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Are we seeing the light at the end of the tunnel for high Lipoprotein(a)?

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ABSTRACT

Lipoprotein(a) (Lp(a)) attests to be of interest as a new lipoprotein target. However, Lp(a) was discovered in 1963 and since then was recognized as a low-density lipoprotein (LDL)-like lipoprotein with a structurally similar domain to plasminogen. We are increasingly recognizing the importance of Lp(a) and cardiovascular pathologies including atherosclerotic cardiovascular disease, aortic valve stenosis, heart failure, and atrial fibrillation. However, we neither have a standardized measurement method nor an appropriate agent to intervene with this old threat that we have recognized for 60 years. Herein, we present an up-to-date review of our knowledge about Lp(a) covering measurement methods, its associates, and summary of the currently available therapies and emerging therapeutic agents for the management of high Lp(a) in the light of recent evidence and guideline recommendations.

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Introduction

With the improvement of the novel drug technologies, lipoprotein(a) (Lp(a)) attests to be of interest as a new lipoprotein target. Lp(a) was discovered in 1963 and since then was recognized as a low-density lipoprotein (LDL)-like lipoprotein with a structurally similar domain to plasminogen (1-3).

For almost 50 years, Lp(a) could not find a place in clinical practice due to the lack of standardized method of measurement and lack of effective treatment. During the last decade, a large amount of information has accumulated about its role in atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis. However, there are still many unknowns and discrepancy between the consensus of societies. The purpose of this review is to provide insight to the possible clinical use of Lp(a) and the currently available therapies and emerging therapeutic agents for the management of patients in the light of recent evidence and guideline recommendations.

What is Lp(a)?

Lp(a) is a unique liver-derived lipoprotein, consisting of an LDL-like particle and apolipoprotein (apo)(a) which is disulfide-linked to the apo-B100. Apo(a) is a homologue of plasminogen, containing multiple copies of plasminogen kringle IV, a single copy of plasminogen kringle V, and an inactive protease domain (4, 5). The similarity between Lp(a) and plasminogen allows Lp(a) to interfere with tissue plasminogen activator (tPA) – mediated plasminogen activation, as a result, possibly contributing to hypercoagulability (6). Interestingly, observational human studies showed only a slightly increased risk for venous thromboembolism at very high Lp(a) levels (>95th percentile) (7), whereas Mendelian randomization studies did not support any causality for thrombotic events (7, 8).

Lp(a) has a close association with inflammation due to the interleukin-6 (IL-6), an acute-phase cytokine, response element located on *LPA gene* (9). Lp(a) activates endothelial cells by enhancement

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of PFKFB3-mediated glycolysis, which can be reversed by inhibition of glycolysis. An increase in vascular glycolysis, then, facilitates inflammation through the promotion of trans-endothelial migration of monocytes (10), a phenomenon seen mostly in Lp(a) concentrations over >50 mg/dL (>125 nmol/L) (9). Lp(a) as an opsonin, can also alone enhance the phagocytic function of macrophages, as proven against the encapsulated bacterium *Haemophilus influenzae,* a function dependent on scavenger receptor CD36 (11).

As suggested by the Mendelian Randomization studies, absolute changes in Lp(a) plasma levels modify the risk of ASCVD (2). Lp(a) levels are strongly determined through genetic variants in the *LPA* gene, particularly by a size polymorphism in apolipoprotein(a) [apo(a)] (12).

The *LPA gene* locus on chromosome 6q explains up to 90% of Lp(a) variance. While the *LPA gene* locus controls the synthesis of Lp(a), 30-70% of Lp(a) concentration is attributed to apo(a) isoform size, which is determined by the number of Kringle IV repeats. Kringle IV repeats in the *LPA gene* results in polymorphisms leading to apo(a) varying in size (5). All these apo(a) variants account for apo(a) isoforms. There is an inverse relationship between the number of Kringle IV repeats and Lp(a) concentration. Median Lp(a) concentrations are 4-5 times higher in individuals with small apo (a) isoforms, i.e., with low number of Kringle IV repeats (< 22 repeats) compared to those carrying only large isoforms (> 22 repeats). This inverse correlation is caused by more efficient maturation of smaller apo(a) isoforms in the endoplasmic reticulum (3, 12). Lp(a) is also assembled out of the hepatocyte membrane. Individuals carrying the same isoforms of Lp(a) may still have varying plasma concentrations since the plasma concentration is not only dependent on precursor size but also the rate of the production (13).

Of all Kringle IV types and the number of Kringle IV type 2 domains are associated independently with the risk of ASCVD along with plasma Lp(a) concentrations. On the other hand, significant difference in average Lp(a) concentration among different populations independent of apo(a) allele frequency is also noted (14). In addition to the wide *LPA gene*, *APOE*, *CETP*, and a novel variant of *APOH* coding beta2-glycoprotein I (β2GPI) are associated with Lp(a) levels (3, 15).

What conditions other than genetics affect the Lp(a) levels?

Though Lp(a) concentration is mainly determined by genetics (>90%), several physiologic and pathologic factors have been suggested to influence Lp(a) levels. **Table 1** depicts these factors including ethnicity, sex, hormones, and chronic pathologies such as hepatic and renal diseases.

ARIC and Dallas Heart studies have shown that Lp(a) levels are increased and less skewed in Black individuals compared to other ethnicities (3, 16, 17). UK Biobank data revealed that median Lp(a) levels are highest in Black individuals and sequentially decreasing in South Asian, White, and Chinese individuals (75, 31, 19 and 16 nmol/L, respectively) (3, 18).

Table 1 | Summary of conditions that affect Lp(a) levels.

Conditions/ interventions		Effect on Lp(a) levels
Genetics	More than 90% of the levels of Lp(a) are determined genetically. *LPA* is the major gene regulating Lp(a). Other genes including *APOE*, *CETP*, and a novel variant of *APOH* may have some influence.	
Ethnicity	Ethnicity differs Lp(a) concentration. Lp(a) levels are sequentially increased in Chinese, White, South Asian, and highest in Black individuals	
Fasting	No change	
Lifestyle	*Diet*	Replacement of dietary saturated fat with carbohydrate or unsaturated fat is associted with ~10%–15% ↑
		Low carbohydrate diet high in saturated fat ~15% ↓
	Alcohol consumption	No association or minor ↓
	Physical activity	No or minor change
Sex hormones	*Sex*	No change or minor in women compared to men
	Endogenous sex hormones	No or minor change
	Menopause	No change or minimal ↑
	Postmenopausal HRT	Almost 20–25% ↓; Decrease is greater with oral *vs* transdermal estrogen. No difference between continuous *vs* cyclic HRT
	Surgical or biochemical castration in males	Small ↑
	Ovariectomy, estrogen receptor antagonist	Small ↑
	Pregnancy	2-fold ↑

