

Frontiers in Cardiovascular Medicine

# Lipoprotein(a): the revenant

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In the mid-1990s, the days of lipoprotein(a) [Lp(a)] were numbered and many people would not have placed a bet on this lipid particle making it to the next century. However, genetic studies brought Lp(a) back to the front-stage after a Mendelian randomization approach used for the first time provided strong support for a causal role of high Lp(a) concentrations in cardiovascular disease and later also for aortic valve stenosis. This encouraged the use of therapeutic interventions to lower Lp(a) as well numerous drug developments, although these approaches mainly targeted LDL cholesterol, while the Lp(a)-lowering effect was only a 'side-effect'. Several drug developments did show a potent Lp(a)-lowering effect but did not make it to endpoint studies, mainly for safety reasons. Currently, three therapeutic approaches are either already in place or look highly promising: (i) lipid apheresis (specific or unspecific for Lp(a)) markedly decreases Lp(a) concentrations as well as cardiovascular endpoints; (ii) PCSK9 inhibitors which, besides lowering LDL cholesterol also decrease Lp(a) by roughly 30%; and (iii) antisense therapy targeting apolipoprotein(a) which has shown to specifically lower Lp(a) concentrations by up to 90% in phase 1 and 2 trials without influencing other lipids. Until the results of phase 3 outcome studies are available for antisense therapy, we will have to exercise patience, but with optimism since never before have we had the tools we have now to prove Koch's extrapolated postulate that lowering high Lp(a) concentrations might be protective against cardiovascular disease.

**Keywords** Cardiovascular prevention • Lipids • Risk factors • Pharmacological therapies

## Introduction

Lipoprotein(a) [Lp(a)] consists of an LDL particle to which an additional apolipoprotein named apolipoprotein(a) [apo(a)] is covalently linked to the apolipoprotein B-100 (ApoB) part of the LDL particle. Plasma concentrations of Lp(a) are mainly determined by the *LPA* gene (~90%).<sup>1</sup> The physiological function of Lp(a) is unclear, but Lp(a) has a pathogenic role in atherosclerosis and thrombosis formation.<sup>2</sup> Several observational studies, including meta-analyses and genomic studies suggest an association between Lp(a) concentrations and myocardial infarction, stroke, and calcific aortic valve stenosis.<sup>1</sup> It is estimated that 20% of the population have Lp(a) levels above 50 mg/dL, and the risk of myocardial infarction is elevated by roughly 2- to 2.5-fold in individuals with Lp(a) levels above the 90th percentile.<sup>3</sup> The European Society of Cardiology (ESC) guidelines recommend measuring Lp(a) levels in selected patients at high risk of cardiovascular disease (CVD) and consider the cut-off of 50 mg/dL as an additional factor that indicates a very high cardiovascular risk.<sup>4</sup> For many years strategies to lower Lp(a) were sparse, and while several approaches showed a lowering of Lp(a) most of them did not make it to cardiovascular outcome studies for various reasons.<sup>2</sup> However, the recent approval of proprotein

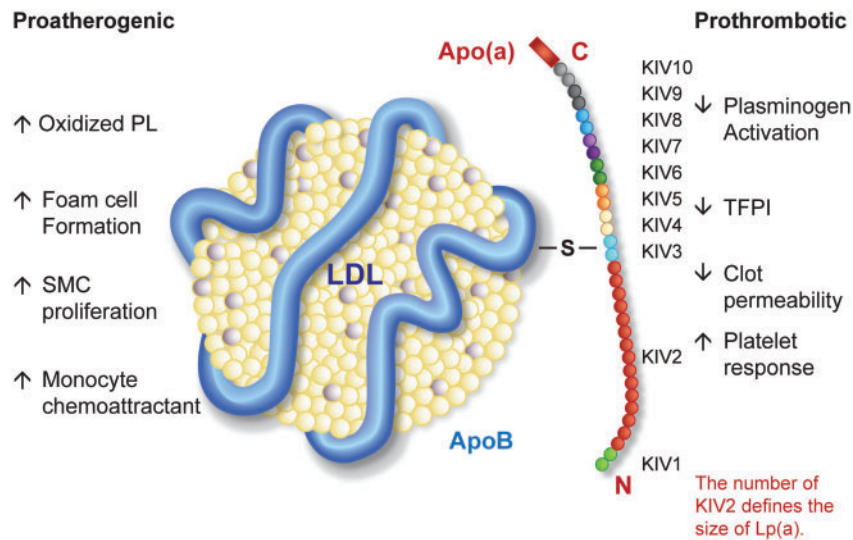
convertase kexin 9 (PCSK9) inhibitors for the treatment of primary hypercholesterolemia<sup>5</sup> might change this situation as this new class of substances has proven to be more effective than maximally tolerated statin therapy in decreasing both low-density lipoprotein cholesterol (LDL-C) and Lp(a) levels.<sup>6</sup> Other promising approaches include the use of antisense therapy directed against the mRNA of apo(a) which was able to independently lower Lp(a) by up to 90% in phase 1 and 2 studies. Following these promising and exciting developments, we hereby aim to provide an update on the role of Lp(a) as a potential target in the management of dyslipidaemia.

