinase and tissue plasminogen activator, either endogenously or iatrogenically. Apo(a) does not contain KI to KIII of plasminogen, but instead contains 10 subtypes of KIV (with KIV1 and KIV3-10 present in 1 copy, and KIV2 present in 1 to >40 copies), 1 copy of KV, and an inactive protease domain. Unlike apoB, apo(a) does not contain lipid domains or transport lipid, but instead, it is hydrolphilic, and can bind to denuded and exposed lysine-rich vascular endothelium, similar to and also in competition with plasminogen. However, except for high Lp(a) levels, on a molar basis, plasminogen is almost always in excess of apo(a), which calls into question its in vivo potency in inhibiting plasminogen activity in most patients.

Within populations, there is extensive apo(a) protein size heterogeneity, with >40 different isoforms, and thus, >40 different sizes of Lp(a) particles, which is a unique occurrence unlike other circulating proteins, which usually have 1 defined mass (5). Within individuals, >80% carry 2 different-sized apo(a) isoforms, each inherited from 1 parent. For example, an individual may carry 2 small isoforms, a small and a large one, or 2 large isoforms, with plasma Lp(a) levels determined by the net production of apo(a) in each isoform, with the major contribution generally driven by the small isoform (Figure 1).

**METABOLISM OF Lp(a)**

Circulating Lp(a) levels are primarily determined by the LPA gene locus, without significant dietary or environmental influences (6). Apo(a) is synthesized almost exclusively in the liver, but the site of assembly of Lp(a) has not been confirmed, and may be within the hepatocyte, the space of Disse, or the plasma compartment (7). The steps of assembly include apo(a) docking to LDL, and then formation of a covalent disulfide bond between KIV-9 of apo(a) and apoB of LDL. It appears that the LDL component is derived from a newly synthesized apoB-100 and is not derived from a very low-density lipoprotein precursor. Lp(a) has a longer plasma residence time than LDL. This may due to the fact that the apo(a) component, which is covalently attached near the LDL receptor (LDLR) binding site of apoB and which can be larger than apoB, interferes with docking to the LDLR, reduces clearance through the LDLR, and also requires clearance through alternative pathways. The size of the apo(a) isoform correlates modestly and inversely with plasma Lp(a) levels due to the constitutive hepatoocyte production of apo(a), and because small isoforms can be made in higher molar quantities per unit time versus large isoforms. The mechanisms through which Lp(a) is cleared from plasma remain controversial. The LDLR likely has a modest role, as evidenced by the fact that statins raise LDLR numbers, yet do not lower Lp(a), and proprotein convertase subtilisin/kexin-type 9 (PCSK9) inhibitors increase LDLR numbers, yet reduce Lp(a). However, animal and human turnover studies with labeled Lp(a) suggest minimal (if any) effect, but cell culture studies and clinical phenotypes of LDLR deficiency, such as those in patients with familial hypercholesterolemia due to LDLR mutations, show higher Lp(a) levels than unaffected siblings. The kidney, as well as other undefined clearance mechanisms, such as scavenger receptor B1 and plasminogen receptors, and proteolytic cleavage of apo(a), may also have a role in catabolism.

**WHAT ARE THE MECHANISMS THROUGH WHICH Lp(a) MEDIATES CVD?**

Lp(a) contributes to CVD risk via multiple, nonredundant mechanisms. Lp(a) quantitatively carries all of the atherogenic risk of LDL particles, including their propensity to oxidize after entry into the vessel wall, creating highly immunogenic and proinflammatory oxidized LDL (8). However, on an equimolar basis, Lp(a) is more atherogenic than LDL because, by definition, it not only contains all the proatherogenic components of LDL, but also of apo(a). Apo(a) potentiates atherothrombosis through additional mechanisms, including inflammation...
Lipoprotein [Lp(a)] is composed of apolipoprotein B-100 (apoB-100) covalently bound to apolipoprotein (a) [apo(a)], which is derived from kringles IV (KIV) and KV, and the protease domain of plasminogen. Plasminogen has 1 copy each of KI to KV and an active protease domain. Apo(a) contains 10 subtypes of KIV repeats, composed of 1 copy each of KIV1, multiple copies of KIV2, and 1 copy of KIV3. 10, KV, and an inactive protease-like (P) domain. In these examples, apo(a) isoforms of 4, 8, 24, and 40 KIV2 repeats are shown, representing 13, 17, 33, and 49 total KIV repeats. Oxidized phospholipids (OxPL), represented here by 1-palmitoyl-2-oxovaleryl-sn-glycero-3-phosphocholine (POVPC), are present covalently bound to apo(a), and also dissolved in the lipid phase of apoB-100.
through its content of oxidized phospholipids (OxPL), the presence of lysine binding sites that allow accumulation in the arterial wall, and potential anti-fibrinolytic effects by inhibiting plasminogen activation (Figure 2) [9]. However, Lp(a)-mediated CVD risk should be considered in a quantitative manner because most patients (70% to 80%) at risk for CVD have low Lp(a) levels, such that LDL-C is present in significant excess to Lp(a), and therefore, most of the apoB-driven risk is due to a higher number of LDL particles. However, as Lp(a) levels increase to >25 to 30 mg/dl, which represents ~30% of the population, the risk of Lp(a) rises in a linear fashion according to absolute circulating Lp(a) mass.

