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POSITION STATEMENT

Consensus document on Lipoprotein(a) from the Italian Society for the Study of Atherosclerosis (SISA)

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Small interfering RNA

Abstract *Aims:* In view of the consolidating evidence on the causal role of Lp(a) in cardiovascular disease, the Italian Society for the Study of Atherosclerosis (SISA) has assembled a consensus on Lp(a) genetics and epidemiology, together with recommendations for its measurement and current and emerging therapeutic approaches to reduce its plasma levels. Data on the Italian population are also provided.
Data synthesis: Lp(a) is constituted by one apo(a) molecule and a lipoprotein closely resembling to a low-density lipoprotein (LDL). Its similarity with an LDL, together with its ability to carry oxidized phospholipids are considered the two main features making Lp(a) harmful for cardiovascular health. Plasma Lp(a) concentrations vary over about 1000 folds in humans and are genetically determined, thus they are quite stable in any individual. Mendelian Randomization studies have suggested a causal role of Lp(a) in atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis and observational studies indicate a linear direct correlation between cardiovascular disease and Lp(a) plasma levels. Lp(a) measurement is strongly recommended once in a patient's lifetime, particularly in FH subjects, but also as part of the initial lipid screening to assess cardiovascular risk. The apo(a) size polymorphism represents a challenge for Lp(a) measurement in plasma, but new strategies are overcoming these difficulties. A reduction of Lp(a) levels can be currently attained only by plasma apheresis and, moderately, with PCSK9 inhibitor treatment.
Conclusions: Awaiting the approval of selective Lp(a)-lowering drugs, an intensive management

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of the other risk factors for individuals with elevated Lp(a) levels is strongly recommended.

1. Lipoprotein(a) structure and metabolism

Lp(a) is a lipoprotein particle with a unique feature consisting in the apolipoprotein(a) (apo(a)), a glycoprotein exclusively synthesized by the hepatocytes [1], characterized by loop-like structures named kringles. Lp(a) has a curious evolutionary distribution, being found only in the plasma of the hedgehog and Old World monkeys, apes and humans [2]. The human gene encoding for apo(a), located in chromosome 6, possibly evolved millions of years ago from the plasminogen gene [3]. Kringle IV, kringle V and the protease domain of plasminogen were retained, this latter with an inactive sequence. Kringle IV, present in plasminogen in a single copy, expanded and differentiated in the apo(a) gene in ten subtypes (1–10) (Fig. 1). Of those, subtype 2 further expanded in a variable number of copies, from 1 to over 40, and that explains the wide size polymorphism of the encoded apo(a) in humans, which spans from 300 to 800 kDa [4].

Each Lp(a) particle is constituted by one apo(a) molecule and a lipoprotein closely resembling to a low-density lipoprotein (LDL). These two components are joined together by non-covalent bindings and by a disulfide bond between the apoB100 of the LDL-like particle and the apo(a) molecule (Fig. 1) [5].

How Lp(a) is generated is still an open question. Lp(a) does not seem to be, unlike LDL, a metabolic product of very low-density lipoprotein (VLDL) particles [6]. In vivo and ex vivo studies suggest that Lp(a) can originate from the extracellular assembly of apo(a) with the LDL-like particle [7,8], whereas in vitro experiments have shown that Lp(a) formation may start intracellularly, within the hepatocytes, with the formation of non-covalent bindings between apoB100 and apo(a) [9]. Kinetic studies also provided conflicting results [10,11].

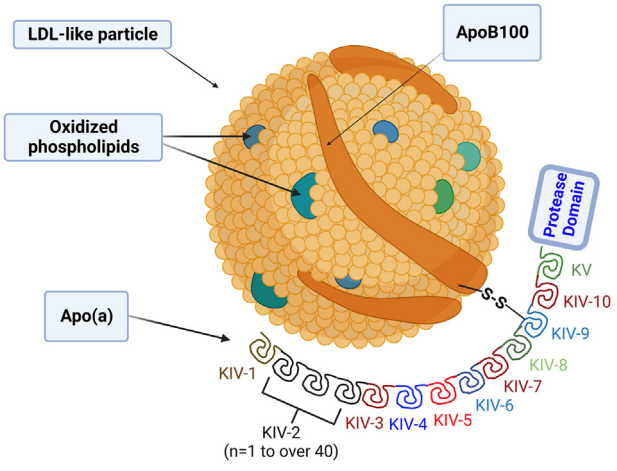

Figure 1 Schematic representation of the lipoprotein(a). The black line indicates the disulfid bond between apo(a) and apoB100.

The clearance of the Lp(a) particle occurs mainly in the liver [12] and in a small proportion in the kidney and in the vessel wall [13]. Several receptors have been implied in Lp(a) catabolism. Those include lectins, plasminogen receptors, the toll like receptor 2, which emerged from a genome-wide meta-analysis as a regulator of Lp(a) plasma levels [14] and SR-B1, which mediates the selective uptake of cholesteryl esters. Within the LDL receptor family, the VLDL receptor, as well as the LDL receptor related protein (LRP)1 and LRP8, may play a role in Lp(a) uptake and degradation. The involvement of the LDL receptor in Lp(a) catabolism has been the object of numerous studies, but the relevance of this pathway in Lp(a) turnover is still unclear [15].