## Structure and function

Lp(a) particles have two major and distinct components: (1) a structure similar to an LDL particle («LDL-like») containing apoB-100; and (2) a specific glycoprotein apo(a) particle similar to plasminogen with a size ranging from 300 to 800 kDa (Figure 1).<sup>1</sup> The variability in size of apo(a) is caused by copy number variations within the *LPA* gene that determines the number of kringle IV (K-IV) repeats.<sup>1</sup> Lp(a) particles increase arterial wall cholesterol deposition, enhance foam cell

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**Figure 1** Structure of lipoprotein(a). Lipoprotein(a) is composed of an LDL-like particle and an additional apolipoprotein called apolipoprotein(a) [apo(a)] that is bound to apolipoprotein B (apoB) by a disulfide bridge. Apo(a) protein is formed of cysteine-rich «kringles» with a variable number of KIV repeats, a KV kringle and a protease domain. KIV repeats are available in 10 different types and the number of kringle-IV type 2 repeats is highly variable, resulting in different isoforms. KIV, kringle IV type; LDL, low-density lipoprotein; PL, phospholipids; SMC, smooth muscle cell; TFPI, tissue factor pathway inhibitor.

formation, generate oxidized radicals in monocytes, promote smooth muscle cell proliferation, and induce monocyte-chemotactic activity in sub-endothelial spaces.<sup>7</sup> Lp(a) is recognized by inflammatory cells (e.g. foam-cell receptor) in the atherosclerotic wall and has been identified as the major carrier of a wide array of oxidized phospholipids (OxPL) with the ability to trigger multiple pro-inflammatory pathways.<sup>7</sup> In addition, Lp(a) has shown to compete with plasminogen for binding sites *in vitro*, resulting in a decrease of plasmin synthesis and inhibition of fibrinolysis.<sup>8</sup> In the absence of clinical trials, the relevance of these findings remains controversial. Large genetic studies found that neither Lp(a) concentrations nor genetic variants associated with high Lp(a) concentrations were connected with the risk of venous thrombosis or venous thromboembolism.<sup>9,10</sup> It has been proposed that the situation might be different for thromboembolism in childhood.<sup>11</sup>

## Lp(a): a cardiovascular risk factor

Several observational studies, including meta-analyses and genetic studies have suggested an association between elevated Lp(a) concentrations and myocardial infarction, stroke, and aortic valve stenosis. (Table 1)<sup>12,13</sup> The Emerging Risk Factors Collaboration pooled individual data from 126 634 participants in 36 prospective studies, and showed that the risk ratio for CVD adjusted for age and sex was increased for each increase in Lp(a) standardized concentrations and remained similar after adjustment for traditional cardiovascular risk factors.<sup>12</sup> The risk was also increased for stroke events but not for non-cardiovascular mortality.<sup>12</sup> Similarly, three studies from