The atherogenicity of Lp(a) can be broadly classified in 3 categories: proatherogenic, proinflammatory, and potentially anti-fibrinolytic. The major individual mechanisms within each category are listed. EC = endothelial cell; IL = interleukin; MCP = monocyte chemoattractant protein; PAI = plasminogen activator inhibitor; SMC = smooth muscle cell; TFPI = tissue factor pathway inhibitor; other abbreviation as in Figure 1.

The OxPL components of Lp(a), which can be present in the lipid phase of Lp(a) and also be covalently bound to apo(a) [10-12], are proinflammatory and impart many of the proatherogenic properties of Lp(a) (Figure 2). This has been shown in clinical studies by measuring levels of OxPL on apoB-containing particles (OxPL-apoB), which primarily reflect the OxPL content of Lp(a) [10,11], which demonstrates that elevated OxPL-apoB levels are either similar or superior predictors to Lp(a) in the diagnosis or prognosis of CVD [13-18] and CAVS [19,20]. In a recent study that validated these mechanisms in vivo, patients with elevated Lp(a) had increased arterial inflammation detected by increased accumulation of 18-fluorodeoxyglucose in the carotid arteries and aorta. In addition, their monocytes demonstrated increased production of proinflammatory cytokines upon stimulation and an enhanced capacity to transmigrate in an in vitro system, which reflected vascular penetration of monocytes through an endothelial cell barrier. These proinflammatory effects were associated with enhanced in vivo monocyte trafficking to the arterial wall using autologous radiolabeled monocytes, and were abrogated by inactivating OxPL with a specific antibody or using recombinant apo(a) constructs lacking OxPL, which suggested that these effects...
FIGURE 3 Presence of SMCs, Macrophages, ApoB, Apo(a), and OxPL in Ruptured Human Coronary Plaques and in Distal Protection Devices Following Percutaneous Coronary Intervention

A. Ruptured atheroma
B. SMCs
C. MACs
D. ApoB
E. Apo(a)
F. OxPL

G. Thrombus
H. OxPL (POVPC)
were largely driven by the presence of OxPL on Lp(a) (12). In separate studies, OxPL on Lp(a) also up-regulated inflammatory genes, and induced release of interleukin-8 (21) and monocyte chemotactant protein-1 (22). Monocyte chemotactant protein-1 is physically present on Lp(a), and thus, may enhance its entry into the vessel wall. Finally, apo(a) contains lysine-binding sites that allows it to bind tightly to exposed surfaces on denuded endothelium, enter, and accumulate into subintimal spaces or aortic valve leaflets, which leads to inflammation. Additional mechanisms are shown in Figure 2.

Human coronary lesions from subjects with sudden death or carotid endarterectomy specimens showed a progressive increase in the presence of Lp(a) and OxPL as lesions progressed, with the highest presence of these epitopes in ruptured plaques (Figures 3A to 3D) (23). These findings were later confirmed in patients who underwent coronary, carotid, renal, and peripheral interventions, in which similar strong immunostaining for Lp(a) and OxPL, and the direct presence of OxPL in debris from distal protection devices by liquid chromatography-tandem mass spectrometry, was documented (Figures 3E and 3F) (24).

**WHAT IS THE CLINICAL EVIDENCE THAT ELEVATED Lp(a) MEDIATES CVD?**

Elevated Lp(a) mediates myocardial infarction, stroke, and peripheral arterial disease. Over the last decade, data in subjects without previous CVD from epidemiological studies and meta-analyses (25), Mendelian randomization studies (26), and genome-wide association studies (27,28) have conclusively shown that elevated Lp(a) levels are associated with a higher risk of CVD. In 63,746 coronary artery disease (CAD) cases and 130,681 control subjects from the CardiogramPlus+4CD Consortium, 46 loci and 104 independent variants that reached genome-wide significance for susceptibility for CAD were identified, with the most potent variants clustered in networks linked to lipid metabolism and inflammation. Analyzing individual variants revealed that the most potent genetic association with CAD was the LPA locus, which was numerically more potent than LDL-, PCSK9-, and 9p21-related variants. This observation that the LPA gene is 1 of the strongest (if not the strongest) monogenetic risk factors for CAD is underappreciated, and points to the potential of targeting Lp(a) lowering to reduce CVD risk with specific therapies (29).