2. Distribution and determinants of Lp(a) plasma levels

Plasma Lp(a) levels vary over about 1000 folds, ranging from 0.1 to over 100 mg/dL. Populations of Caucasian ancestry show a skewed frequency distribution of Lp(a) plasma concentrations, with most of the subjects presenting very low levels. That is also evident in Italy, both in the Northern [16,17] and the Southern area [18] of the country (Fig. 2). A similar distribution is observed in populations of Arabian and Asian ancestry, while Blacks differ, presenting a more homogeneous distribution of values [19] and a higher number of subjects exhibiting high Lp(a) levels.

Plasma Lp(a) concentrations are highly heritable and about 90% of Lp(a) level variation is determined by sequences linked to the apo(a) gene. Up to 70% of the interindividual variability in Lp(a) levels is explained by the number of Kringle IV subtype 2 repeats in the apo(a) gene [20]. Individuals carrying small apo(a) isoforms generally have higher Lp(a) plasma concentrations than subjects with large isoforms, and an inverse correlation between the size of the apo(a) isoform and Lp(a) levels has been extensively reported [21]. In addition to the KIV subtype 2 polymorphism, single-nucleotide polymorphisms (SNPs) contribute to the genetic control of Lp(a) levels [19]. The genetic analysis of Lp(a) levels among populations showed that the different distributions across ancestries are mostly related to the ethnic genetic background, as demonstrated in the Dallas Heart Study subjects by the identification of at least six SNPs in the apo(a) locus (rs3798220, rs10455872, rs9457951, rs1801693, rs41272110, G+1/inKIV-8A) which were correlated with different Lp(a) levels and had different frequency in Whites, Blacks and Hispanics [22,23]. These

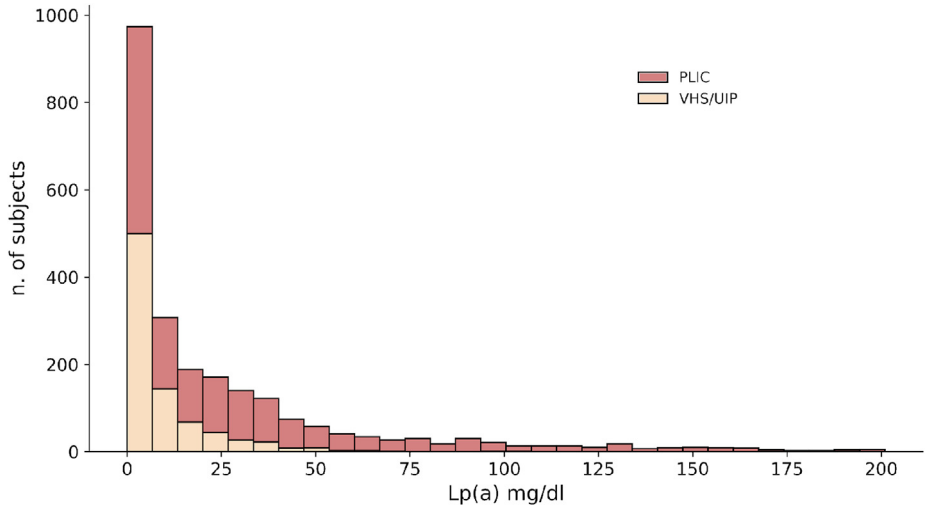

Figure 2 Distribution of plasma Lp(a) concentration in two Italian populations. Lp(a) plasma levels were measured in 1534 participants of the Progressione delle Lesioni Intimali Carotidee (PLIC) Study [136] representative of the general population residing in the northern area of Milan and in a pooled representation (n = 842) of two Sicilian populations, from the Ventimiglia Heart Study (VHS) [18] and the Ustica Island Project (UIP) [137].

polymorphisms thus contribute to the genetic control of Lp(a) levels together with the number of Kringle IV repeats, whose distribution is also different in Blacks compared with other populations [23,24].

Among possible genetic determinants of Lp(a) levels besides the apo(a) locus, apoE polymorphisms have been considered, but results have not been consistent, and a clear relationship has been questioned [25].

Non genetic determinants have little impact on Lp(a) levels. It has been suggested that Lp(a) levels increase with age, but results have not been consistent, showing some degree of association only in a few studies [26]. Similar inconsistencies limited the claim of higher Lp(a) levels in females compared to males, due to the prevalent effect of confounding variables [26]. Dietary habits able to increase LDL cholesterol as a high saturated/polyunsaturated dietary fatty acids ratio minimally affect Lp(a) levels [27], and no significant differences were found between fed/fasting status [28]. Due to presence of an element responsive to interleukin 6 in the LPA gene promoter, a clear effect of proinflammatory conditions on Lp(a) levels has been demonstrated [29]. Modification in the hormonal setting, as in pregnancy or menopause, or occurrence of some diseases as diabetes mellitus and kidney diseases are also able to increase Lp(a) levels [26,30], while liver damage decreases Lp(a) production together with other apoB100-containing lipoproteins [26]. Thyroid function is known to modulate lipid levels, mainly LDL cholesterol, but a marginal effect on Lp(a) values has been described [31].