Denmark were analyzed adding genotype data for Lp(a) kringle IV type 2 (KIV-2) polymorphism. The Copenhagen City Heart Study showed that persons with Lp(a) concentrations between 30 and 76 mg/dL (corresponds to the 67th–90th percentile) had a 1.6-fold increased risk for incident myocardial infarction compared to persons with Lp(a) concentrations below 5 mg/dL. This risk increased to 1.90 for individuals with Lp(a) concentrations between 77 and 117 mg/dL (90th–95th percentile) and to 2.60 for individuals with Lp(a) concentrations above 117 mg/dL (>95th percentile).<sup>3</sup> Genetically confirmed elevated Lp(a) concentrations were associated with a 22% risk increase of per doubling of Lp(a) values. Recently, in the same cohort, elevated Lp(a) levels and their corresponding LPA risk were also shown to be associated with increased rates of heart failure but about two thirds of the heart failure risk was mediated via myocardial infarction and aortic valve stenosis combined.<sup>14</sup>

Data in patients with familial hypercholesterolemia (FH) showed that the high cardiovascular risk in these patients is further increased by their unusual Lp(a) concentrations, which tend to be 2–3-fold higher than in the general population.<sup>15,16</sup> In the Copenhagen general population study with 46 200 individuals, the risk of myocardial infarction was highest in patients classified as having FH with Lp(a) values > 50 mg/dL (HR = 5.3, 95%CI 3.6–7.6), followed by those with FH and Lp(a) values ≤ 50 mg/dL (HR = 3.2, 95%CI 2.5–4.1) compared to the reference group of subjects without FH and Lp(a) values ≤ 50 mg/dL.<sup>17</sup>

The strongest evidence for a causal association between Lp(a) and CVD risk comes from a genetic study using the Mendelian randomization approach, a principle that was applied for the first time (but not named as such) in the early 1990s.<sup>18</sup> This study clearly

**Table 1** Association between Lp(a) concentrations and clinical CVD outcomes

<b>1. Association between Lp(a) levels and CHD events in large major prospective cohorts</b>	
The emerging risk factors collaboration <sup>12</sup>	Pooled individual participant data analysis from 126 634 subjects in 36 cohorts showed a 16% higher risk of CHD events for each 1 SD increase of Lp(a).
The Copenhagen city heart study (N = 8637)	HR for CHD events was 2.6 (95% CI 1.6–4.1) for the 95th vs. 22th percentile of Lp(a), HR 1.22 (95% CI 1.09–1.37) per doubling of Lp(a), and HR 1.08 (95% CI 1.03–1.12) for continuous Lp(a).
The Copenhagen general population study (N = 29'388)	
The Copenhagen ischaemic heart disease study (N = 2461). <sup>3</sup>	HR for incident CVD was 1.37 per 1-SD higher Lp(a) level (SD = 32 mg/dL) and 2.37 when comparing the top fifth quintile with other quintiles.
The Bruneck study. <sup>20</sup>	
<b>2. Association between Lp(a) levels and heart failure events</b>	
The Copenhagen general population study. <sup>14</sup>	HR for heart failure events was 1.79 (95% CI 1.18–2.73) for the 99th vs. 34 percentiles.
<b>3. Association between Lp(a) levels and recurrent MACE in secondary prevention</b>	
Meta-analysis of 18 978 subjects with CHD from 11 studies. <sup>27</sup>	OR for MACE was 1.40 (95% CI 1.15–1.71) for the highest vs. lowest quantile of Lp(a).
Cohort of patients treated with percutaneous coronary intervention for acute coronary syndromes. <sup>24</sup>	In 569 patients and well controlled LDL-C, higher vs. lower median Lp(a) value was associated with mortality and recurrent acute coronary syndromes (HR 1.69, 95% CI 1.03–2.70).
<b>4. Association between Lp(a) levels and aortic valve disease</b>	
Cohorts for Heart and Aging Research in Genomic Epidemiology consortium. <sup>28</sup>	Lp(a) genetic variation was associated with incident aortic stenosis (HR per allele, 1.68; 95% CI, 1.32–2.15) and aortic-valve replacement (HR 1.54; 95% CI, 1.05–2.27) in a large Swedish cohort; the association with incident aortic stenosis was also replicated in an independent Danish cohort.
The Copenhagen City Heart Study and the Copenhagen General Population Study. <sup>29</sup>	Elevated Lp(a) levels were associated with aortic valve stenosis of 1.2 (95% CI 0.8 to 1.7) for 22nd to 66th percentile levels (5 to 19 mg/dL), 1.6 (95% CI 1.1 to 2.4) for 67th to 89th percentile levels (20 to 64 mg/dL), 2.0 (95% CI 1.2 to 3.4) for 90th to 95th percentile levels (65 to 90 mg/dL), and 2.9 (95% CI 1.8 to 4.9) for levels greater than 95th percentile (>90 mg/dL), vs. levels less than the 22nd percentile (<5 mg/dL; trend, $P < 0.001$ ).
Cohort of patients with aortic valve stenosis. <sup>30</sup>	The progression rate from mild-to-moderate aortic stenosis and aortic valve replacement was higher in top tertiles of Lp(a).