In meta-analyses of clinical outcomes, the risk of Lp(a) for CVD is curvilinear (25). In contrast, genetic studies, which reflect life-long elevated Lp(a) and less confounding by the multiple heterogeneous limitations in meta-analyses, show a more potent and linear risk, with odds ratios as high as 4 relative to subjects with low levels (27,30). Figure 4 represents the salient studies that show such associations, but the overall data in published reports are consistent in their preponderance of evidence of a causal association. Finally, there is evidence that some individuals have alleles that do not express apo(a); therefore, they have either very low or absent circulating Lp(a) levels, have a reduced risk of CVD, but they are not at increased risk for non-CVD events, which is consistent with the causality of Lp(a) for vascular disease (31,32).

**WHAT IS THE CLINICAL EVIDENCE THAT Lp(a) MEDIATES CAVS?** Although it has long been suspected that Lp(a) is a risk factor for CAVS; only recently has Lp(a) become appreciated as a potent risk factor (33). Recent studies have shown that of >2.5 million single-nucleotide polymorphisms (SNPs) analyzed, the LPA SNP rs10455872, which is associated with markedly elevated Lp(a) levels, was the only monogenetic risk factor for aortic valve calcification and CAVS in multiple racial groups (34–37). Similar to the studies with myocardial infarction, a
strong case for causality can be made because these studies linked a genetic trait (LPA SNPs) that could not be altered by environment or diet to a quantitative and substantial (5- to 20-fold) increase in plasma Lp(a) levels, and to a clinical phenotype of aortic valve calcification and CAVS.

However, the genetic readouts are often binary (i.e., risk of disease; yes/no), and additional insights into natural history would be helpful to clinicians who manage such patients over time. In that regard, recent data from the ASTRONOMER Trial (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) (38) showed that patients with pre-existing mild-to-moderate aortic stenosis and elevated levels of Lp(a) and OxPL-apoB (third tertile or >58.5 mg/dl and >5.5 nM, respectively) had a faster progression rate, with annual changes in peak aortic jet velocities of 0.26 ± 0.26 m/s per year versus 0.17 ± 0.21 m/s per year in the highest versus the lowest tertiles (Figures 5A and 5B), and a need for aortic valve replacement (Figures 5C and 5D), which occurred in 20.4% of the entire group (19). Similar rates of progression were noted in patients with tricuspid valves versus bicuspid valves, which represented 48% of the study patients. Interestingly, younger patients (median: younger than 57 years of age) had nearly double the progression rate and the highest need for aortic valve replacement, which is consistent with the primary driver of genetically elevated Lp(a). Interestingly, rosuvastatin was shown not to affect progression of CAVS, and it actually increased Lp(a) levels by 20% and OxPL-apoB levels by 46% (Figures 5E and 5F). However, it has been acknowledged that the beneficial effects of lowering LDL-C may confound the appropriate interpretation of the effect of statins on CAVS in these trials. There are several potential explanations for these findings. For example, an adverse effect of raising Lp(a) with a statin might be offset by a beneficial effect of lowering LDL-C. Other possibilities include that most patients had low Lp(a) on entry, only patients with an initially high Lp(a) level would have been adversely affected, and that the Lp(a)-raising effect of statins is modest.

In more recent work, the enzyme autotaxin has been identified as an important contributor molecule in CAVS (39). Oxidation of phospholipids generates lysophosphatidylcholine, which is present in calcified aortic valves in mouse models and explanted calcified human valves (39). Autotaxin is a lysophospholipase that converts lysophosphatidylcholine into lysophosphatic acid, which promotes inflammation, fibrosis, and cell motility. In a case-control study in 150 patients with CAVS plus CAD and 150 matched patients with CAD without CAVS, patients with CAVS had elevated autotaxin mass and activity, Lp(a) (>50 mg/dl) and OxPL-apoB (>2.02 nM), and autotaxin activity in combination with either Lp(a) or OxPL-apoB, which significantly increased the risk of CAVS, with odds ratios of 3.46 and 5.48, respectively,
compared with patients with lower levels (Figures 5G and 5H) (20).