3. Pathophysiological role of Lp(a)

Plasma Lp(a) levels are extremely variable, and negligible or absent concentrations, today, do not seem to constitute a risk for human health. Several observations indicate that Lp(a) could have represented an evolutionary advantage for its contribution to accelerated would healing and tissue repair [32]. Millions of years ago, with very different dietary habits from the modern era, primates were possibly characterized by very low circulating LDL, and Lp(a) could have been a relevant source of cholesterol, important for cell regeneration. Additionally, in vitro studies have indicated that Lp(a) may exert pro-thrombotic activity [33] and through the ability of apo(a) to inhibit plasminogen activation [34] slow clot lysis, allowing its growth factor properties to favor tissue repair. These features, possibly advantageous during evolution, are the same which make this lipoprotein harmful for cardiovascular disease today.

Lp(a) contributes to cardiovascular risk by several mechanisms. Like an LDL particle, it can enter the vessel wall and become oxidized, thus stimulating inflammatory cell recruitment and uptake by monocyte/macrophages [35]. Lp(a) is the lipoprotein with the highest content of oxidized phospholipids (oxPL) (Fig. 1) [36], which are present both in the lipid phase and covalently bound to the protein moiety of Lp(a) [37]. OxPL are proinflammatory molecules and are believed to importantly contribute to the proatherogenic properties of Lp(a). Specifically, they can enhance the secretion of inflammatory cytokines and the expression of adhesion molecules in endothelial cells, promote smooth muscle cell proliferation and monocyte/macrophage activation, and induce valve cell mineralization [38].

The prothrombotic and antifibrinolytic properties of Lp(a) and apo(a), well demonstrated in vitro and in animal models, do not seem to represent a risk for non-atherosclerotic thrombotic disease in the clinic, but they could contribute to the vulnerability of atherosclerotic plaques [39].

4. Lp(a) as a causal factor for ASCVD and aortic valve stenosis

Plasma Lp(a) concentrations are almost exclusively determined by sequences linked to the apo(a) gene; thus,

genetic studies, and more specifically Mendelian Randomization (MR), appear to be the ideal approach to assess causality between Lp(a) levels and atherosclerotic cardiovascular disease (ASCVD).

The first genetic study, without being still named MR, evaluating the causal association between Lp(a) and ASCVD risk, was performed in patients with heterozygous familial hypercholesterolemia [40]. In this case-control study, the apo(a) allele LpS2, which was associated with higher plasma Lp(a) concentrations, had higher frequency in patients with coronary heart disease (CHD) and conversely, the allele LpS4, associated with lower plasma Lp(a) concentrations, was more frequent in subjects without CHD [40]. Similar conclusions were reported in additional genetic multi-ethnic case-control studies [41,42]. Further relevant data supporting the causative association between Lp(a) and ASCVD risk came from subsequent larger genetic studies. In a case-control study including 3100 CHD patients genotyped for approximately 49,000 genetic variants, the LPA locus showed the strongest association with ASCVD risk. Specifically, two LPA SNPs (intronic rs10455872 and missense rs3798220) were identified as positive predictors of ASCVD risk. Subjects carrying these SNPs had higher plasma Lp(a) levels and smaller isoform sizes [43]. In the Copenhagen study, LPA genotypes associated with higher Lp(a) concentrations were associated with higher cardiovascular and total mortality, and CHD events as well [44,45]. Conversely, in the PROCARDIS study on over 4000 coronary artery disease (CAD) cases and a similar number of controls, subjects carrying genetic variants associated with lower Lp(a) concentrations had a significantly lower CAD risk [46]. Confirmation of causality of the association between Lp(a) and ASCVD risk came from data on genetically predicted Lp(a) values within the UK Biobank study [20] and other MR studies. A large meta-analysis of GWAS (185,000 CAD cases and controls recruited and 9.4 million allele variants examined) further supported the strong link between apo(a) genotype and ASCVD [47].

Despite the link between plasma Lp(a) concentration and risk of stroke is not fully consistent in observational studies [48,49], a 13% lower risk of stroke was found in a MR study for 1-SD genetically lowered Lp(a) levels [50]. However, either sex or race disparities have been reported in several studies (e.g., Cardiovascular Health Study, ARIC study, MESA study, REGARDS study), possibly due to different patients' characteristics, but also to heterogeneity of ischemic strokes analyzed. In this latter regard, the large Multiancestry Genome-Wide Association Study of Stroke consortium [51] examining predictors of ischemic stroke and its subtypes, concluded that genetically predicted 1-SD log-transformed increase in Lp(a) levels was associated with a significantly increased risk of large artery stroke and a reduced risk of small vessel stroke, further confirming the relevance of ischemic stroke subtypes and heterogeneity as a major confounder in the search for their independent predictors.