CHD, coronary heart disease; CI, confidence intervals; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events; MI, myocardial infarction; OR, odd ratio.

demonstrated that carriers of small apo(a) isoforms who are exposed to high Lp(a) concentrations from their early life have a markedly increased risk for CVD events.<sup>18</sup> A later meta-analysis of 30 studies with 7382 cases and 8514 controls applied broadly comparable phenotyping and analytic methods to determine apo(a) isoforms and revealed that small apo(a) isoforms were associated with a two-fold increased risk for CHD compared to large isoforms (RR = 2.08, 95%CI 1.76–2.58). Similar relative risks were observed for ischaemic stroke (RR = 2.14; 95% CI: 1.85–2.97).<sup>19</sup> This is particularly relevant from a public health point of view taking into account that approximately 25–35% of the population carry small apo(a) isoforms, and points toward *LPA* genes belonging to those associated with the highest CVD risk.<sup>1</sup> Recent data from primary prevention studies have suggested that the addition of Lp(a) to risk scores, such as the Framingham Risk Scores improves the reclassification of patients originally classified as intermediate cardiovascular risk.<sup>20</sup> This has shown to be especially true when Lp(a) concentrations above the 80th percentile are used as the cut-off.<sup>21</sup> Despite these results, the clinical relevance of biomarkers in general has been questioned, as several of them are not

used in clinical practice despite having shown to be relevant in risk score assessments (e.g. inflammatory marker).<sup>22,23</sup>

In the secondary prevention setting, among 569 patients having undergone percutaneous coronary intervention and whose LDL-C levels were well-controlled (< 100 mg/dL), those with higher Lp(a) levels had significantly more major adverse cardiovascular events (MACE) ( $P = 0.04$ ) compared to patients with lower Lp(a) levels, while elevated Lp(a) values were an independent predictor of mortality and recurrence of acute coronary syndromes (ACS).<sup>24</sup> These findings were also confirmed in a clinical trial including 904 patients with chronic kidney disease: the occurrence of all-cause death and ACS was higher in patients in the upper median compared to the lower median ( $P = 0.01$ ), and higher Lp(a) values were independently associated with mortality.<sup>25</sup> Among patients who presented with premature ACS, the prevalence of subjects with elevated Lp(a) values (> 50 mg/dL) was higher than in the general population (30% vs. 20%,  $P < 0.001$ ), and more likely to be associated with elevated levels of LDL-C.<sup>26</sup>

A meta-analysis from 11 studies in secondary prevention reported that higher levels of Lp(a) were associated with a 40% increased risk

of MACE for the highest vs. lowest quintile.<sup>27</sup> Finally, a recent systematic review of 60 studies in primary and secondary prevention was able to suggest only a modest association between Lp(a) levels and the risk of future CVD events.<sup>13</sup> However, all of the primary and secondary prevention studies reporting the use of more reliable apo(a) isoform-independent assays concluded that Lp(a) was an independent risk factor for CVD events.<sup>13</sup>

## Lp(a) and aortic valve stenosis

Genome-wide association studies and Mendelian randomization studies suggest that Lp(a) is strongly associated with aortic valve calcium and clinical aortic stenosis.<sup>28,29</sup> Data from a large prospective cohort found a continuously increasing risk for aortic valve stenosis with roughly three-fold increases in Lp(a) concentrations, as was in case for Lp(a) levels >90 mg/dL (95th percentile).<sup>29</sup>

In a cohort of 220 patients with mild-to-moderate aortic stenosis, the progression rate of aortic stenosis was faster and the need for aortic valve replacement was also increased in the top tertiles of Lp(a) and OxPL-apoB.<sup>30</sup> Further cohort studies in older patients treated for aortic valve disease should address the role of Lp(a) as a predictor of clinical outcomes.

