HyperLp(a)lipoproteinaemia: unmet need of diagnosis and treatment?

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Lipoprotein(a) (Lp[a]) is a complex of a low-density lipoprotein (LDL)-like particle and apolipoprotein-B100 covalently bound to apolipoprotein (a) (apo[a]). Lp(a) was first described about 50 years ago (1963) by Kåre Berg, who found that high serum levels of Lp(a) are inherited and associated with an increased risk of premature cardiovascular disease (CVD)[1]. Apo(a) is composed of repeated loop-shaped units called kringles, the sequences of which are highly similar to a kringle shape present in the fibrinolytic pro-enzyme plasminogen. Variability in the number of repeated kringle units in the apo(a) molecule gives rise to differently sized Lp(a) isoforms in the population. Based on the similarity of Lp(a) to both LDL and plasminogen, it has been hypothesised that the function of this lipoprotein may represent a link between atherosclerosis and thrombosis. Lp(a) is able to pass through the intima of blood vessels in humans and animals. Accordingly, high plasma levels of Lp(a) may share with LDL atherogenicity, and may stimulate lipid peroxidation and infiltration, smooth muscle cell proliferation and inflammation in the arterial intima in humans.

Utermann *et al.* highlighted an inverse relationship between the size of the apo(a) isoform and the Lp(a) concentration[2-4]. In 1990, Rosengren *et al.* examined the association between plasma Lp(a) concentration and coronary heart disease (CHD). They found that men with CHD had significantly higher serum Lp(a) levels than controls. The incidence of CHD in men with the highest fifth of serum Lp(a) levels (cut-off point 365 mg/L) was double that in men with the lowest four-fifths of concentrations. Logistic regression analysis showed that plasma Lp(a) levels were significantly associated with CHD, independently of other risk factors[5]. Similar conclusions were reported in the same year by Niendorf *et al.*, in 1993 by Schreiner *et al.* and in 1994 by Valentine *et al.* who furtherly confirmed that Lp(a) had a role in the pathogenesis of atherosclerosis and was an independent and predictive risk factor for intima-media carotid thickening in individuals without CVD, and for premature peripheral vascular disease among white men[6-8]. In 1994, Cremer *et al.* suggested that Lp(a) and fibrinogen should be seriously considered as additional risk factors and should be included in diagnostic sets for the estimation of myocardial infarction (MI) risk correlates[9].

In a meta-analysis in 2007, Smolders *et al.* evaluated 31 studies including 56,010 subjects with >4,609 stroke events. In case-control studies (23, corresponding to 2,600 strokes) unadjusted mean Lp(a) concentration was more frequently elevated in stroke patients. In nested case-control studies (three, corresponding to 364 strokes) Lp(a) was not a risk factor for incident stroke. On the other hand, in prospective cohort studies (five with >1,645 strokes), incident stroke was more frequent in patients in the highest tertile of Lp(a) distribution compared with those in the lowest tertile of Lp(a). The authors concluded that high Lp(a) levels were a risk factor for incident stroke[10].

In 2008, Kamstrup *et al.* studied 9,330 men and women from the general population in the Copenhagen City Heart Study. During 10 years of follow-up, 498 participants developed MI. These authors observed a stepwise increase in risk of MI with increasing Lp(a) levels, with no evidence of a threshold effect. Extremely high Lp(a) levels predicted a 3- to 4-fold increase in the risk of MI in the general population and absolute 10-year risks of 20% and 35% in high-risk women and men, respectively[11].

Erqou *et al.* reviewed long-term prospective studies which reported Lp(a) level and major vascular morbidity and/or cause-specific mortality. Lp(a) level was weakly correlated with several established vascular risk factors, and was stable within individuals over several years. The authors concluded that there was a continuous, independent, and modest association of Lp(a) level with risk of CHD and stroke, which appeared to be restricted to vascular endpoints[12]. Erqou *et al.* also studied the association of apo(a) isoforms with CVD risk and found that high Lp(a) levels and low molecular weight apo(a) isoforms were associated with a high risk of CVD. Moreover, subjects with smaller apo(a) isoforms had an approximately 2-fold higher risk of CHD or ischaemic stroke than those with larger proteins[13].

Karmstrup *et al.* reported a study carried out on 8,720 Danish participants to investigate whether extremely high Lp(a) levels and/or corresponding Lp(a) risk genotypes could improve MI and CHD risk prediction,

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beyond usual risk factors. They found that very high Lp(a) levels or the corresponding Lp(a) KIV-2/rs10455872 risk genotype substantially improved MI and CHD risk prediction[14]. The same authors published a further paper confirming that high Lp(a) levels and corresponding genotypes were associated with an increased risk of aortic valve stenosis in the general population, with levels >90 mg/dL predicting a 3-fold increased risk[15].