Therefore, a unifying hypothesis for the development and progression of CAVS is that Lp(a) carries both autotaxin and OxPL into aortic valve leaflets, and initiates inflammation and calcification via OxPL metabolites that induce up-regulation of pro-calciﬁng genes, which ultimately results in hemodynamically signiﬁcant disease and clinical sequelae (Figure 5I) (33).

**AREA OF CONTROVERSY I: WHAT ARE THE AVAILABLE Lp(a) ASSAYS, AND IS THE MEASUREMENT OF Lp(a) ADEQUATELY STANDARDIZED FOR ROUTINE CLINICAL CARE?**

Lp(a) levels are generally expressed as milligrams per deciliter of the mass of the entire particle, which includes the protein content of apoB-100 and apo(a), and their associated lipids (cholesterol, cholesteryl esters, phospholipids, and triglycerides), as well as carbohydrates attached to apo(a), or in nanomoles per liter as a particle number of apo(a). Lp(a) mass assays have an inherent limitation due to the heterogeneity of Lp(a) particle sizes, making it difficult to standardize assays with appropriate calibrators. In addition, because most antibodies used in assays are polyclonal and cross-react with multiple KIV2 repeats, these assays may overestimate Lp(a) levels in patients with large isoforms and underestimate levels in patients with small isoforms. Most clinical laboratories have overcome this limitation by using appropriate calibrators, along with linking the results to the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine International Reference Reagent, making the assays relatively isoform independent. Lp(a) cholesterol content can also be estimated with gel electrophoresis techniques, but these techniques are not validated in terms of accuracy or in predictive value. This topic was recently reviewed by Marcovina and Albers (40), which provided full details of assay methodologies and limitations. For routine clinical care, currently available assays, except for Lp(a) cholesterol assays, can be considered fairly accurate for separating low-risk patients from high-risk patients, except perhaps when patients are near the assay thresholds for what is considered elevated, which is generally >30 mg/dl or >75 nmol/l in the United States. Currently available assays linked to the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine standard are able to detect high-risk patients (i.e., levels >50 mg/dl or >125 nmol/l) with acceptable accuracy. Future efforts should focus on performing comparison studies of different assays (41), and fully standardizing assays across all platforms and instruments.

**AREA OF CONTROVERSY II: WHAT ARE CONSIDERED ELEVATED Lp(a) LEVELS AND WHAT ARE APPROPRIATE RISK CUTOFFS FOR CVD AND CAVS?**

Previous data that showed an inflection for risk of myocardial infarction at Lp(a) >30 mg/dl (42) were recently conﬁrmed by a large meta-analysis of 126,634 participants and 1.3 million person-years of follow-up, in which the risk was curvilinear, but started to accelerate at >24 mg/dl (25). The European Atherosclerosis Society (EAS) proposed <50 mg/dl (approximately <100 to 125 nmol/l) as an optimal level, which represents 20% of the population with higher levels. However, this recommendation misses risk in patients with levels between 25 and 50 mg/dl, as shown by the Copenhagen data (43) and recent Lp(a) analyses of randomized trials (44,45). The 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia consider Lp(a) >30 mg/dl to be a risk factor, and suggest measuring Lp(a) to inform decision-making, particularly in patients at intermediate risk and those with a family history of premature CAD, and in younger patients who may not meet treatment risk criteria (46).

Unlike normally distributed LDL-C or other laboratory values, Lp(a) levels are skewed leftward, and most individuals (~70%) have values in the normal range of <30 mg/dl. However, it must be emphasized that 30% of the global population amounts to ~2 billion people with Lp(a) levels in the atherogenic range. Both the German and U.K. apheresis guidelines use Lp(a) >60 mg/dl to speciﬁcally allow reimbursement for patients with both isolated Lp(a) elevation and recurrent CVD events, or in conjunction with uncontrolled elevated LDL-C.