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Conditions/ interventions		Effect on Lp(a) levels
Hormones and related conditions	*Hyperthyroidism*	↓ and Treatment of hyperthyroidism results in 20–25% ↑
	Hypothyroidism	↑ and Treatment of Hypothyroidism is associated with 5%–20% ↓
	Growth hormone replacement therapy	2-fold ↑
Chronic kidney disease	*Chronic kidney disease and hemodialysis*	↑; an inverse association with kidney function; a 2–4-fold higher level only in patients with large size apo(a) *vs* controls
	Nephrotic syndrome	Almost 3–5-fold ↑
	Peritoneal dialysis patients	2-fold ↑
	Kidney transplantation	Significant ↓ or normalization
Hepatic impairment	*Hepatocellular damage*	Decreased in parallel with the disease progression >40% reduction in hepatitis; a 2-fold increase with antiviral treatment
	Liver transplantation	Changes of apo(a) isoform to that of the donor, with corresponding changes in Lp(a) levels
	Non-alcoholic fatty liver disease	Inconsistent association across population groups
Inflammation and related conditions	*Severe, life-threatening acute-phase conditions*	In sepsis, severe burns ↓
	Several inflammatory conditions	↑
	Tocilizumab (IL-6 inhibitor)	Almost 30%–40% ↓
	Protease inhibitors or antiretroviral therapy	↑
	Statins	May slightly increase Lp(a) (but reports are heterogeneous)
	Air pollution	Slight ↑

HRT: hormone replacement therapy; IL: interleukin, Lp(a): Lipoprotein(a).

Sex hormones may also affect Lp(a) levels. Women generally have 5–10% higher Lp(a) levels than men (17, 19). There are reports of elevated Lp(a) in pregnant women that return to baseline postpartum. Lp(a) levels also increase at menopause but remain relatively constant in men (20). Moreover, exogenous androgens and estrogen reduce Lp(a) level. Other hormones, particularly those affecting lipoprotein metabolism, may influence Lp(a) concentrations. Thyroid dysfunctions modestly affect Lp(a) levels, and treatment of overt or subtle hypothyroidism decreases Lp(a).

Research on the interaction between lifestyle and Lp(a) is expanding. Physical activity seems to have no or minimal effect on Lp(a) levels, with conflicting variations in younger or diabetic populations (3, 18). Though diet was initially suggested not to affect Lp(a) levels, recent studies denote some interaction between eating pattern and Lp(a). Replacement of dietary saturated fat with unsaturated fat or protein may increase Lp(a) up to 10-15%. A diet regimen enriched with walnuts (41-56 g/day) or pecans (72 g/day) can only result in a minimal (6-15%) reduction of Lp(a) (18).

Both liver and kidney diseases affect Lp(a) levels. Hepatic damage is associated with Lp(a) decrease in parallel with the disease progression (3, 18). Contrary, decreasing glomerular filtration rate results in elevation of Lp(a) levels (21). In chronic kidney disease, the catabolism of Lp(a) is reduced, leading to elevation of larger apo(a) isoforms. Meanwhile, in patients with nephrotic syndrome, Lp(a) synthesis is increased with subsequent elevation of both large and small sized apo(a)s due to urinary protein loss (3, 18, 21). Lp(a) levels are highest in patients with nephrotic syndrome or in those treated by peritoneal dialysis (22). Following renal transplantation, Lp(a) concentration reduces independent of the type of immunosuppressive therapy (21-23).

Lp(a) levels show association with both acute and chronic inflammatory states (9). Lp(a) reduction is reported in severe, life-threatening acute phase conditions such as sepsis etc, whereas increased levels are reported in several acute and chronic inflammatory conditions (18, 21). As an example in patients with systemic lupus erythematosus, Lp(a) higher than >125 nmol/L is associated with lupus proteinuria, reduced glomerular filtration rate, and elevated erythrocyte sedimentation rate (24). Moreover, moderately increases of Lp(a) are related to IL-6 levels and may reduce with IL-6 blockade through tocilizumab therapy (25). This effect is not observed with TNF-α blockade (25, 26). The clinical impact of inflammation on Lp(a) concentration is small in population studies (1,18). In human immunodeficiency virus infected patients with baseline Lp(a) concentrations >20-30 mg/dL, treatment with protease inhibitors or antiretroviral therapy is associated with Lp(a) increase (27). Lp(a) levels are increased in patients with coronavirus disease 2019 (COVID-19) and correlate positively with the disease severity, which includes acute kidney damage, and also positively associated with IL-8, fibrinogen, and creatinine levels (28). COVID-19 alone is known to cause five-times higher frequency of thromboembolic

events. Though elevated D-dimer levels are more common in COVID-19 patients with elevated Lp(a) (29), the thromboembolic risk is not influenced by Lp(a) levels. However, the risk for ischemic heart disease (IHD) is higher in patients with COVID-19, if elevated Lp(a) levels are additionally present (8). Air pollution as an inflammatory trigger is associated with elevated Lp(a) levels. Long term exposure to fine particles (PM2.5) has the strongest effect on Lp(a)- which is stronger than for any other lipoproteins (18).

Clinical implications of high Lp(a)

Observational and genetic studies consistently recognize the causal association between high Lp(a) and ASCVD, aortic valve stenosis and mortality (cardiovascular and all-cause) in both sexes and across ethnic groups (3). Extreme Lp(a) elevation is one of the few conditions which faces affected individuals with high or very high cardiovascular risk category without additional risk scoring, along with familial hypercholesterolemia (FH), documented ASCVD, long-standing diabetes mellitus, and chronic kidney disease (2, 3). Therefore, current guidelines recommend the Lp(a) measurement for every adult to identify Lp(a) levels >180 mg/dL (>430 nmol/L) (2). An elevation of Lp(a) may increase the risk for an incident CAD without familial risk factors or even in those with LDL-C<70 mg/dL (30). ACCELERATE trial has shown that high Lp(a) levels are associated with an increased risk of major adverse ASCVD events at low levels of LDL-C (<80 mg/dL) (8). Also, smaller apo(a) accompanying high Lp(a) concentration is associated with higher risk of ASCVD (3). Elevated Lp(a) levels may activate macrophages and coronary artery smooth muscle cells and result in coronary artery spasm by upregulating α7-nAChR/IL-6/p38 MAPK signaling, resulting in secretion of proinflammatory IL-6 and reduction of the inducible nitric oxide synthase expression through M1 polarization of macrophages, which are not triggered by LDL-C (31).

Many different ASCVD presentations have been shown to be associated with high Lp(a) levels. Men with Lp(a) levels above 95th percentile have a 4-fold increased risk of severe angina, likewise women have 2-fold increased risk for IHD with same Lp(a) levels (32). Copenhagen City Heart Study proved a continuous relation between Lp(a) levels and risk of IHD and myocardial infarction (MI), and in the general population, where levels exceeding the 95th percentile predict a 3-4 fold increased risk of MI (33). Higher Lp(a) levels are reported as a culprit for premature CAD (34). It also correlates with the CAD severity (35) and the volume and progression of the coronary atheroma (36). High Lp(a) levels are associated in men aged >45 years with higher coronary artery calcium (CAC) scores, which has a positive correlation with traditional cardiovascular risk factors (37). High Lp(a) levels are also associated with the progression of CAC (38). Furthermore, in individuals with established ST-elevation MI, very high (>135 mg/dL) levels of Lp(a) can predict the worse long-term outcomes as proven by the prospective cohort studies, highlighting the need for Lp(a)-based risk stratification in these patients (39). Combining Lp(a) with other risk estimates such as fibrinogen, Syntax Score etc have been shown to increase the prediction of cardiovascular events in acute or chronic ASCVD states (40, 41). Even slightly elevated Lp(a) levels may result in early loss of vein grafts in the first year of the coronary artery bypass grafting surgery (42) Lp(a) levels have been shown predict mid and long term ASCVD events in patients undergoing percutaneous coronary intervention (PCI) (43). Lp(a) levels have been also suggested to predict contrast induced kidney injury following emergent PCI (44).