Regarding the association between Lp(a) and peripheral artery disease (PAD), three independent populations (i.e., CAVASIC, KORA F3, KORA F4 studies) reported significant associations between plasma Lp(a) concentrations, low molecular weight apo(a) phenotypes, and rs10455872 with PAD [52]. Thus, using a MR approach, a causal link between Lp(a) and peripheral localizations of the atherosclerotic disease may be also suggested.

The rs10455872 genetic variant in LPA is associated with higher Lp(a) levels. Genetic studies have also explored the influence of this genetic variant on aortic valvular calcium and stenosis. In Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, rs10455872 was found to be a susceptibility SNP for aortic valvular calcium [53]. Importantly, the same association was replicated in the Copenhagen City Heart Study and the Malmö Diet and Cancer Study [54,55]. The same LPA genetic variant was prospectively associated with an increased risk of aortic valve stenosis in the 17,553 participants of the (EPIC)-Norfolk study [56].

5. Lp(a) levels and cardiovascular risk

Along with several experimental data and MR analyses supporting the causative role of Lp(a) in ASCVD, additional strong evidence for such an association derives from observational studies, which attempted to estimate the association between plasma Lp(a) levels and increased cardiovascular risk. Studies up to the 1990s provided inconsistent data, possibly in relation to analytical limits and lack of cut-off values standardization [57,58]. In more recent years, however, larger and validated studies provided more relevant data. In 2008, the Copenhagen City Heart Study showed a progressive increase in the risk of myocardial infarction (MI) with increasing Lp(a) concentrations in the absence of a threshold effect. An increased MI risk of 3–4 folds was calculated for Lp(a) levels $\geq$120 mg/dL vs $<$ 5 mg/dL [59]. In 2009, an independent and modest increased risk of CHD (+13%) and ischemic stroke (+10%) was documented for 3.5 higher usual Lp(a) concentrations in a large meta-analysis of the Emerging Risk Factors Collaboration, with no particular racial difference [60]. In the large cohorts of the Copenhagen City Heart Study, Copenhagen General Population Study (CGPS), and Copenhagen Ischemic Heart Disease Study, a 2-fold increase in Lp(a) level was associated with a 20% increase in the risk of MI [61]. Recently, Langsted et al. [62] reported an increased risk of stroke for elevated Lp(a) concentrations and corresponding LPA genotypes in the general Copenhagen population, whereas a similar trend, but no significant association was found in the Copenhagen City Heart Study. From the analysis of the first cohort, it would appear that a concentration higher than 50 mg/dL of genetically determined Lp(a) is associated with an increased risk of stroke of 20–27%.

In a very large study (over 100,000 individuals) based on 4 LPA SNPs strongly associated with low plasma concentrations of Lp(a), Emdin et al. reported that a genetic decrease of 28 mg/dL was associated with a 29% decrease in the risk of CHD, but also a decreased risk of arterial

disease peripheral, aortic valve stenosis, heart failure and stroke [50]. Data on aortic valve stenosis are of particular relevance. This chronic disease represents an atherogenic equivalent, but, above all, a condition progressing independently of medical treatments. Results from observational or genetic epidemiological studies, including the EPIC-Norfolk Study, have shown an increased risk of this condition both for high Lp(a) concentrations and the presence of specific genetic variants [54,56,63,64].

Other evidence is also available for the causal association between high levels of Lp(a) with either peripheral atherosclerosis or the risk of venous thromboembolic disease (VTE). Kamstrup et al. reported that genetically determined doubling of Lp(a) levels was associated with a 12–16% increase in the risk of coronary, carotid and femoral atherosclerosis and Helgadottir et al. an increased risk of PAD and abdominal aortic aneurysm in carriers of LPA variants associated with higher Lp(a) levels [65,66]. Instead, despite the prothrombotic effect of Lp(a), epidemiological studies have not been able to provide evidence of causal associations of Lp(a) with risk of VTE [65–67]. This latter conclusion has been recently supported by a recent EAS consensus statement [68].

In a prospective study in 79 patients with coronary artery disease and at least one coronary stenosis ≥50%, Terres et al. found Lp(a) to be a predictor for rapid angiographic progression of coronary artery disease [69]. Also, Tamura et al. demonstrated that serum Lp(a) concentrations are closely related to the progression of coronary artery disease without new myocardial infarction in a two-years follow-up [70]. In an angiographic cohort study, patients with higher Lp(a) levels (≥30 mg/dL) exhibited a higher prevalence of lipid-rich plaques at the site of the culprit stenosis, thus identifying a subset of patients with features of high-risk coronary atherosclerosis [71]. After percutaneous transluminal coronary angioplasty, Lp(a) was also associated with restenosis which was prevented by reducing of Lp(a) levels with low-density lipoprotein apheresis [72,73].