As a consequence of the above-mentioned findings, therapeutic approaches are being targeted at lowering Lp(a) levels. Novel pharmaceutical agents such as the apolipoprotein-B100 synthesis inhibitor, mipomersen, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (alirocumab, evolocumab, bococizumab) have shown interesting, although not impressive, effectiveness at lowering Lp(a) levels[16].

Mipomersen may lower apolipoprotein-B100-containing lipoproteins such as LDL and Lp(a) in patients at high risk of CVD. Indeed, studies investigating the effect of mipomersen on Lp(a) levels documented a reduction of 19.6-31.1% from baseline levels, depending on the study design[17]. Santos *et al.* found that mipomersen consistently and effectively reduced Lp(a) levels in patients with dyslipidaemia and cardiovascular risk[18].

PCSK9 is an enzyme involved in LDL-receptor degradation. PCSK9 inhibitors affect the levels of Lp(a). Koren *et al.* investigated the efficacy and safety of evolocumab, a monoclonal antibody against PCSK9, in a 52-week study in 1,104 randomised subjects. The authors found a median reduction of Lp(a) levels of roughly 30% (Figure 1)[19].

Anacetrapib (MK-0859, Merck) is a cholesteryl ester transfer protein (CETP) inhibitor developed to treat hypercholesterolaemia and prevent CHD. In 2013 a study of 407 Japanese subjects showed that anacetrapib, with or without atorvastatin, is effective at lowering LDL and raising high-density lipoprotein (HDL) concentrations[20]. Early results from the DEFINE (Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib) phase III trial showed that at a dose of 100 mg/day, LDL decreased by 36%, Lp(a) decreased by 36.4%, while HDL increased by 138%. There was no increase in systolic blood pressure and no association with increased cardiovascular deaths