High Lp(a) also attenuates the ASCVD risk in patients with CKD. In patients with impaired renal functions, Lp(a) at levels of 30-50 mg/dL is associated with acute coronary syndrome related adverse outcomes, whereas in patients with normal kidney functions, Lp(a)>50 mg/dL is usually required for such a risk level (45). Similarly, in both pre-diabetic and type 2 diabetic patients, recurrence of ASCVD events is more prominent in those with elevated Lp(a) (46).

Apart from being a risk factor for CAD, elevated Lp(a) levels (> 30-50 mg/dL) are associated with calcific aortic valve stenosis, especially the *LPA* single nucleotide polymorphism rs10455872 is responsible for a 2-fold increased risk of aortic-valve calcification (47). Additionally, Lp(a) levels >90 mg/dL is associated with a 3-fold increase in the risk of aortic-valve calcification (48). The Copenhagen General Population Study also presented that elevated Lp(a) is not only associated with the calcification of the aortic valve but also of the mitral valve (OR 1.53) (49). The risk of aortic involvement with high Lp(a) levels is especially important in patients with FH who already have smaller aortic valve areas and increased inflammatory markers, therefore susceptible to accelerated valvular dysfunction even within the normal range of Lp(a) levels (50). Lp(a) is of use, along with hypertension and LDL-C, for predicting the need of aortic valve replacement in FH. However, the effect of Lp(a) reduction on the progression of aortic valve stenosis is currently a mystery requiring clinical trials to ascertain (51). High levels of Lp(a) in the upper 4th quartile also have been shown to result in aortic dissection, a correlation independent from any other risk factor (52).

Elevated Lp(a) levels are also associated with the risk of heart failure, peripheral arterial disease (PAD) or stroke but higher Lp(a) concentrations are required than those associated with the risk of coronary or aortic diseases (1). The increased risk of heart failure associated with high Lp(a) levels is attributed to ASCVD and calcific aortic valve stenosis (53). Likewise, elevated Lp(a) (≥30 mg/dL) is associated with higher serum N-terminal pro-B natriuretic peptide levels and lower left ventricular ejection fraction at follow-up (54). Increased cardiovascular mortality and hospitalization rates are reported within the first year of the diagnosis of heart failure in those with high Lp(a) (≥30 mg/dL) (55).

Different studies suggest that patients within the highest quartiles for Lp(a) are at increased risk for PAD, an association generally not affected by LDL-C levels. In patients with established PAD, extremity amputations are more common in those with elevated Lp(a). However, it's important to note that the predictive value of Lp(a) levels in PAD is higher than CAD (56). The strongest genetic predictor of PAD is the *LPA gene* locus (57). Lp(a) is also a non-traditional risk factor for premature lower extremity PAD (57). High Lp(a) may not only result in a worse long-term overall prognosis including ASCVD related mortality in patients with PAD, but also with an increased risk for major adverse limb events after iliofemoral endarterectomy (58).

Increased Lp(a) levels are associated with cerebrovascular atherothrombotic events. High Lp(a) is reported to be associated with the presence of carotid atherosclerosis independent of the conventional risk factors including LDL-C level (59). Interestingly elevated luminal levels of Lp(a) in the aneurysm sack is associated with enlargement of the aneurysm wall within the unruptured intracranial aneurysms (60) Additionally, elevated Lp(a) is not only responsible for large artery atherosclerosis, but also for recurrence of cerebrovascular events primarily in Caucasian individuals aged <60 years or with evident ASCVD (61). High Lp(a) (>137 nmol/L), also predicts major ASCVD events following the carotid endarterectomy (62).

The relationship between atrial fibrillation (AF) and Lp(a) levels is another popular topic. A recent study from the UK Biobank showed that each 50 nmol/L (23 mg/dL) increase in Lp(a) is associated with an increased risk of incident AF for both the measured and genetically predicted Lp(a) (63). Mendelian randomization analyses

also denoted similar results. Interestingly there was no evidence of risk-conferring effect from LDL-C or triglycerides, and only 39% of Lp(a) risk was mediated through ASCVD and aortic valve stenoses, suggesting that Lp(a) may partly influence AF independent of its known effects on ASCVD (64). Apart from these results, presence of left atrial thrombus or thromboembolic events are shown to be increased in patients with non-valvular chronic AF with Lp(a) levels ≥30 mg/dL (64).

Lp(a) seems to be an important marker in extra cardiovascular pathologies, too. In mildly preeclamptic patients, serum Lp(a) level > 40.5 mg/dL predicts the development of severe preeclampsia later during the pregnancy (65). Several neuro-vascular pathologies are also shown to be associated with high Lp(a) levels. For example, Lp(a) levels correlate with major extracranial arterial vessel size in patients with multiple sclerosis (66). Similarly, high Lp(a) levels are reported in several forms of early-onset vascular dementia and ceroid lipofuscinosis due to accelerated atherosclerotic disease (67). Meanwhile a weak association between elevated serum Lp(a) levels and worse motor symptoms in Parkinson disease is noted (68). Serum Lp(a) levels are also associated with the severity of diabetic retinopathy and primary angle-closure glaucoma and resultant neuropathy (69, 70).

In addition, Lp(a) has some special implications for FH patients, as it has been shown as a culprit for aortic valve calcification in these patients. Furthermore, high Lp(a) may interfere with the diagnostic accuracy of the clinical diagnosis of FH with Dutch Lipid Clinic Network (DLCN) criteria. Lp(a)-adjusted LDL-C level (LDL-C – 0.3 × Lp(a)) might be helpful, leading to the differences during the placement of patients into different risk categories after DLCN criteria scores. In patients with already diagnosed FH, a Lp(a) level ≥40 mg/dL has resulted in FH re-diagnosing with a sensitivity of 63% and specificity of 78% (area under the curve = 0.7, 95% CI 0.7–0.8, $p < 0.001$) after adjustment according to the proposed formula (71). In the same patient group with Lp(a) ≥ 40 mg/dL, 51% were reclassified after DLCN criteria score and 34% reclassified in means of diagnosis. The rates of reclassification after DLCN criteria score and reclassification in means of diagnosis in FH patients with Lp(a) <40 mg/dL were only 15% and 11%, respectively (71, 72).