Analyses from clinical trials have also proposed that elevated plasma Lp(a) levels may also function as a marker for residual cardiovascular risk in those patients with established cardiovascular disease receiving adequate cholesterol-lowering therapy. This conclusion has emerged from different trials such as the AIM-HIGH, LIPID, ACCELERATE, FOURIER, ODYSSEY and additional trials [74–79].

There is evidence showing that inclusion of Lp(a) levels as a continuous variable in regression analyses improves only slightly ASCVD risk prediction over traditional cardiovascular risk factors in unselected populations. This conclusion emerged from the Women Health Study and was confirmed by additional studies and meta-analytical data; however, if LPA genotypes or specific cut-off levels are taken into account, Lp(a)-related risk prediction substantially improves [80–83]. Thus, for instance, the top quintile of Lp(a) (≥47 mg/dL) in the Copenhagen City Heart Study resulted in a 100% correct reclassification of those patients experiencing a major acute coronary event over 10 years [81].

Finally, among risk factors for cardiovascular disease, the data on the relationship between Lp(a) and diabetic complications are inconsistent, although much of the evidence suggests that high or very high Lp(a) levels are associated with a greater risk of microangiopathic and, in particular, macroangiopathic complications [84–88], independently of other cardiovascular risk factors. On the other hand, of interest and quite intriguing are the epidemiological data showing a consistent, inverse, nonlinear association between Lp(a) levels and risk of diabetes, in particular type 2 diabetes, with a significantly higher risk particularly for very low Lp(a) levels (i.e., <1–7 mg/dL) [84,89–91]. The presence of an association does not imply a causal link, and MR studies, taken as a whole, do not seem to indicate a cause-effect relationship [84]. In the absence of a clear evidence supporting the association between low Lp(a) levels and increased risk of type 2 diabetes, this observation might be explained by the interaction of Lp(a) with other risk factors for diabetes and/or by the possible effects that insulin/insulin resistance may have on Lp(a) concentrations [92–94].

6. Lp(a) in familial hypercholesterolemia

Familial hypercholesterolemia (FH) is an autosomal codominant disorder associated with elevated LDL-cholesterol and the early onset of atherosclerotic cardiovascular disease (ASCVD). Although FH and elevated Lp(a) are both inherited disorders associated with an increased risk of ASCVD, they have distinct genetic bases, and elevated Lp(a) has been shown to be an important predictor of ASCVD in FH [95].

In a Norwegian cohort of genetically determined FH, independently of LDL-cholesterol levels and other risk factors, extremely high Lp(a) levels [≥90 mg/dL, approximately ≥200 nmol/L] emerged as an important additional risk factor, capable of doubling the prevalence of coronary heart disease compared to Lp(a) < 90 mg/dL [96]. Moreover, the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) Risk Equation, which includes the measurement of Lp(a) levels, has been shown to predict ASCVD events in patients with FH with significantly greater accuracy than other conventional cardiovascular disease risk equations [97] and identified FH with normal life expectancy in young females with a defective LDL-receptor mutation, high levels of plasma HDL-C, absence of hypertension and low Lp(a) levels [98].

Furthermore, elevated Lp(a) levels are also associated with calcified aortic valve stenosis [99,100] and that condition can worsen the valve disease observed in FH.

Nevertheless, there is widespread lack of awareness of the conjoint role of FH and Lp(a) in the acceleration of ASCVD, and most cases of elevated Lp(a) in the community remain undiagnosed. Cascade screening, that is the screening of close family members of an index case, is a cost-effective approach for identifying new cases of FH and elevated Lp(a) [101], particularly when the proband has both FH and elevated Lp(a) [102].

7. Plasma Lp(a) measurement: a critical issue

The quantification of Lp(a) plasma levels necessarily goes through the measurement of apo(a), and the size polymorphism of this glycoprotein has always made Lp(a) measurement very challenging. Lp(a) is generally quantified by immunoturbidimetric and nephelometric assays, which use polyclonal antibodies recognizing different epitopes of apo(a). Those include sequences repeated in a variable number, and therefore Lp(a) levels can be potentially underestimated or overestimated as a function of the presence of small or large isoforms, respectively. Additionally, some of the available assays provide Lp(a) concentration as mg/dL, indicating the mass of the differently sized Lp(a) particles, while others as nmol/L, referring to the actual number of particles. This latter unit of measurement is considered the gold-standard unit, even though a conversion factor of 2–2.5 is accepted to approximately turn mg/dL into nmol/L, at least for clinical use [103]. Considering all these issues, a comparability among different tests is difficult. Indeed, a recent analysis of five-point calibrator assays testified significant inter-laboratory and inter-assay variations, only partially explained by apo(a) size polymorphism [104].