## Lp(a) measurement

The molecular mass of the apo(a) protein depends heavily on the number of K-IV repeats of the protein with a very wide range of 300 to 800 kDa. The repetitive kringle structure of the highly homologous K-IV type-2 repeats could create a problem, especially for immunological assays that are based on antibodies that recognize this type of antibodies. However, most of the assays cannot specify which epitope in which kringle is recognized by the antibodies they use. In an effort to be more specific, several assays compared their results against an assay that recognizes a unique kringle IV (type 9), and were able to demonstrate equal consistency in their results, independent of the isoform used.<sup>31</sup> Even if an assay does not recognize a unique epitope, steric hindrance might, in most cases, avoid a dramatic overestimation or underestimation of Lp(a) concentrations for the respective isoforms. Theoretical and practical considerations on an underestimation of Lp(a) concentrations of small apo(a) isoforms and an overestimation of Lp(a) of large apo(a) isoforms lead to the conclusion that this might result in an underestimation of the association between Lp(a) concentrations and clinical outcomes, which in turn could explain why some studies were unable to demonstrate any correlation between Lp(a) and cardiovascular risk. In the meantime, some laboratories have used a conversion factor of 2.4 to convert mass-based concentrations (mg/dL) of Lp(a) to molar concentrations (nmol/L), which may be inaccurate since it ignores the size heterogeneity of apo(a) in the case of antibodies that are directed against the repetitive structure of apo(a).

Yet another issue is that Lp(a) concentrations can often not be compared between different assays as they often omit to mention which of the many traceable calibrators available they use.<sup>31</sup> Furthermore, storage conditions and storage duration might have an influence on the measured results for some assays.

## Interventions lowering Lp(a)

Lifestyle changes, such as increased physical activity or the adoption of a healthy diet are also expected to have a positive impact on Lp(a) values and are desirable treatment options for many reasons. However, the effects of these interventions on Lp(a) concentrations are so far either only marginal or lacking in evidence from controlled trials. In general, most interventional studies, and in particular those that include the use of drugs, do not target the lowering of Lp(a) concentrations alone. It is therefore hard to evaluate whether an effect on outcomes can singly be attributed to the lowering of Lp(a), or whether other concomitant factors, such as the lowering of LDL-C levels or improvement of other risk factors, also play a role.

After much controversy, recent data from the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial provided strong evidence that statins have a slight Lp(a)-increasing effect rather than a lowering one.<sup>32</sup> Furthermore, Yeang and co-workers found that various lipid-lowering strategies, including statins in combination with ezetimibe and/or niacin, lead to an 11% increase in Lp(a) levels, with a concomitant 24% increase in OxPL-apoB.<sup>33</sup> The lack of a clear association between the effect of statins and a reduction in Lp(a) has probably contributed to the discovery of the novel role that Lp(a) is being given in the clinical setting.

Niacin (vitamin B family) is associated with an Lp(a) reduction by about 30%, as shown in two clinical trials, but with detrimental adverse effects.<sup>34,35</sup> However, these trials were not designed from the perspective of patients with high Lp(a) concentrations. Therapies with CETP-inhibitors, thyroid hormone analogues, or MTP inhibitors did show initial promising Lp(a)-lowering effects, however, no data are available from outcomes studies since research activities around these substances were, for the most part, stopped.<sup>36</sup> Three therapies with pronounced effects on Lp(a) concentrations are the object of continued trials, as discussed in the following paragraphs.