Low Lp(a) levels

The implications of low Lp(a) levels are not well known. Certain associations with very low Lp(a) levels are noticed. For example, low circulating levels of Lp(a), along with transaminases may serve as a mean to noninvasively measure the severity of Non-alcoholic fatty liver disease (NAFLD), as Lp(a)-synthesis also depends on hepatocyte function (73). Patients with Child-Pugh class B and C levels have significantly lower levels of Lp(a) levels than those in Child-Pugh class A, with lower levels of total cholesterol and Lp(a) relating with decompensatory events in cirrhotic patients (74).

Lower concentrations of Lp(a), bottom 10%, are associated with increased susceptibility to incident type 2 diabetes, another cause of vascular glycolysis leading to endothelial dysfunction (32) Meta-analysis of all available studies showed a 38% (95% CI 29-48%, $P < 0.0001$) higher risk for the lowest quintile compared to highest quintile of the Lp(a) levels (3). Likewise, an observational cross-sectional study demonstrated an association between low Lp(a) and increased risk of pre-diabetes, insulin resistance, and hyperinsulinemia (3, 75). The mechanisms underlying this association are still unclear and not explained by recognized risk factors or known variants of diabetes (3). Furthermore, we do not know if aggressive Lp(a) lowering may exacerbate diabetes.

Copenhagen General Population Study proved recently that low Lp(a) levels do not correlate with any cancer or infectious disease (76). Despite that, in breast cancer patients, when compared to healthy controls, higher levels of Lp(a) are prominent in the Han Chinese population (77) Moreover, receptor tyrosine-protein kinase erbB-2 proto-oncogene expression is inversely associated with serum Lp(a) levels in these patients, which is of clinical importance as the expression of this growth factor receptor may change the treatment regimen and prognosis.

The big challenge - How to measure Lp(a) levels?

Lp(a) plasma or serum levels can be measured using several immunochemical methods including enzyme-linked immunosorbent assay (ELISA), immunoturbidimetry, nephelometry, and dissociation-enhanced lanthanide fluorescent immunoassay (78) Although measurements with these immunoassays are made with polyclonal antibodies against apo(a), there are studies regarding a monoclonal antibody binding on a single-site on Lp(a) (79).

As there is no standardized assay to measure Lp(a) in serum or plasma, immunochemical methods are also divided into mass dependent and independent assays (**Table 2**). Mass-independent assays use antibodies against non-repeating kringles of Lp(a) therefore measure the actual particle number, i.e., each apo(a) molecule is only recognized once. These assays are reported in nanomoles per liter (nmol/L). Contrary, mass-dependent assays calculate the entire molecular components of the Lp(a) including proteins, lipids, and carbohydrates, and are reported in milligrams per liter (mg/dL). As only the total amount of Kringle domains are recognized and distinguishment of one Kringle domain from the others is not made; detected Lp(a) levels may be mistaken in patients with smaller or larger apo(a) isoforms, resulting in underestimated or overestimated Lp(a) levels, respectively (80). In a systematic comparison of apo(a) isoform dependent and independent assays, Lp(a) was underestimated by ~10% in patients with smaller isoforms (associated

Table 2 | Methods of Lp(a) Measurements.

Lp(a): Lipoprotein(a)	Mass-Dependent	Mass-Independent
Measured component	The entire molecular components of the Lp(a) including proteins, lipids, and carbohydrates	Antibodies against non-repeating kringles of Lp(a)
Reported in units	Milligrams per liter (mg/dL)	Nanomoles per liter (nmol/L)
Disadvantages	Isoform size can alter the measured levels of Lp(a)	Measurements are made with polyclonal antibodies against Lp(a), there is no standardized immunoassay while different methods are in use

Lp(a): Lipoprotein(a).

with high Lp(a) levels and high ASCVD risk) and overestimated by up to 35% in those with large isoforms (associated with low Lp(a) concentrations and low ASCVD risk) (3, 81). Such a variance might be interpreted as an average absolute bias of ±10 nmol/L (or 4 mg/dL) which might be clinically ignored as will not result in a major alteration of the risk classification. However, several studies showed biases varying between -25% and +35% (3, 81).

Another important problem in clinical practice is the conversion of Lp(a) concentrations from mass unit to molar units. As assays vary extensively, using a standard converting factor between mg/dL and nmol/L values of Lp(a) is not recommended (1). Some investigators who use both units in clinical practice suggest conversion factor of 2-2.5 as 'best guess' from mg/dL to nmol/L (3, 81, 82). In anyway, apo(a) isoform-sensitive assays are not reliable and manufacturers are suggested to provide an appropriate conversion factor if both measures are given (3, 81). Guidelines and consensus statements also define clinical assays using an antibody for a unique non-repetitive epitope in apo(a), i.e. recognizing each Lp(a) particle once that report in molar units as ideal for Lp(a) measurements (3). However, generating such antibodies is difficult and assays mostly use polyclonal antibodies which recognize different epitopes leading to inaccurate Lp(a) measurements (81). It's also suggested that integrating multiple calibrators spanning a range of sizes in the assay can at least partly address this issue (3). But further standardization of Lp(a) measurement is warranted. Meanwhile, earlier studies have failed to detect the association between Lp(a) and IHD, due to the use of fresh-frozen plasma samples stored for years, which resulted in false lower concentrations of Lp(a) (83).

Prevalence of high Lp(a)

Distribution of Lp(a) in the general population, as determined by the Copenhagen General Population Study, is very positively skewed direkt kaldırabiliriz bu ifadeyi with 80% of all the subjects having Lp(a) levels <50 mg/dL. The rest, 20%, having levels ≥50 mg/dL, proving that elevated Lp(a) is not a rarity (84).

Though Lp(a) is proven to be associated with many pathologies, we still do not have enough epidemiological data providing the prevalence of high Lp(a) levels in many countries. INTERHEART study has evaluated variations in Lp(a) concentrations and isoform sizes in multiple ethnicities including African, Arab, Chinese, European, Latin American, South Asian, and Southeast Asians by using an immunoassay (83). According to the INTERHEART investigators, Lp(a) > 50 mg/dL was not associated with increased risk of MI in Africans and Arabs, contrarily, South Asians and Latin Americans had higher population attributable risks. Additionally, mean Lp(a) concentration was 27.2 mg/dL in Africans and only 7.8 mg/dL in Chinese individuals with the lowest concentration among the studied populations. Also, Chinese and South Asians had greater isoform sizes when compared to other populations.

The investigators of the Copenhagen Heart Study described different median Lp(a) concentrations under 3 categories for their cohort (33). In women with no history of ASCVD event, the mean Lp(a) concentration was 18 mg/dL, in women with a previous history of MI, it was 24 mg/dL and finally, in women with IHD history was 22 mg/dL. In men, the median values were 15 mg/dL for the no event group and 17 mg/dL for both MI and IHD groups. Like the INTERHEART study, Copenhagen Heart Study used polyclonal antibody-based immunoassay (33, 83).

Another study published by Varvel et al. in 2016, in which 532,359 subjects whose records were in the databases in the United States were evaluated, the mean Lp(a) for this group was 34 mg/dL, with the median of 17 mg/dL (19). Being in rapport with the Copenhagen Heart Study findings, Varvel et al. found that females had a higher mean Lp(a) when compared with the males (with 37 mg/dL vs 30.7 mg/dL, respectively (19, 33).