Notwithstanding, large epidemiological studies confirmed a linear positive correlation between Lp(a) plasma levels and atherosclerotic CVD risk, by using these same techniques of measurement, which therefore appear suitable at least for a first-stage, reliable risk assessment in clinical practice. Joining a consensus regarding Lp(a) measurement would however represent a valuable endeavor of immediate interest to both epidemiologists and clinicians to optimize cardiovascular risk stratification. Indeed, some technical progresses are in development. To overcome the abovementioned criticisms on the use of polyclonal antibodies, the ideal strategy would be to harness an antibody for a unique non-repetitive epitope in apo(a), recognizing each Lp(a) particle once, and reporting levels as nmol/L. After several years and attempts, an immunoassay has been developed by Marcovina et al. [105], which uses a monoclonal antibody directed against a single antigenic site, present on kringle IV subtype 9. Finally, a standardization of mass spectrometry techniques for the measurement of apo(a) and other apolipoproteins is ongoing [106]. This strategy will be extremely valuable for the validation of existing and developing immunoassays.

8. Lp(a) lowering therapies

Epidemiological and genetic studies support the role of Lp(a) as contributor to ASCVD, therefore Lp(a) has to be considered an important therapeutic target. So far, there are no drugs approved to selectively reduce Lp(a) levels.

Lp(a) plasma concentrations can be effectively reduced by lipoprotein apheresis (LA) [107]. The most frequently used LA systems share the specific absorption of apoB, constitutive of VLDL, LDL and Lp(a), and the removal efficiency for LDL as for Lp(a) is up to 80%. There is a general agreement on the reduction of major adverse cardiovascular events by LA. In a 5-year prospective multicenter study including 170 patients with Lp(a)-hyperlipidemia and progressive cardiovascular disease, a significant decline of mean annual cardiovascular event rate after regular LA treatment was observed [108] (Fig. 3A). The Italian data of the G. I.L.A. pilot study [109] confirmed the long-term efficacy and positive impact of LA on morbidity in patients with high Lp(a) levels and chronic ischemic heart disease on maximally tolerated lipid-lowering therapy (Fig. 3B).

Beyond apheresis, niacin treatment has been shown to decrease Lp(a) levels by 20–40% [110], but because of several side effects associated to its administration [111], its use is currently not advised as Lp(a)-lowering therapy. Ezetimibe treatment is associated to modest Lp(a) reductions (about 7%) [112]. Bempedoic acid, a novel drug that inhibits cholesterol biosynthesis, does not seem to significantly affect Lp(a) levels [113]. Some studies have suggested that statins may increase Lp(a) plasma

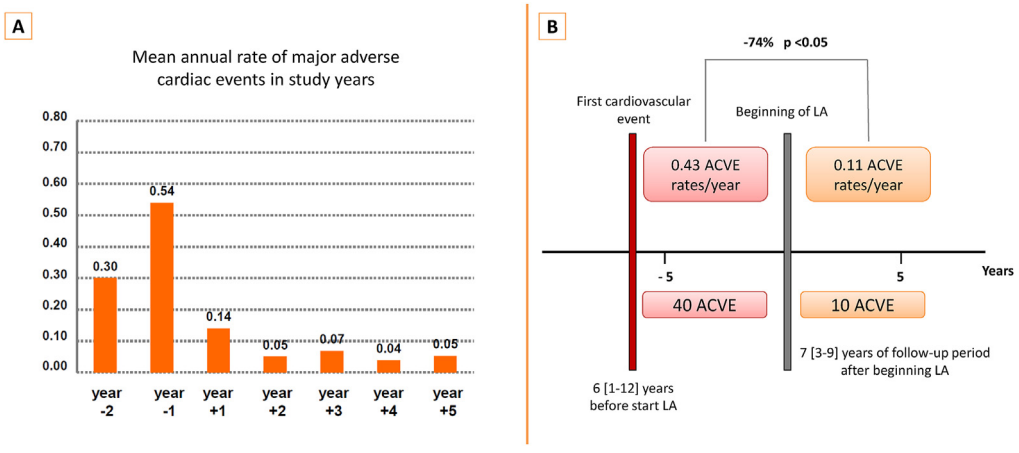

Figure 3 Effect of lipoprotein apheresis (LA) on major cardiovascular events. A) Clinical course of patients with lipoprotein(a)-hyperlipoproteinemia and progressive cardiovascular disease (Pro(a)LiFe-Study [108]); B) adverse cardiovascular events (ACVE) rate/year in pre-LA versus in-LA (GILA pilot study [109]).

Table 1 Effect on Lp(a) plasma levels by currently available hypolipidemic drugs.