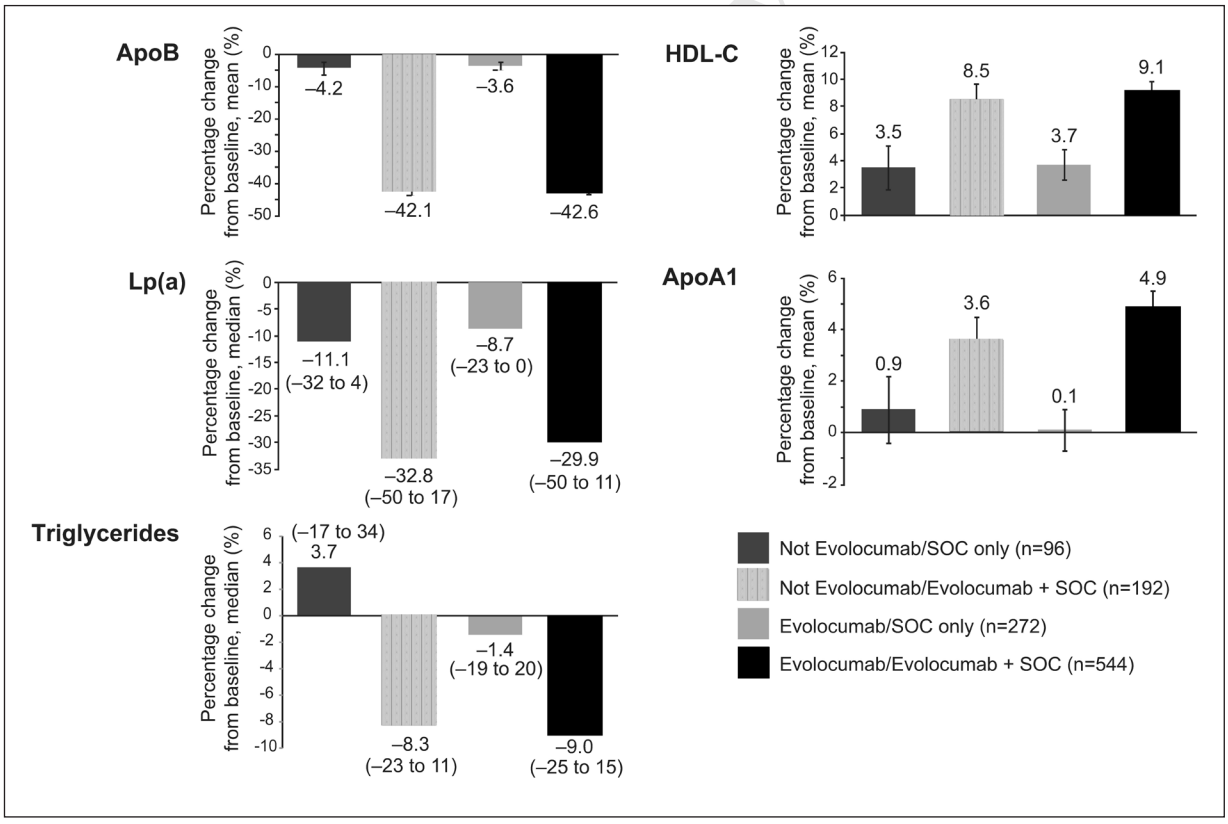

Figure 1 - Percentage change from the phase 2 parent study baseline at week 52 in apolipoprotein B (ApoB), lipoprotein(a) (Lp[a]), triglycerides, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A1 (ApoA1).
The changes in lipid parameters from baseline in patients receiving evolocumab were all statistically significant ($p<0.0001$, except for the changes in triglycerides which were $p<0.05$). The reductions in lipid parameters were greater for patients receiving evolocumab+SOC *vs* SOC alone ($p\leq0.0002$). Error bars represent the standard error. Data in parentheses represent interquartile ranges. Adapted from Koren *et al.*[19]. SOC: standard of care.

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or events[21]. The results were later updated to a 39.8% decrease of LDL[22]. Unfortunately, a study published in 2014 found that HDL and anacetrapib levels remained elevated 2 to 4 years after discontinuation of the drug, raising considerable concern[23].

It is not surprising that at present the only suggested therapy to treat hyperLp(a)lipoproteinaemia (hyperLp[a]) is extracorporeal lipoprotein apheresis (LA), which reduces Lp(a) levels effectively. It is suggested that LA treatment be continuous (on a long-term basis) and administered weekly. Different LA methods have shown similar efficacy at lowering Lp(a) levels by about 60-70% per therapeutic session. However, apart from one small-scale study, there are no randomised, controlled trials that firmly prove that lowering Lp(a) by LA reduces the risk of CVD[16].

In Germany, hyperLp(a) with Lp(a) levels ≥600 mg/L is officially recognised by the authorities as an indication for LA treatment[24]. In Italy, hyperLp(a) was recognised as an indication for treatment with LA when associated with premature CHD, in secondary prevention, by a consortium of scientific societies that, in 2009, developed the 2nd Italian Consensus Conference on LDL-apheresis (recently renamed LA), but not specifically by regulatory authorities[25]. Also in 2009 in Italy, a multicentre study showed that long-term treatment with LA (3.1±2.7 years; weekly and biweekly sessions) was at least able to stabilise CHD in the majority of individuals (19 subjects aged 53.8±9.3 years) with symptomatic hyperLp(a) (Figure 2)[26].

In Germany, a large multicentre longitudinal cohort study enrolled 120 subjects with coronary artery disease (CAD) and elevated Lp(a) levels (≥95th percentile) on regular LA and maximum lipid-lowering therapy. The study was conducted to investigate the effect of Lp(a) lowering on the progression of CAD. LA reduced the median Lp(a) concentration by 73.3% and the annual major adverse coronary event rate per patient by 86.4%. Lowering Lp(a) levels by LA was recommended for patients in whom maximally tolerated doses of usual lipid-lowering medications fail to control CAD-related events[27].

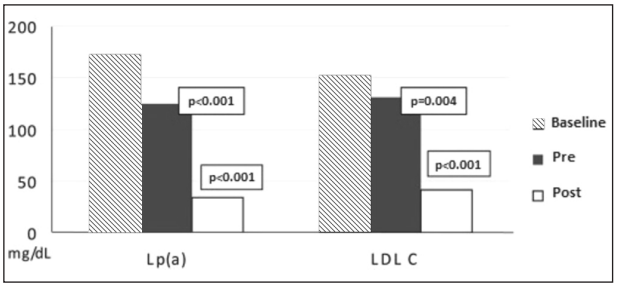

Figure 2 - Mean plasma Lp(a) and LDL-C levels at baseline, and before/after LA.
Reproduced from Stefanutti *et al*.[26]
Lp(a): lipoprotein(a); LDL-C: low-density lipoprotein cholesterol; LA: lipoprotein apheresis.