In whom should we have Lp(a) measurement?

Current guidelines recommend that Lp(a) should be measured at least once in an adult's lifetime, preferably in the first lipid profile, to identify those with high ASCVD risk (2, 3). Lp(a) measurement is more valuable especially in patients with premature ASCVD (men <55 years, women <60 years), family history of premature ASCVD, FH, or recurrent ASCVD even on optimal statin therapy to determine ASCVD risk and characterization of dyslipidemias (2). Incorporation of Lp(a) level in risk assessment has been shown to recuperate risk stratification, especially for those with very high levels of Lp(a) (>99th percentile) in 31%-63% of whom were reclassified from moderate to higher risk (3, 85). Guidelines also recommend its measurement in patients with aortic valve stenosis (3).

For children, Lp(a) screening is recommended in only cases with a history of ischemic stroke or a family history of premature ASCVD or elevated Lp(a) with no other identifiable risk factors (3, 86). In the setting of FH, family history of very high Lp(a), and personal or family history of early ASCVD, systematic or opportunistic screening, especially the cascade screening is also suggested (3). As Lp(a) levels may increase until adulthood repeated testing may be required (3, 15).

For adults it is not necessary to include Lp(a) in the traditional lipid profile in repeated measurements, as Lp(a) serum and plasma concentrations do not exhibit significant variations over time and in response to food intake (3, 18). Some instances, in which variations can be expected are transition to menopause, oral contraceptives, pregnancy, hypothyroidism, chronic kidney disease, nephrotic syndrome, growth hormone treatment, and specific Lp(a)-lowering treatment. Inflammation can also cause mild increases in circulating Lp(a) levels (18). Another cause of significantly increased Lp(a) levels is bariatric surgery, especially within the 12 months following the surgery, however followed by an overall decrease in Lp(a) levels (87).

What should be the goal for Lp(a) reduction?

Though the association between Lp(a) and ASCVD outcomes is linear, determining a threshold level of Lp(a) which can be applied to every individual is a challenge, as risks associated with Lp(a) plasma concentrations are affected by many factors including the structural differences of Lp(a), LDL-C levels, underlying cardiovascular or metabolic disease (3, 18) etc. However, many centers measuring with mass-dependent methods uses 30 mg/dL, while many others using mass-independent methods use 72 nmol/L as a threshold for increased atherosclerotic risk (3, 18, 33). Contrarily, it is known that plasma Lp(a) levels greater than 24 mg/dL puts the individuals at an increased risk for CAD (88), so using 30 mg/dL threshold will eventually result in overseeing the risk of CAD for individuals who has Lp(a) plasma levels greater than 24 mg/dL but lesser than 30 mg/dL. As INTERHEART study proved Lp(a) > 50 mg/dL, on the other hand, is not associated with increased risk of MI in African and Arab individuals, yet, may put a South Asian or Latin American individual at a great risk, so when setting a threshold for Lp(a), population difference is another issue to be considered (3, 83, 88). Additionally, baseline and on-statin elevated levels of Lp(a) in Chinese patients with heterozygous FH are associated with cardiovascular events (89).

A recent Mendelian randomization analysis estimated that the same effect size achieved by a 38.67 mg/dL lowering of LDL-C can

be achieved with a Lp(a) reduction of 65.7 mg/dL (90). Additionally, it is already known that the contribution of Lp(a) to the risk attributed to the LDL-C is less relevant with lower Lp(a), however, when Lp(a)>50 mg/dL, 14% of the risk attributed to LDL-C is due to Lp(a), with Lp(a)>100 mg/dL, the risk attributed is 28%. This attribution is especially important when treating high-risk patients with elevated Lp(a) and trying to achieve the LDL-C targets of <70 mg/dL while the measured LDL-C levels might be higher than the exact LDL-C, due to the contribution of Lp(a) (91, 92). As cholesterol enclosed in Lp(a) and LDL-C particles cannot be separated, reported collectively as LDL-C concentration. Analyses of isolated Lp(a) particles denoted that cholesterol accounts for 30%-45% of Lp(a) mass concentration (3, 93, 94). Therefore, Lp(a)-cholesterol is estimated by multiplying Lp(a) mass (mg/dL) by 0.3 and used to correct LDL-C with the formula (=Lp(a)-cholesterol-corrected LDL-C) (3). However, estimated Lp(a)-cholesterol shows 6% to 60 % variation from the direct measured Lp(a)-cholesterol (95), thus routine correction of LDL-C for Lp(a)- cholesterol is not recommended (3).

All considered, a stratified approach for the evaluation of individuals with elevated Lp(a) by risk factors, polymorphisms, ethnicity etc., as done for LDL-C in the 2019 EAS/ESC Guidelines on Management of Dyslipidemias, might be necessary, while a single threshold does not seem to be effective for determining the risk for everyone. To do so, studies targeting Lp(a) as a single risk factor wouldn't be enough but studies handling combined risk factors might prove to be useful (2, 3). EAS 2022 Lp(a) consensus panel accepts a pragmatic approach, with Lp(a) cut-offs to 'rule out' (<30 mg/dL or <75 nmol/L) and 'rule-in' (>50 mg/dL or >125 nmol/L) the ASCVD risk (3, 96). Panels also defines Lp(a) levels ranging 75-125 nmol/L (30-50 mg/dL) as a relevant grey zone, when considering Lp(a)-attributable risk in the presence of other risk factors in risk stratification (3, 96). And finally, panel highligths that Lp(a) plasma concentration is sufficient to estimate the Lp(a)-related risk without need for further analysis including genotyping, polygenic risk scores, or investigation of expressed apo(a) isoform sizes (97).

Interventions to reduce Lp(a) levels

Lp(a) has not received much attention for many years as a lipid fraction without an effective therapeutic agent, meanwhile nicotinic acid and Lp(a)-apheresis were the only treatments available for high Lp(a) with limited use. Table 3 depicts the summary of lipid modifying therapies and their effect on Lp(a) levels.

Effect of conventional LLT on Lp(a)

Conventional lipid-lowering therapies including statins, ezetimibe, and fibrates reduce ASCVD risk without affecting Lp(a) levels. Conversely, nicotinic acid reduces Lp(a) without substantially changing cardiovascular risk.

Statins. Clinical Statin trials denote varied effects on Lp(a) levels (3, 98).Rosuvastatin had no effect on median Lp(a) levels, and shifted the overall distribution of Lp(a) to higher percentiles in the JUPITER trial (98). Moreover, rosuvastatin showed similar cardiovascular benefits in those with higher and lower levels of Lp(a). Similarly, statin therapy did not significantly change Lp(a) levels in a meta-analysis covering 7 placebo-controlled statin trials (n=29,069 patients) (91) and there was a significant relationship between Lp(a) levels and ASCVD risk despite statin therapy. Another meta-analysis enrolling 6 statin trials with overall 5256 patients showed a significant increase of Lp(a) levels ranging from 8.5% to 19.6% in statin groups where the increase was more pronounced with atorvastatin therapy than the other statins. The investigators also showed that incubating HepG2 hepatocytes with atorvastatin increased the expressions of *LPA* mRNA and apo(a) (99). Conversely, a meta-analysis of 39 placebo-controlled trials with various statins covering 24,448 subjects demonstrated a non-significant increase of 0.1% in Lp(a) levels with statin therapy compared to controls with no significant differences among individual statins. Intensities of statin therapies also did not differ regarding Lp(a) lowering effect (100, 101).