Hypolipidemic therapy	Effect on Lp(a) levels	Evidence
Lipoprotein apheresis	70% acute reduction 35% time-averaged reduction	Longitudinal prospective trials [107]
Nicotinic acid	20–40% reduction	Randomized control trials [110]
Ezetimibe	7% reduction	Systematic review and meta-analysis of randomized controlled trials [112]
Statins	no variation	Large meta-analysis [116]
Bempedoic acid	no variation	Meta-analysis of randomized controlled trials [113]
PCSK9 inhibitors	15–30% reduction	Meta-analysis of randomized-controlled trials and phase III double-blind trial [117,118]
Lomitapide	17% reduction	Phase 2 and 3 randomized, placebo-controlled trials [120]

concentrations [114], possibly because the up-regulation of the LDL-receptor consequent to the reduced cholesterol biosynthesis, by favoring the catabolism of high affinity LDL, could increase the plasma levels of lower affinity Lp(a) particles [115]. However, a recent meta-analysis on a very large number of patients showed a lack of significant changes by statins on Lp(a) plasma concentrations [116]. PCSK9 inhibitors, instead, significantly decrease Lp(a) levels: both monoclonal antibodies (alirocumab and evolocumab) and the small interfering RNA molecule inclisiran, have been shown to reduce Lp(a) by 15–30%, mostly by increasing its fractional catabolic rate [117–119]. Lomitapide, approved for homozygous familial hypercholesterolemia, by inhibiting the microsomal triglycerides transfer protein, reduces Lp(a) levels by about 17% [120] (Table 1).

Two strategies of intervention for a selective modulation of Lp(a) levels are currently under development: antisense oligonucleotides (ASOs) and small interfering RNA (siRNA). ASOs are short single-stranded oligonucleotides which directly target complementary mRNA sequences causing their degradation by RNase H, whereas siRNAs are non-coding double-stranded RNA molecules which promote the degradation of a target mRNA via the formation of the RNA-Induced Silencing Complex (Fig. 4).

IONIS-APO(a)-LRX (more recently referred to as pelacarsen), is an N-acetyl-galactosamine- conjugated ASO targeting hepatic apo(a) mRNA. In healthy subjects with Lp(a) ≥75 nmol/L (~30 mg/dL) pelacarsen led to a dose-dependent reduction of Lp(a) levels, with mean reductions ranging from 66% with a 10-mg multidose regimen, to 92% with a 40-mg multidose regimen [121]. In a phase 2 randomized study of individuals with elevated Lp(a) levels and ASCVD at baseline, pelacarsen lowered Lp(a) levels up to 80% [122]. The HORIZON trial, a phase 3 randomized controlled ASCVD endpoint study, is currently being carried out to examine if lowering Lp(a) levels by the ASO will reduce the risk of CVD.

Olpasiran (Amgen) is a siRNA able to selectively target the LPA transcript. Like pelacarsen, it is conjugated with N-acetylgalactosamine to drive its uptake by the hepatocytes. In a phase I trial [123], olpasiran was administered as a

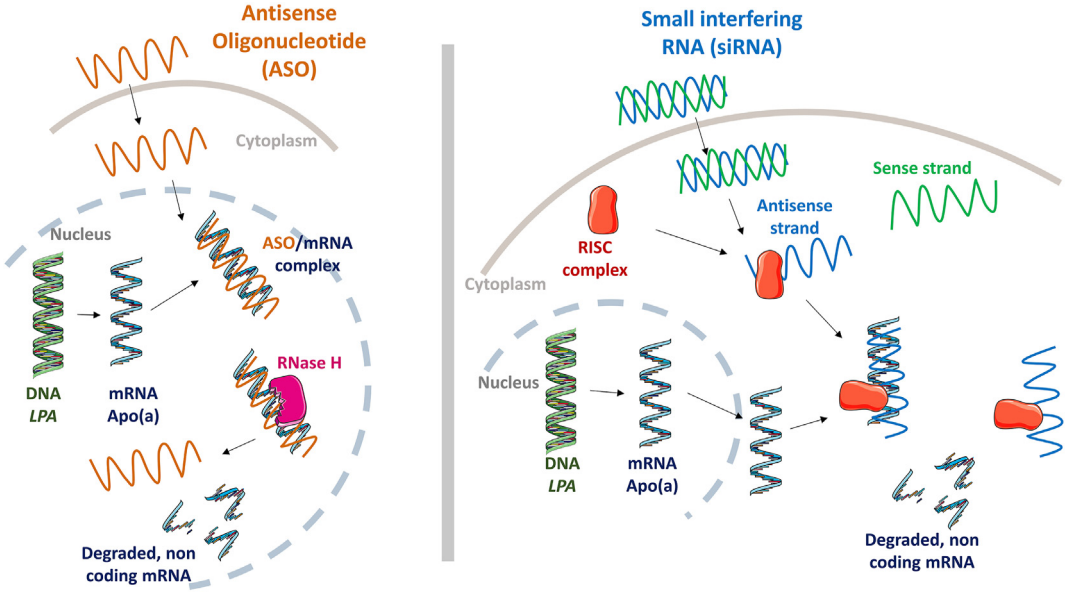

Figure 4 Mechanism of action of the two therapeutic strategies under development (antisense oligonucleotides and small interfering RNA) to selectively lower plasma Lp(a) levels.