**AREA OF CONTROVERSY III: DOES MEASURING Lp(a) ENHANCE RISK PREDICTION AT THE BEDSIDE?**

Although genetic and epidemiological data strongly support the prognostic causality of Lp(a), the
clinician and patient are most interested in being able to recategorize the potential risk into a lower or higher risk category, and to change therapy on the basis of the value. This was addressed by the Brunneck study (47) in 826 subjects from the general community with a 15-year prospective follow-up. In subjects at intermediate risk based on Framingham risk score and Reynolds risk score variables, which are the categories of highest need of risk stratification, the addition of Lp(a) to these risk scores...
allowed reclassification of 39.6% of individuals into either lower or higher risk categories, depending on the Lp(a) level. Allele-specific Lp(a) levels and apo(a) isoforms did not add to the predictive ability of the Framingham risk score or Reynolds risk score, or the Lp(a) level. These findings suggest that measuring Lp(a) levels in intermediate-risk groups will allow reclassification of risk in 4 of 10 patients (Figure 6). The impact of risk restratification in not treating with a statin has not been assessed prospectively, whereas the benefit of a statin as a result of upgrading risk is high. Furthermore, when the distribution of risk has high frequency near dichotomous boundaries of risk categories, a relatively small change in absolute predicted risk can result in a relatively large difference in classification, as demonstrated by Kamstrup et al. (26). Additional studies are needed to validate these findings, particularly with the new American College of Cardiology/American Heart Association and SCORE (Systematic Coronary Risk Evaluation) trial risk score algorithms.
**AREA OF CONTROVERSY IV: IS IT POSSIBLE TO ONLY MEASURE Lp(a) ONCE IN A PERSON’S LIFETIME TO ASCERTAIN RISK, AND WHICH PATIENTS SHOULD HAVE A Lp(a) LEVEL MEASURED?**

Because >90% of circulating Lp(a) levels are genetically determined, and the levels are quantitatively related to the LPA gene, with little influence from diet and environment, and because plasma levels do not fluctuate significantly around a pre-set baseline over a lifetime, this test can be considered similar to measuring a SNP in a gene. However, unlike measuring a particular SNP, there are tens (if not hundreds) of LPA SNPs that can influence Lp(a) levels; thus, an Lp(a) level is the most appropriate measurement (19, 25–27).

Most laboratories charge $50 to $100 for an Lp(a) level; therefore, this is likely to be a cost-effective test because it only has to be done once for screening or diagnostic purposes. Because most patients are not aware of their Lp(a)-mediated risk, there is a rationale to add an Lp(a) measurement to the lipid panel of a patient in whom lipids are measured for the first time. If Lp(a) is in the normal range, then subsequent measurements are not needed, irrespective of any change in the patient’s medical therapy.

In 2010, the EAS recommended Lp(a) measurement once in all patients with premature CVD, and in patients with intermediate or high CVD risk, familial hypercholesterolemia, family history of premature CVD and/or elevated Lp(a), recurrent CVD despite statin treatment, or a 3% 10-year risk of fatal and/or 10% 10-year risk of fatal and nonfatal coronary heart disease (44). The U.S. National Lipid Association provided similar recommendations on testing (48). The 2016 European Society of Cardiology/EAS guidelines recommended measurement of Lp(a) in selected cases at high risk, in patients with a family history of premature CVD, and for reclassification in subjects with borderline risk, with a Class IIa, Level of Evidence: C (49).

**AREA OF CONTROVERSY V: IS THERE A DIFFERENCE IN Lp(a)-MEDIATED CVD RISK IN DIFFERENT RACIAL GROUPS?**

It is well appreciated that racial differences exist in Lp(a) levels, apo(a) isoforms, and LPA SNPs...
(Figures 7A and 7B) (26,27,50–52). For example, individuals of African descent have the highest levels of these, and are generally followed by South Asians, Caucasians, Hispanics, and East Asians. The differences likely reflect the geographic migration of the LPA gene out of Africa, with additional changes in genetic architecture over the past ~40 to 60 million years because the LPA gene duplicated itself from the plasminogen gene and expanded in humans over the last 3 million years or so. It is now evident that elevated Lp(a) is an independent CVD risk factor in all racial groups studied to date (51,53–57). For example, in the ARIC (Atherosclerosis Risk In Communities) study, with 20 years of follow-up in 3,467 black and 9,851 white subjects, Lp(a) levels were positively and similarly associated with CVD events in both groups, despite a larger range of distribution in black subjects compared with white subjects (Figure 7C). However, because the prevalence of elevated Lp(a) is different among racial groups, the overall clinical expression of disease and incidence ascribed to Lp(a) relative to other risk factors may be variable.