## PCSK9 inhibitors

A pooled analysis of 4 phase II trials investigating evolocumab (AMG 145) in 1359 patients reported significant dose-related decreases in Lp(a) levels compared to placebo. The administration of evolocumab 140 mg every 2 weeks reduced Lp(a) levels by 29.5% (95%CI: 23.3% to 35.7%), while 420 mg every 4 weeks reduced Lp(a) levels by 24.5% (95%CI: 20.4% to 28.7%).<sup>37</sup> The reduction in Lp(a) levels was associated with a decrease in LDL-C and apolipoprotein B, while the absolute reduction was higher in those with Lp(a) levels > 125 nmol/l ( $\approx$ 50 mg/dL).<sup>37</sup> In a pooled analysis from 3 phase II randomized controlled trials, alirocumab (150 mg every 2 weeks) resulted in a significant reduction of Lp(a) levels by 30% compared to placebo after 8 to 12 weeks.<sup>38</sup> The median reduction in the percentage of Lp(a) levels was similar across a range of baseline Lp(a) values, with the most absolute benefit reported in those patients with higher initial Lp(a) levels. In addition, the extent to which Lp(a) levels decreased was not correlated with the levels of LDL-C reduction.<sup>38</sup> In a cohort of Chinese patients, no significant association was found between PCSK9 levels and Lp(a) levels, suggesting that the reduction in Lp(a) levels induced by PCSK9 inhibitors might not be mediated by the PCSK9 pathway.<sup>39</sup> Currently, the discussion of how PCSK9 influences Lp(a) concentrations is still ongoing and it is not clear why

Lp(a) is decreased by PCSK9 inhibitors and not by statins although both act through the LDL receptor pathway.

## Antisense therapy

Antisense therapy belongs to the group of biologics (e.g. small molecules and monoclonal antibodies) that directly bind to apo(a) mRNA in the nucleus of hepatocytes, thereby inhibiting its synthesis.<sup>40</sup> Several companies are interested in the specificities of RNA therapeutics in general, and antisense drugs in particular.<sup>41</sup> To date, only mipomersen, a second-generation antisense oligonucleotide to apolipoprotein B-100 has been approved for the treatment of homozygous familial hypercholesterolemia in some countries and shown to also lead to significant reductions in Lp(a) concentrations.<sup>42</sup>

In the IONIS-APO(a)<sub>Rx</sub> phase I study that investigated an antisense oligonucleotide that selectively reduces the synthesis of apo(a) in the liver, and consequently Lp(a) plasma levels,<sup>43</sup> 47 volunteers aged 18–65 years with Lp(a) concentrations higher than 10 mg/dL were randomized to receive either one single-dose of IONIS-APO(a)<sub>Rx</sub> or placebo administered subcutaneously at varying concentrations (50–400 mg), or six consecutive doses at varying concentrations or placebo administered on days 1, 3, 5, 8, 15, and 22. No serious or severe adverse events occurred during the study. In the single dose arm, no significant changes were observed in Lp(a) concentrations at day 30. In the multi-dose arm, significant dose-dependent decreases in Lp(a) levels compared to baseline were observed after one month: 39.6% with 100 mg, 59.0% with 200 mg and 77.8% with 300 mg (all *P* values  $\leq 0.005$  vs. placebo).<sup>43</sup> Significant positive changes in the levels of oxidized phospholipids on apo(B) and oxidized phospholipids on apo(a) were also noted, while no significant changes were observed for total cholesterol and LDL-C.<sup>43</sup>

A further phase II trial of IONIS-APO(a)<sub>Rx</sub> also showed a significant 67–72% reduction of mean Lp(a) concentrations accompanied by a reduction of oxidized phospholipids and a reduced monocyte inflammatory activation that returned close to baseline levels after stopping the medication. In a second part of the study (phase I/IIa first-in-man trial) the authors applied a new chemistry in which a modified IONIS-APO(a)<sub>Rx</sub> antisense oligonucleotide is conjugated with a GalNAc<sub>3</sub> complex (IONIS-APO(a)-L<sub>Rx</sub>). This formulation guides the drug to the hepatocyte via the asialoglycoprotein receptor, making it 30 times more potent than the parent antisense oligonucleotide. This enabled the administered dose to be reduced 10-fold, thereby improving its tolerability. The highest dose administered resulted in a 92% mean reduction of Lp(a) with no side-effects.<sup>44</sup> Upcoming trials will be able to test the effect of an isolated Lp(a)-lowering therapy on cardiovascular outcomes without the direct influence on other atherogenic parameters.