Nicotinic acid (Niacin). Nicotinic acid is an essential micronutrient, that has favorable effects on all lipid profile at pharmacologic doses. Nicotinic acid was so far the only known therapeutic agent able to lower Lp(a) levels (3). However, this drug could not find a place as a Lp(a) lowering agent in clinical practice due to low tolerability. Moreover, its effect on Lp(a) was prominent at only very high baseline levels which was in overall less than 30% reduction. A meta-analysis of 14 randomized placebo-controlled trials showed extended-release niacin reduced Lp(a) by a mean of 23% (102). The effect of niacin to lower Lp(a) concentration is likely due to decreased apo(a) production rate (3, 98). This Lp(a) lowering effect was only limited to lower molecular weight apo(a) containing isoforms (103).

Two placebo-controlled trials (AIM-HIGH and HPS2-THRIVE) have evaluated the effect of extended-release niacin (with or without the anti-flushing agent laropiprant) added to background simvastatin treatment on ASCVD events. Neither trial showed cardiovascular efficacy of niacin and HPS2-THRIVE, documented increase of non-cardiovascular adverse events. In AIM-HIGH, Niacin reduced Lp(a) by a placebo-corrected mean of 19.6%, with greater absolute Lp(a) reduction as baseline Lp(a) concentration increased (104). However, there was no interaction of baseline Lp(a) and treatment on cardiac adverse events. In HPS2-THRIVE Lp(a) was reduced with niacin/laropiprant to a similar extent as with niacin in AIM-HIGH (101). In the light of these data denoting no cardiovascular benefit, and high adverse events, niacin is no more recommended for Lp(a) lowering (3, 98). Meanwhile, niacin, is no longer in use as it didn't provide clinical evidence regarding its benefit as a substitute to statins over statins alone (3, 98).

Other agents. The effect of ezetimibe on Lp(a) is not clear (3, 98). A meta-analysis covering 10 trials of ezetimibe showed no effect on Lp(a) levels either with ezetimibe monotherapy or combined with a statin (105). However, ezetimibe monotherapy significantly decreased Lp(a) level by only 7.1% in a meta-analysis of 7 trials, but such a small reduction in Lpa(a) could be ignored to be clinically significant (106). Similarly, bile acid sequestrants have no significant effect on Lp(a) levels (3, 98). Interestingly an inverse relationship between plasma triglycerides and Lp(a) levels has been observed (98). Thus, fibrate therapy may be associated with an increase in Lp(a) in patients with severe hypertriglyceridemia. However, fibrates do not substantially change Lpa(a) therapy (107).

New lipid modulating agents and Lp(a)

PCSK9 inhibitors. Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to LDL-receptor and promotes ingestion of LDL particles into the cell, which results in decreased LDL-C concentrations. The blockage of PCSK9 leads to an increased number of LDL-receptors on the cell surfaces to remove LDLs from circulation. Monoclonal PCSK9 inhibitors along with LDL-C, also decrease Lp(a) levels by 19-27% (108-112). The mechanisms of this decrease remain uncertain, but suggested to include increased receptor-mediated clearance, decreased production of apo(a), and/or decreased Lp(a) particle assembly due to reduced availability of apo-B (3, 98).

Monoclonal PCSK9 inhibitors comprise the only approved drug class that has been shown to reduce both the Lp(a) levels and the

Table 3 | Lp(a) targeting therapeutics, their mechanisms of action, and their effects on Lp(a) levels.

	Mechanism of Action	Effect on Lp(a) level	Effect on ASCVD risk
Conventional Lipid Modifying Agents			
Statins	HMG-CoA reductase inhibition	Results in increase of Lp(a) levels in low molecular weight apo(a) containing isoforms, however resulted in no change in high molecular weight isoforms Possible increase, 0–10%	Reduced 20–30%
Ezetimibe	NPC1L1protein inhibition	Possible reduction, 0–7%	Reduced 6% when added to statin therapy
Bile acid sequestrants (Cholestyramine, Colestipol & Colesevelam)	Decrease reabsorption of bile acids Reduce cholesterol content in hepatocytes	No effect	Reduced 20%
Nicotinic acid (Niacin)	Hormone-sensitive lipase inhibition in adipose tissue	%20-28 only in low molecular weight apo(a) containing Lp(a), high molecular weight containing isoforms are not affected Overall reduction, 20%	Neutral
Fibrates	Minimal, possible increase in the setting of hypertriglyceridemia	Reduced 22% with gemfibrozil monotherapy, non-significant reduction with fenofibrate	Variable
Novel Lipid Modifying Agents			
Bempedoic acid	ACL inhibition	No effect	Under investigation
Alirocumab Evolocumab	Monoclonal PCSK9 inhibition	Reduction, 20–30%	Reduced by 15%
Inclirisan	SiRNA inhibiting the translation of PCSK9	15-26% reduction in standard deviations depending on the dosing regimen	
Lerodalcibep	PCSK9 inhibition	Ongoing Phase 3 studies comparing safety and efficacy with Evolocumab	Unknown yet
CETP inhibitors	Cholesteryl ester transfer protein inhibition	Reduction up to 25%	Favorable anacetrapib neutral dalcetrapib & evacetrapib; unfavorable torcetrapib
Lomitapide	MTP inhibition	15% reduction (in addition to the standart treatment regime in HoFH)	Reduced in HoFH
Evinacumab	Monoclonal antibody targeting ANGPTL3	5.5±4.0 % reduction from the baseline	
Mipomersen	ASO targeting Apo B100 synthesis	Reduction, 20–25%	Not determined
Targeted LPA therapeutics			
Pelacarsen (formerly AKCEA-APO(a)-L_{RX}, TQJ230)	ASO targeting *LPA* mRNA in liver	35-80% reduction depending on the dosing and timing of the regimen	Phase 3 outcomes RCT is ongoing-HORISON
Olpasiran (formerly AMG-890, ARO-LPA)	siRNA to apo(a)	Phase 1-2: reduction, 70–98%	Phase 2 ongoing Phase 3 underway (OCEANS)
SLN360	siRNA to apo(a)	Phase 1: reduction, 46–98% Only patients with Lp(a) ≥ 150 nmol/L is planned to be included in the study. The study is still in Phase 1.	Phase 2 planned