**AREA OF CONTROVERSY VI: IS Lp(a) A RISK FACTOR WHEN LDL-C IS CONTROLLED?**

Previous data from angiographic progression studies suggested that Lp(a) was no longer a risk factor when LDL-C was controlled. For this reason, many clinicians have practiced with the assumption that when an elevated Lp(a) level is discovered, the most appropriate course of action was to treat the LDL-C and not the Lp(a). Recent studies have suggested that this is a false assumption, and that elevated Lp(a) remains a risk factor even in patients who achieve LDL-C <70 mg/dl (44,45,58). Furthermore, the concept of diminishing returns is now apparent in outcomes trials of LDL-C lowering, in which the starting LDL-C is now often <100 mg/dl, but the absolute risk reduction is small. For example, in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) (59), after a median of 6 years of follow-up, the major adverse cardiac event (MACE) rate was 32.7% in the simvastatin/ezetimibe group, which achieved LDL-C of 54 mg/dl, and 34.7% in the simvastatin-alone arm, which achieved LDL-C of 70 mg/dl. Although this was a laudatory achievement, a 32.7% recurrent hard MACE rate in the setting of an LDL-C of 54 mg/dl suggests that LDL-C-directed risk reduction might not reduce events optimally, even with PCSK9 inhibitors. Recent reports from the AIM-HIGH (Atherosclerotic Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on CVD) study (51) and VIRANI et al. (53), ARIC – Atherosclerotic Risk In Communities; CHD – coronary heart disease; other abbreviations as in Figures 1 and 4.
Global Health Outcomes) (45), JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) (44), and LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) (58) trials have suggested that a portion of this "residual risk" is due to highly elevated Lp(a) in the setting of controlled LDL-C. For example, in AIM-HIGH, patients who achieved LDL-C levels of 65.2 mg/dl and had Lp(a) >125 nmol/l (~50 mg/dl), which was ~75th percentile of Lp(a) levels, had an 89% higher risk of MACES compared with those who had a similar LDL-C level, but low Lp(a). In JUPITER, patients who achieved LDL-C of 55.0 mg/dl and Lp(a) >54 nmol/l (~21 mg/dl) had a 71% higher risk of MACES. In LIPID, in patients who achieved LDL-C of ~112 mg/dl and Lp(a) >73.7 mg/dl, a 23% increase in MACES was present (Figure 8). The overall data encompassing 13,167 statin-treated patients shows a weighed hazard ratio of 1.61 in the setting of LDL-C of 89.1 mg/dl and Lp(a) of 54.9 mg/dl. These data strongly support the independent role of Lp(a) in mediating CVD events that may explain some of the residual risk in patients on statin therapy. It should also be acknowledged that clinical benefit has not been seen in cholesterol ester transfer protein inhibitor trials, despite a modest 20% to 30% reduction in Lp(a), along with LDL-C reductions and HDL-C increases. These data, together with the AIM-HIGH study, suggest that a potential benefit of Lp(a) lowering may not be seen unless >50% mean reductions in Lp(a) can be achieved with no detrimental off-target cardiovascular effects.

AREA OF CONTROVERSY VII: DO STATINS INCREASE Lp(a) LEVELS?

The knowledge on the effect of statins on Lp(a) is evolving. It has been believed that statins do not affect Lp(a) levels because the LDLR is thought to play either no role or a minor role in Lp(a) clearance. Although definitive data do not currently exist, a close assessment of published reports has suggested that statins tend to raise Lp(a) by 10% to 20%, particularly when the data are evaluated as pre- and post-statin levels in individual patients rather than mean levels in groups. For example, in a recent analysis of 3,896 patients in whom Lp(a) and OxPL-apoB were measured pre- and post-statin therapy, including atorvastatin, pravastatin, rosvastatin, pitavastatin, and simvastatin/ezetimibe, the mean patient-level Lp(a) increased by 11% (and up to 50% in some studies), and OxPL-apoB increased by 24% (Figure 9) (60). This might also explain why some patients do not respond well to LDL-C lowering by statins, because most of their cholesterol is on Lp(a), rather than LDL particles (61), and Lp(a) can increase with statin therapy. This should be a clue to physicians that lack of response to statin therapy could be
due to highly elevated Lp(a). Thus, although statin therapy results in overall benefit, it is possible that patients who have increased Lp(a) post-statin therapy do not obtain the full benefit of the statin. A formal patient-level meta-analysis that assesses the role of baseline and on-treatment Lp(a), and the change in Lp(a) post-statin therapy would be helpful to confirm the potential change in Lp(a) and its relationship to CVD outcomes. The mechanism(s) by which statins raise Lp(a) and OxPL-apoB on Lp(a) are undefined, and require further investigation.

**Area of Controversy VIII: Are Current Therapies to Lower Lp(a) Effective and Have They Really Failed in Clinical Trials?**