## Lipid apheresis

Two interesting LDL apheresis studies that had high Lp(a) concentrations in their focus provided interesting results.<sup>45,46</sup> Measurements taken before and after an apheresis session showed that Lp(a) levels dropped by 60–70%, as did LDL-C levels, and that levels gradually increased until the next session. Both studies demonstrated a marked reduction of major cardiovascular event rates by 80–85%. Interestingly, in one of the studies a subgroup of patients analyzed had LDL-C  $\leq 100$  mg/dL even before the start of the apheresis phase.<sup>45</sup> The LDL-C reportedly measured in the patients' plasma was

mainly cholesterol resulting from the very high Lp(a). It is indeed important to bear in mind that roughly 30–45% of an Lp(a) particle consists of cholesterol and is measured together with the cholesterol located in the LDL particles. Therefore the 'true' LDL-C levels in the subgroup mentioned above were, in average, only 23 mg/dL and dropped only by a few mg/dL during the LDL apheresis. Therefore the apheresis selectively and dramatically lowered Lp(a) in these patients without an important effect on the true LDL-C. Intriguingly, the effect on MACE in this subgroup was of the same magnitude as in the subgroup that started with measured LDL-C concentrations above 100 mg/dL. Studies of this kind are hard to control in a blinded fashion but provide the best evidence currently available. The second 5-year prospective observational study included 170 patients with high Lp(a) concentrations and progressive CVD at baseline. When comparing the mean annual cardiovascular event rate measured two years preceding the start of regular lipid apheresis to the rate thereafter, a significant decline was noted ( $0.58 \pm 0.53$  vs.  $0.11 \pm 0.15$ ).<sup>46</sup>

Additional evidence comes from a small study applying a specific Lp(a) apheresis, where Lp(a) decreased on average by 73% without significant changes in true LDL-C and other risk factors. The mean percent diameter stenosis of the coronary arteries after 18 months decreased by 5% in the Lp(a) intervention group and increased by 5% in the control group that received only statins.<sup>47</sup>

## Lp(a): what do guidelines tell us?

### Measurement

The 2010 consensus document on Lp(a) delivered by the European Society of Cardiology proposed a linear association between Lp(a) concentrations and CVD events (Table 2).<sup>2</sup> Measurement of Lp(a) is recommended in a selected number of subjects, for those at intermediate or high risk of CVD ( $\geq 3\%$  over 10 years of fatal CVD and/or  $\geq 10\%$  over 10 years of fatal and non-fatal CVD), subjects with premature CVD, familial hypercholesterolemia, a family history of premature CVD and/or elevated Lp(a), recurrent CVD despite statin treatment.

### Treatment

The treatment goal for CVD patients is first to lower LDL-C levels, and subsequently to reach desirable Lp(a) levels ( $< 50$  mg/dL). However, no randomized controlled trial has shown that reaching such an Lp(a) target would have a positive impact on the reduction of CVD events. Trials that could demonstrate this are hard to perform since most interventions that lower Lp(a) have also an effect on other atherogenic risk factors, such as LDL-C. In addition, the cut-off of 50 mg/dL has been defined empirically, mainly based on the fact that 20% of subjects from the general population have levels above 50 mg/dL. Moreover, this threshold is assay-specific, as some studies have shown a significant risk increase already at Lp(a) levels above 30 mg/dL (see also chapter on measurement of Lp(a)).

Niacin was initially prescribed as a 'magic bullet' that increases HDL cholesterol and decreases LDL-C, triglycerides as well as Lp(a) concentrations. However, following the disappointing results of the AIM-HIGH and HPS2-THRIVE trials, that were not even designed to target patients with high Lp(a) concentrations, niacin was withdrawn from the market by the FDA, including its combined forms with

**Table 2** Summary of recommendations from the European Atherosclerosis Society (EAS) and European Society of Cardiology (ESC) regarding the screening for lipoprotein(a)

2010 EAS Consensus Panel. <sup>2</sup>	Lp(a) should be measured once in all subjects at intermediate or high risk of CVD who present with: <ul style="list-style-type: none"><li>• Premature CVD.</li><li>• Familial hypercholesterolemia.</li><li>• A familial history pf premature CVD and/or elevated Lp(a).</li><li>• Recurrent CVD despite statin treatment.</li><li>• ≥3% 10-year risk of fatal CVD according to the European guidelines and</li><li>• ≥10% 10-year risk of fatal and/or non-fatal CHD according to AHA guidelines.</li></ul>
2016 ESC Guidelines for the management of dyslipidaemias. <sup>4</sup>	Lp(a) should be recommended in selected cases at high risk, in patients with family history of premature CVD, and for reclassification in subjects with borderline risk. Lp(a) screening should be considered in individuals with: <ul style="list-style-type: none"><li>• Premature CVD (&lt; 55 years in men and &lt; 65 years women).</li><li>• Familial hypercholesterolemia.</li><li>• A family history of premature CVD and/or elevated Lp(a).</li><li>• Recurrent CVD despite optimal statin treatment.</li><li>• ≥5% 10-year risk of fatal CVD according to SCORE.</li></ul> Treatment with a PCSK9 antibody may be considered in FH patients with CVD or with other factors putting them at very high risk for CHD, such as other CV risk factors, family history and high Lp(a).