Continue >>>

	Mechanism of Action	Effect on Lp(a) level	Effect on ASCVD risk
Lp(a) Apheresis	Removal of apo-B containing lipoproteins	50-75% reduction, depending on the method, with dextran sulphate immunoadsorption providing the most prominent decrease by 72%	Observational data suggest a substantial clinical benefit
Drugs other than lipid modifying agents			
Aspirin	Reduction of the expression of apo(a)	None to 30% reduction	Mortality reduction of 25% in high-risk patients
HRT	Estrogens reduce the transcription of the *LPA* gene	Almost 20–25% reduction; Decrease is greater with oral *vs* transdermal estrogen. No difference between continuous *vs* cyclic HRT	None

ACL: Adenosine triphosphate-citrate lyase; ANGPTL3, angiopoietin-like protein 3; Apo: Apolipoprotein; ASCVD: Atherosclerotic cardiovascular disease; ASO; Antisense oligonucleotide, FH, familial hypercholesterolemia, HRT: Hormone Replacement Therapy HoFH, homozygous FH; LDL: low-density lipoprotein, LDLR; low-density lipoprotein receptor, MTP; microsomal triglyceride transfer protein; NPC1L1; Niemann-Pick C1-like 1 protein PCSK9; pro-protein convertase subtilisin/ kexin 9. SiRNA; Small interfering RNAs,

risk of cardiovascular events (3). Two cardiovascular outcomes trials which evaluated the effects of PCSK9 monoclonal antibodies, added to statin therapy, resulted in 27% (FOURIER Trial) and 23% (ODYSSEY OUTCOMES Trial) decrease in circulating Lp(a) levels (109, 112). Absolute Lp(a) reductions were directly related to baseline levels. Moreover, the reduction in ASCVD risk with PCSK9 inhibition was observed in patients with elevated Lp(a) levels, and was achieved with only 16-22% reduction of Lp(a) levels in the highest baseline Lp(a) quartile (3, 98, 109, 110, 112). Moreover, the reduced risk of major adverse limb events including acute limb ischemia, major amputation, or urgent limb revascularization for ischemia observed with PCSK9 inhibition was strongly associated with the baseline Lp(a) level but not with LDL-C levels in ODYSSEY OUTCOMES trial. Furthermore, a meta-analysis of the FOURIER and ODYSSEY OUTCOMES trials showed a consistent, favorable effect of PCSK9 inhibition on the incidence of venous thromboembolic events. Interestingly this benefit was evident when the baseline Lp(a) was higher than the median of 37 nmol/L despite the similar reductions in LDL-C with evolocumab in both Lp(a) categories (higher and lower than the median 37 nmol/L) (113).

Inclisiran is a small interfering RNA (SiRNA) reducing PCSK9 synthesis with the potential advantage of twice-yearly dosing (98). Inclisiran provides similar Lp(a) and LDL-C reductions as monoclonal PCSK9 inhibitors. Lp(a) levels were reduced by 25.6% and 18.6%, in the ORION-10 and ORION-11 trials respectively (114). The ongoing ORION-4 trial will address the potential benefit of inclisiran on ASCVD events.

Bempedoic acid. Bempedoic acid is an oral adenosine triphosphate citrate lyase inhibitor decreasing synthesis of cholesterol in the liver, thereby upregulating the LDL-receptors. Bempedoic acid has been shown to safely decrease LDL-C and improve cardiovascular outcomes, however it has no shown definite effect on Lp(a). Similar to statins the phase 2 data of bempedoic acid denotes a non-significant small increase in Lp(a) (115).

Mipomersen. Mipomersen is an antisense-oligonucleotide (ASO) targeting apo-B with a significant LDL-C lowering effect. Weekly injections of mipomersen has been shown to decrease Lp(a) levels by 21% in a study of 14 healthy individuals and by 26% in patients with or without FH in a meta-analysis of 4 trials (116, 117).

CETP inhibitors. Cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl esters from HDL to apo-B containing particles, thereby raising the levels of HDL-C. These agents also lower Lp(a) levels and potent CETP inhibitors (except dalcetrapib) decrease apo-B and LDL-C (98). Torcetrapib and dalcetrapib lead to almost a 10% reduction in Lp(a) levels, while anacetrapib and evacetrapib induce a 25-31% decrease (98).The reduction in Lp(a) with anacetrapib, was documented to be due to reduced apo (a) production (118). Despite substantial lipoprotein changes, only anacetrapib demonstrated a modestly favorable clinical effect. Compared to placebo, anacetrapib significantly induced a 17% decrease in LDL-C levels, 25% in Lp(a) levels, and 9% reduction in the risk of MACE (98, 119). But CETP inhibitors are not approved for therapeutic use.

Targeted LPA therapeutics

Novel ASOs and small interfering RNA (siRNA) molecules, targeting apo(a) production in hepatocytes is underway as Lp(a) lowering therapeutics. These agents are currently investigated for efficacy, safety, and ASCVD outcomes in clinical trials.

Pelecarsen, is an ASO agonist apo(a)-mRNA that is conjugated to N-acetylgalactosamine (GalNAc), which enables specific targeting to hepatocytes. This technology provides enhanced potency, less toxicity, and infrequent dosing (3, 98). Pelecarsen therapy is associated with sustained dose-dependent Lp(a) reductions of 35–80% in patients with Lp(a) ≥60 mg/dL (≥150 nmol/L) and ASCVD (120). In early trials, mean decreases of 80% and 72% were reported with pelacarsen injected 20 mg weekly and 60 mg monthly, respectively, with 98% and 81% of participants attaining Lp(a) levels <125 nmol/L at the end of the study with mild adverse events related to the mild injection-site reactions (98, 120). The ongoing Horizon study (NCT04023552) will address the effect of lowering Lp(a) with pelacarsen on ASCVD outcomes in patients with established cardiovascular disease and elevated Lp(a) (≥70 mg/dL). Another trial on patients with GFR<30 ml/min/1.73m^2 is underway (121). So far, no difference has been reported regarding the efficacy of pelacarsen on Lp(a) isoforms (122).

Oplesiran is a GalNAc-conjugated siRNA with a Lp(a) lowering

effect ranging between 71% and 97% in patients with baseline Lp(a) ≥70 nmol/L to ≤199 nmol/L after the administration of a single-dose (123). Studies denote a favorable safety profile (97). The phase 3 trial investigating cardiovascular outcomes (OCEANS Study) is underway. Another GalNAc-conjugated siRNA (SLN360, Silence Therapeutics) is in early development (124).