single subcutaneous dose of 3, 9, 30, 75 or 225 mg to subjects with Lp(a) ranging between 70 and 199 nmol/L and to a subgroup of subjects with Lp(a) ≥200 nmol/L. The treatment was well tolerated at each dose administered. Lp(a) reduction occurred in a dose-response manner, with a maximum percent reduction ranging from −71 to −97% between days 43 and 71 after treatment. Lp(a) levels then gradually increased but remained well below baseline up to 225 days. A phase 2 study, the Olpasiran trials of Cardiovascular Events And lipoproteiN(a) reduction-DOSE finding study (OCEAN(a)-DOSE) is ongoing [124]. Subjects with established ASCVD and Lp(a) > 150 nmol/L have been enrolled to receive subcutaneous injections of placebo or 10, 75, 225 mg olpasiran for four times every 12 weeks. The primary endpoint of the study is the percent change in Lp(a) levels from baseline at week 36.

Another siRNA targeting the LPA transcript, named SLN360 (Silence Therapeutics) is currently under development. The results from the phase I trial showed that SLN360 was well tolerated and Lp(a) reduction was up to 98% [125].

9. How to manage Lp(a) in the clinic

In the past years, Lp(a) values higher than 50 mg/dL - representing the 80th percentile of the Caucasian population - have been proposed as a unique threshold above which ASCVD risk increases [126,127]. However, as discussed above, observational studies showed a linear increase in ASCVD risk with increasing Lp(a) concentrations, in the absence of a threshold effect [68]. Interestingly, it has been estimated that Lp(a) levels increase the total ASCVD risk of the same relative amount irrespective of the baseline absolute risk. For example, Lp(a) levels of 100 mg/dL approximately double ASCVD risk, and therefore increase it to 40% in subjects with a 20% baseline risk and shift it from 5 to 10% in case of a lower baseline risk [68]. For this reason, an intensive risk factor management is particularly recommended for those subjects at high baseline risk with elevated Lp(a) levels.

Based on all these considerations, a pragmatic approach to be applied in the clinical practice is suggested by the 2022 EAS consensus [68]: Lp(a) levels below 30 mg/dL (75 nmol/L) should not be considered of clinical concern, whereas Lp(a) concentrations over 50 mg/dL (125 nmol/L) must be considered as a risk factor. The intermediate area (30–50 mg/dL, 75–125 nmol/L) should be taken into consideration when other CV risk factors are present.

Although inflammatory conditions may cause a temporary increase of its plasma levels, Lp(a) remains quite constant throughout the lifespan of the individual. The 2021 Guidelines of the Canadian Cardiovascular Society [128], as well as the 2022 EAS consensus [68], recommend Lp(a) measurement once in a patient's lifetime, possibly expressed as nmol/L, as part of the initial lipid screening to assess cardiovascular risk.

Lp(a) measurement is particularly recommended for high CVD risk patients. FH patients may be at particular risk of accelerated ASCVD when substantially elevated LDL-C is accompanied by elevated Lp(a). Approximately 30% of individuals with FH [102] may have elevated Lp(a), further enhancing CVD-related risk. Cascade testing of Lp(a) levels must be thus performed in the relatives of subjects with high Lp(a) and in first-degree relatives of subjects with FH [129,130].

Adult levels of Lp(a) are achieved by 2 years of age [131] and thereafter may serve as a reliable biomarker in helping to assess CVD risk, especially in children with FH and family history of early-onset ASCVD, who are more likely to have Lp(a) ≥50 mg/dL than children with FH and family history of late-onset ASCVD [132].

Nowadays, elevated Lp(a) levels are very difficult to manage and can be moderately reduced only by PCSK9 inhibitors, whereas statins do not exert any potentially beneficial effect. Awaiting specific Lp(a)-lowering drugs on the market, the 2022 EAS consensus recommends an intensive management of the other risk factors for individuals with elevated Lp(a) levels.

In FH patients, PCSK9 inhibitors are not sufficiently effective to reach LDL-C target and, in addition, the reduction on Lp(a) levels may be lower than expected [133]. In the clinical practice these patients are far from rare and lipoprotein apheresis represents a unique option to effectively reduce both LDL-C and Lp(a) plasma levels [109,134].

It is vitally important to educate youth and their parents about the excessive risk associated with this lipoprotein and the need to avoid the acquisition of other lifestyle-related risk factors such as smoking, excess weight, and physical inactivity to preserve more ideal cardiovascular health in adulthood [135].

Contribution statement

Andrea Baragetti, Carlo M. Barbagallo, Claudio Borghi, Furio Colivicchi, Aldo P. Maggioni, Davide Noto, Matteo Pirro, Angela A. Rivellese, Tiziana Sampietro and Francesco Sbrana equally contributed to the manuscript.

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Declaration of competing interest

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Merck, Mylan, Novartis, PeerVoice, Pfizer, Recordati, Regeneron, Sanofi, The Corpus, Viatris. GC, MGZ, AB, CMB, CB, FC, DN, MP, AAR, TS, FS, M Averna declare no competing interest.

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