AHA, American Heart Association; CV, cardiovascular; CVD, cardiovascular disease; Lp(a), lipoprotein(a); PCSK9, proprotein convertase kexin 9.

statin.<sup>35,48</sup> New emerging therapies, such as apo(B) antisense oligo-nucleotides and PCSK9 inhibitors, have already reported significant reductions in Lp(a) levels in trials that are still ongoing. PCSK9 inhibitors have recently been approved for the treatment of FH in case of statin intolerance or suboptimal control of LDL-C levels despite maximally tolerated statin therapy. In this regard and based on current evidence, the ESC consensus statement has made specific recommendations on the use of PCSK9 inhibitors in very high-risk patients, and included guidance around optimal management of statin intolerance and intervention procedures to follow in order to reach LDL-C targets. Lp(a) ≥ 50 mg/dL is considered as an additional risk factor that should be taken into account in the risk stratification of FH patients whose recommended LDL-C target has been set at 2.5 mmol/l in the absence of CV risk, or 1.8 mmol/l for very high risk subjects.

Gaps in evidence

The issue of lacking evidence regarding the need to treat CVD patients beyond current targets is especially important to address, given that one-third to half of patients with CVD events have LDL-C levels below 130 mg/dL, which is an accepted target for primary prevention. Therefore, additional risk markers/factors are needed for improving risk stratification and medical decisions. The role of Lp(a) in the diagnosis of lipid disorders is a source of controversy. Recent guidelines consider subjects with Lp(a) values ≥ 50 mg/dL to be at high cardiovascular risk, and recommend an intensive lipid lowering therapy besides the strict management of present risk factors to reach recommended LDL-C targets (e.g. by PCSK9 inhibitors).<sup>4</sup> At present, the ANITSCHKOW trial is addressing the impact of the PCSK9-antibody evolocumab on LDL-C, Lp(a) and vascular inflammation, as assessed by PET/CT (NCT02729025). Large ongoing clinical trials

with PCSK9 inhibitors (Fourier (evolocumab), LTS (alirocumab), and SPIRE (bococizumab)) should evaluate the relative impact of lowering Lp(a) on cardiovascular outcomes, adjusting for LDL-C levels. Given the role that Lp(a) plays in prothrombotic mechanisms, clinical trials assessing the impact of antithrombotic therapies (antiplatelet and anticoagulant) should also consider measuring Lp(a) concentrations and evaluate their association with clinical outcomes. While the measurement of LDL-C levels has been widely implemented in clinical practice, it is unclear whether clinicians are familiar with the investigation of Lp(a), and whether analytic methods are available in appropriate quality in usual clinical settings.

Conclusions

About 20% of the population has raised Lp(a) concentrations and evidence suggests that high levels of Lp(a) are an independent cardiovascular risk factor. Both the European Society of Cardiology and the European Atherosclerosis Society recommend measuring Lp(a) values in intermediate- to high-risk patients for risk stratification, as well as in patients already under statin treatment and with recurrent clinical events as a residual risk factor that calls for lipid-lowering therapy intensification. Strategies used to lower Lp(a) concentrations have either been partially disappointing in the past or lack cardiovascular outcome data. Therefore, Lp(a) has often been considered as a non-modifiable cardiovascular risk factor. New and consistent data retrieved from the PCSK9 inhibitor trials now suggest that Lp(a) can be decreased effectively by roughly 30%, while emerging data from apo(a) antisense therapy trials suggest that selective and potent Lp(a) reduction is a feasible treatment approach in the future. The impact of such decreases on the occurrence of cardiovascular outcomes, independent from LDL-C, could, if established, herald Lp(a) as the Revenant in the treatment of atherosclerosis.

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