First, it must be emphasized that there are no approved medications to specifically lower Lp(a), and until the recent trials with the antisense oligonucleotides (ASOs), there have never been any randomized trials of Lp(a) lowering (29,62). The current pharmaceutical armamentarium of approved drugs to lower Lp(a) levels in broad populations is essentially limited to niacin, with PCSK9 inhibitors, mipomersen, and estrogen in more limited populations. When apheresis has been performed to lower Lp(a), a reduction in cardiovascular risk has been suggested (63,64). However, a firm conclusion of benefit of apheresis or an estimation of the magnitude of benefit is hindered by the fact that studies performed to date have had no simultaneous control group; rather, the outcomes of patients who underwent apheresis were compared with historical controls (63). In addition, most sub-studies of Lp(a) risk that have evaluated other therapies have not recruited patients with elevated Lp(a) levels, and all are post hoc analyses with most patients having low levels; therefore, a proper interpretation is difficult. For example, the AIM-HIGH trial showed that niacin added to excellent LDL-C control did not change CVD outcomes. The baseline mean Lp(a) level was ~13.5 mg/dl, and niacin reduced Lp(a) 19% to ~11 mg/dl (43), changes which would be unlikely to result in clinical benefit. However, niacin also did not reduce the event rate in the subgroup of patients in the fourth quartile of Lp(a) (>125 nmol/l or approximately >50 mg/dl), despite achieving a mean Lp(a) reduction of 39%. However, this analysis was underpowered, with only ~700 patients and an event rate of ~16%. Estrogen with progestin lowered Lp(a) by ~15% to 20% in HERS (Heart and Estrogen/Progestin Replacement Study) and, in a post hoc analysis, post-menopausal women with elevated Lp(a) in the fourth quartile (55 to 236 mg/dl) had the most benefit (65), but this is not generally an option in women at risk of atherothrombosis. Mipomersen and PCSK9 inhibitors may reduce Lp(a) by 20% to 30%, but are currently only indicated for rare

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**Figure 9: Effect of Statin Therapy on OxPL-ApoB and Lp(a)**

<table>
<thead>
<tr>
<th>Statin</th>
<th>Study</th>
<th>OxPL-apoB</th>
<th>Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 10mg</td>
<td>Ky et al 2008, Yoshida et al 2012</td>
<td>(n=29)</td>
<td></td>
</tr>
<tr>
<td>Pravastatin 40mg</td>
<td>Rodenberg et al 2006, Choi et al (REVERSAL) 2008, Ky et al 2008</td>
<td>(n=90)</td>
<td></td>
</tr>
<tr>
<td>Pitivastatin 2mg</td>
<td>Yoshida et al 2012</td>
<td>(n=21)</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 40mg</td>
<td>Capoulade et al (ASTRONOMER) 2015</td>
<td>(n=134)</td>
<td></td>
</tr>
<tr>
<td>Simvastatin/Ezetimibe</td>
<td>Yeang et al 2016</td>
<td>(n=162)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=1850)</td>
<td></td>
</tr>
</tbody>
</table>

A forest plot showing the mean percent change in OxPL-apoB and Lp(a) in patients treated with a variety of and different doses of statins, where a baseline and follow-up OxPL-apoB and Lp(a) level were available. Reprinted with permission from Yeang et al. (60). ASTRONOMER = Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy; other abbreviations as in Figure 1.
patient populations (66–69). Thus, it can be concluded that the Lp(a) hypothesis has not been tested with any currently available therapy.

**AREA OF CONTROVERSY IX: IS Lp(a) PROATHEROGENIC AND PROTHROMBOTIC, OR ONLY PROATHEROGENIC?**

Because of its high homology with plasminogen and potential for interfering with plasminogen activation, Lp(a) may not necessarily be prothrombotic a priori, but may tilt the balance towards thrombosis due to the potential loss of fibrinolytic activity. Basic investigations studying plasminogen properties in vitro have documented loss of plasminogen activation to plasmin in the presence of apo(a) or Lp(a) (70). However, a relationship of Lp(a) kringle repeats or LPA SNPs with elevated Lp(a) levels in clinical venous thrombosis studies could not be shown, but associations with factor V Leiden were present (71,72). Although further study is needed, this does suggest that elevated Lp(a) may need a second underlying propensity to propagate thrombus, and that most patients with elevated Lp(a) are at risk primarily for atherosclerosis. Interestingly, in the Women’s Health Study, although the overall trial was negative, the one subgroup that benefited from aspirin use were women with elevated Lp(a), which suggested risk could be modified by antiplatelet therapy (73). Anecdotal evidence exists for use of vitamin K antagonists in patients with recurrent thromboses and
high Lp(a), but formal studies have not been reported. To test the fibrinolysis side of the hypothesis, future studies with Lp(a)-lowering agents could directly assess comprehensive coagulation parameters in patients after lowering of Lp(a).