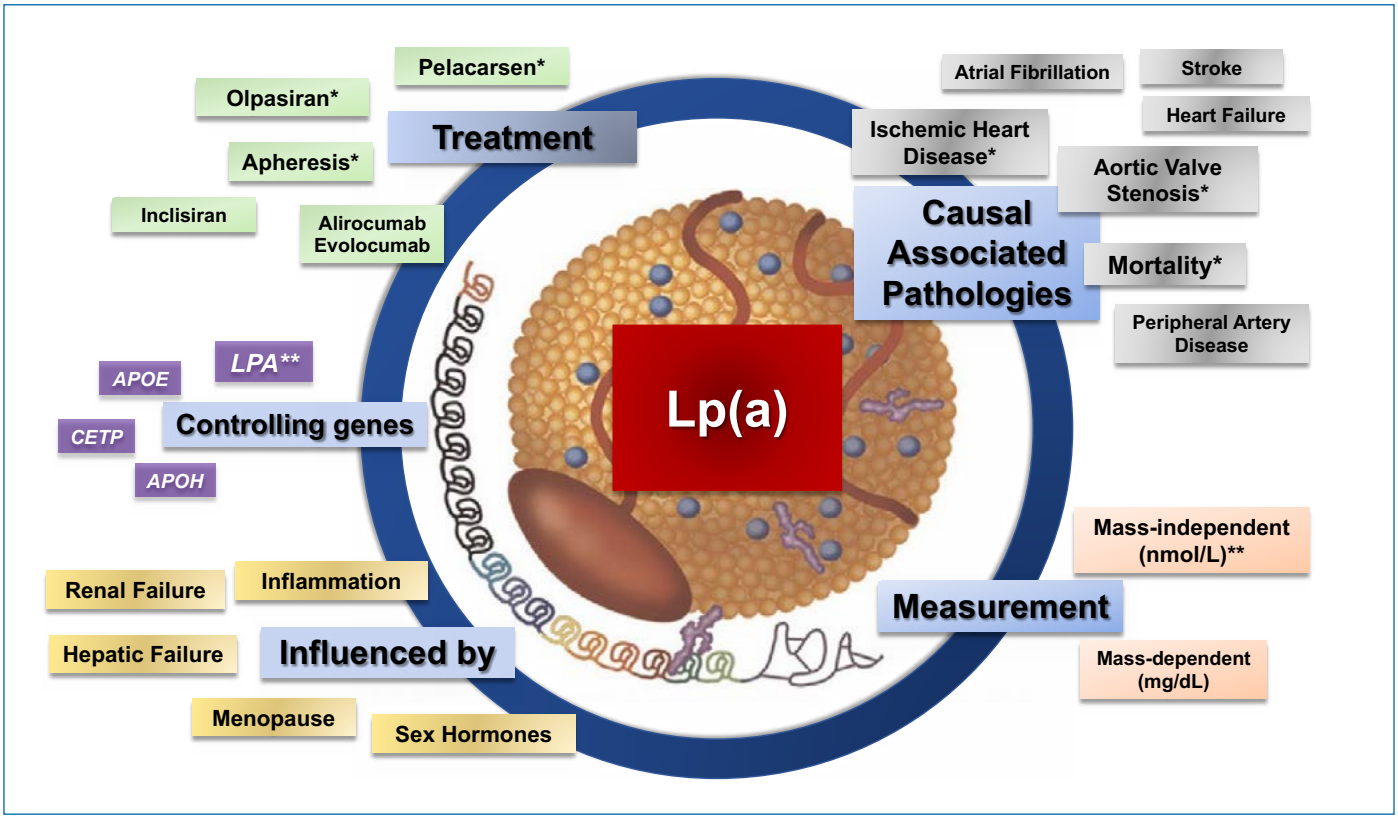
Lp(a) apheresis. Lipoprotein apheresis selectively eliminates apo-B containing particles including Lp(a). An apheresis session may lead to 50-75% acute Lp(a) reduction depending on the method used (125). Due to the lack of effective Lp(a)-lowering agents, in clinical practice Lp(a) apheresis is accepted as the most effective means of Lp(a) lowering therapy. With the special immune-adsorption polyclonal antibody columns being available since 1993, a large amount of experience is now present in some specialized centers. However, the awareness of Lp(a) as an ASCVD risk factor is extremely low, consequently Lp(a) apheresis therapy is still not of widely available. Moreover, clinical benefits of Lp(a) specific apheresis requires more evidence in terms of effectivity in patients with isolated high Lp(a) (125), although it's known" known that Lp(a) specific apheresis can result in coronary atherosclerosis and carotid intima-media thickness regression if practiced consecutively for 18 months, provided that the patients reach their LDL-C goals (126). Lp(a) apheresis also attenuates refractory angina and provides improvement in atheromas, exercise capacity, and myocardial perfusion in patients with extremely high Lp(a) levels (>500 mg/dL) after 3 months of weekly apheresis (127, 128). Given the invasive nature of the procedure, large randomized controlled trials are lacking, but cumulative, consistent observational and cohort data denote an important role of Lp(a) apheresis in the secondary prevention of those with high Lp(a) (125-128).

Drugs other than lipid-modifying agents

Aspirin. Aspirin was shown to reduce the expression of apo(a) in cultured liver cells (129). An observational study of prospective use of aspirin (81 mg/day) in 70 subjects with a history of ASCVD showed a 15% decrease in Lp(a) levels from baseline in those with Lp(a) levels ≥ 30 mg/dL (130). However, in a placebo-controlled study of 56 patients with chronic ASCVD, aspirin showed no effect on Lp(a) levels over 3 months of therapy, irrespective of the baseline concentrations (98,130). Interestingly, Women's Health Study, also showed that aspirin reduced the risk of MACE in minor allele carriers of rs3798220 in the *LPA* gene, but not in non-carriers, with a significant interaction of carrier status and treatment (131). Of note, rs3798220 in the *LPA* gene is associated with high circulating Lp(a) levels. These scarce data may denote a possible benefit of aspirin on the prevention of MACE associated with Lp(a) levels. But prospective testing of this hypothesis is warranted.

Hormones. Anabolic steroids and estrogen treatment may decrease Lp(a), but the clinical benefit of this effect is uncertain. Though unblinded or uncontrolled studies denote an association between testosterone treatment and Lp(a) reduction, RCTs did not confirm such an association (3, 98, 132).

Estrogen and its analogues reduce the transcription of the *LPA* gene. Women already on hormone replacement therapy (HRT) have modestly lower Lp(a) levels compared to those not receiving HRT (9.4 mg/dL vs 11.6 mg/dL, respectively) in the baseline evaluation of Women's Health Study (133). Meta-analysis also revealed similar



Key messages | A summary of Lp(a) with regard to Influencing factors, measurement methods, pathologies, and potential treatments.

results that HRT in post-menopausal women is associated with a 25% decrease in Lp(a) levels (134). In the Heart and Estrogen/progestin Replacement Study (HERS), though Lp(a) levels were reduced there was no overall benefit of HRT with regard to MACE in post-menopausal women with IHD (135).

Thyroid hormone analogues such as eprotirome may result in a significant dose-dependent reduction of Lp(a) up to 55% if combined with statins, however 6-month treatment with levothyroxine may also lower Lp(a) to some extent, in patients with primary hypothyroidism (3, 18, 98). Liver selective thyromimetics are being focused for treatment of nonalcoholic steatohepatitis. These agents also have beneficial lipid effects covering Lp(a), without adverse extrahepatic effects.

Conclusion

We are increasingly recognizing the importance of Lp(a) and cardiovascular pathologies, however we neither have a standardized measurement method nor an appropriate agent to intervene with this old threat that we have recognized 60 years ago (136). It is imperative to extend our knowledge about Lp(a), standardize its measurement, and make sure that it finds its well-deserved place in the daily clinical practice to prevent further ASCVD events.

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