**EMERGING THERAPIES FOR LOWERING Lp(a)**

Small molecules and antibodies that inhibit enzyme activity and/or receptors or inactivate proteins, respectively, are the mainstay of current pharmaceuticals. Because Lp(a) has no enzyme activity, and the circulating mass levels are relatively high, neither of these approaches may reduce Lp(a) levels. Because apo(a) is synthesized by hepatocytes, therapies directed at the hepatocyte are likely to be most efficacious. In this regard, Figure 10 demonstrates the mechanism of ASOs in inhibiting apo(a) synthesis, and thus, Lp(a) secretion. Liver-targeted ASOs are injected subcutaneously, bind to plasma proteins, and enter the liver, where they accumulate intracellularly. They then bind to their target mRNA mainly in the nucleus but also in cytoplasm if mRNA is present in this compartment. Once a double-stranded complex is formed, ribonuclease H1 then cleaves the sense strand to prevent protein synthesis, but the antisense strand (i.e., the ASO) can then bind to additional mRNA targets. In the case of ASO to apo(a), the hepatocytes can continue to synthesize LDL particles and export them; therefore, steatosis should not occur, but both apo(a) alleles will be inhibited, Lp(a) assembly prevented, and plasma Lp(a) levels reduced.

Initial studies suggested that mipomersen, an ASO that inhibited apoB mRNA, could lower Lp(a) and OxPL-apoB in transgenic Lp(a) (75). Interestingly, the mechanism was a marked reduction of apoB production, such that apoB was limiting Lp(a) assembly. Mipomersen did not affect production of apo(a), which continued to be secreted into the circulation as “free” apo(a). These preclinical findings were subsequently confirmed in 4 randomized trials of LDL-C lowering, with mipomersen showing a 25% reduction in Lp(a) (76). This observation confirmed that lowering Lp(a) could be achieved with ASOs, and subsequently, it was reported that an ASO specific to apo(a) reduced circulating apo(a) by 86% without affecting apoB in apo(a) transgenic mice (77). Recently, optimized ASOs to apo(a) have been reported for human trials (78), and 3 randomized, controlled trials (29,62) have reported dose-dependent reductions in mean Lp(a) lowering of >80%. In addition, a significant reduction was noted in proinflammatory OxPL and in the inflammatory effects of monocytes, which are cells that initiate and accelerate CVD, as well as plasma LDL-C (62). A subsequent advance in potency of ASOs was made with IONIS-APO(a)-LRx, which contains an N-acetyl-galactosamine (GalNac3)–conjugated molecule designed to be highly and selectively taken up by hepatocytes, with mean reductions of 66% to 92% and up to 99% reduction of Lp(a) in some patients (Figure 11), together with a reduction in OxPL.

**CONCLUSIONS**

The Central Illustration depicts the current thresholds for what is considered Lp(a)-driven risk, and the effects of approved and emerging therapies. Lp(a) levels <30 mg/dl are considered optimal, and 8% with negligible Lp(a)-mediated risk. Lp(a) levels <50 mg/dl are recommended by the EAS as optimal, and Lp(a) levels >60 mg/dl are used as a cutoff for the reimbursement of apheresis in Germany and the United Kingdom. In a theoretical patient with a Lp(a) level of 150 mg/dl, use of statins tends to increase Lp(a) by 10% to 20%. In contrast, use of niacin, PCSK9 inhibitors, cholesterol
The effect of various therapies on lipoprotein(a) (Lp(a)) in a hypothetical patient with Lp(a) of 150 mg/dl, which is >98th percentile for Lp(a) levels. Statins tend to increase the level by 10% to 20%, to 165 to 180 mg/dl. Niacin, proprotein convertase subtilisin/kexin-type 9 (PCSK9) antibodies, cholesterol ester transfer protein inhibitors (CETPi), and mipomersen decrease levels by 20% to 30%, to 105 to 120 mg/dl. Apheresis results in a time-averaged reduction of 30% to 35%, reducing levels to 98 to 105 mg/dl. Antisense oligonucleotides reduce Lp(a) by 80% to 99%, reaching levels of 1.5 to 30 mg/dl. CAVS = calcific aortic valve stenosis; CVD = cardiovascular disease; EAS = European Atherosclerosis Society.
ester transfer protein inhibitors, and mipomersen leads to a 20% to 30% reduction. Similarly, apheresis leads to a time-averaged reduction of 30% to 35%. Use of ASO, which may reduce Lp(a), and will be able to reach levels in which the risk due to Lp(a) is quite low in most patients. Such potent and specific therapies are currently being developed clinically in patients with elevated Lp(a), and will be able to test the hypothesis that pharmacologically reducing genetically elevated Lp(a) levels may reduce the risk of CVD and CAVS in the setting of what is considered optimal medical therapy at present.

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66. Chapman D, Shiiffman D, Zee RY, et al. Polymorphism in the apolipoprotein(a) gene, plasma lipoprotein(a), cardiovascular disease, and low-


KEY WORDS aortic stenosis, cardiovascular disease, genome-wide association studies, therapy