In 2010, Stefanutti *et al.* reported the findings of a 12-month study to assess LA efficacy at lowering Lp(a) and to compare the effects of LA with those of usual medical care, essentially statins. Twenty-one patients with hyperLp(a) and angiographically documented CAD were randomly assigned to LA every week or to usual medical care. The incidence of new CAD events/need for revascularisation was also monitored. The group treated with LA had a statistically significant reduction of Lp(a) levels of 57.8±9.5% compared to basal values, whereas in the group treated with usual medical care, Lp(a) increased in 1 year by 14.7±36.5%. Stepwise multivariate regression analysis for predictors of Lp(a) concentration, including type of treatment, smoking, hypertension, age, age at first cardiovascular event, initial Lp(a) and LDL cholesterol (LDL-C) levels, and body mass index values, was performed. Only the type of treatment was significantly correlated, with an Lp(a) variation (beta) of 0.863. The model had a R2 adjusted relative risk of 0.725. New CAD events/cardiac interventions were not observed during a 1-year follow-up. The authors concluded that LA could reasonably be the first-line treatment for isolated hyperLp(a) in patients with established CAD[28].

Leebmann *et al.* enrolled 170 patients with elevated Lp(a) levels and progressive CVD treated with regular LA in a prospective observational study. The Lp(a) concentration was reduced by 69.9±9.8% after each apheresis session and there was a 2-year reduction of major adverse cardiovascular events of 78.1%. The authors concluded that in patients with hyperLp(a), progressive CVD, and maximally tolerated lipid-lowering medication, LA effectively lowered the incidence rate of cardiovascular events[29].

Likewise, Rosada *et al.* found that apheresis reduced the progression of atherosclerosis and cardiovascular events in a retrospective analysis of 37 patients with hyperLp(a) treated with LA on a regular basis[30]. The authors did, however, underline that as prospective and controlled trials are lacking, the therapeutic effectiveness of LA can only be supposed/estimated.

Safarova *et al.* carried out a randomised, controlled, interventional study on the effect of Lp(a) reduction achieved by LA on diameter stenosis and minimal lumen diameter of coronary arteries. Thirty subjects were randomised into two groups: 15 patients were treated with atorvastatin and weekly LA, and 15 were given atorvastatin only. The authors found that in the group treated with weekly LA over 18 months, not only were Lp(a) levels reduced by 73±12%, but quantitative coronary angiography also showed a reduction in median percent diameter stenosis by 2.0 compared to that in

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the group treated with atorvastatin only. Safarova *et al.* concluded that specific Lp(a) apheresis for 18 months led to regression of coronary atherosclerosis in patients with stable CHD and high Lp(a) levels and achieved optimal target levels of LDL-C[31].

A further investigation conducted by von Dryander *et al.* found that the reduction of cardiovascular events associated with regular LA was more pronounced in patients with elevated Lp(a) levels than in patients with high LDL-C levels alone. The authors investigated the occurrence of cardiovascular events before and during apheresis in three groups defined by their lipid and lipoprotein patterns at the start of the apheresis treatment: group 1 (LDL-C ≥3.4 mmol/L and Lp(a) ≤600 mg/L; n=35), group 2 (LDL-C ≤3.4 mmol/L and Lp(a) ≥600 mg/L n=37) and group 3 (LDL-C ≥3.4 mmol/L and Lp(a) ≥600 mg/L; n=15). The time from first event until the start of LA treatment was about 10 years in group 2, compared to 2-6 years in the other two groups. The rate of events per patient before beginning apheresis treatment was 2.1, 3.4 and 1.8 among patients in group 1, 2 and 3, respectively. Under apheresis treatment just 0.9 events per subject occurred in group 1, 0.5 in group 2, and 0.5 in group 3. When comparing rates of cardiovascular events in the 2 years prior to starting apheresis with those in the first 2 years under LA, the authors observed the following reductions: group 1, −54%; group 2, −83%; and group 3, −83.5%. Interestingly, the authors suggested that the reduction of cardiovascular events, probably due to LA, was particularly substantial in subjects with high Lp(a) levels compared to that in patients with elevated LDL-C. The authors concluded that clinicians should be more focused on elevated Lp(a) levels as a cardiovascular risk factor[32].

Different apheresis methods show similar lowering effects on Lp(a) of about 60-70% in a single session. Hovland *et al.* studied the effectiveness of different apheresis columns on lowering LDL-C and Lp(a) levels. They found that regardless of the apheresis column used, Lp(a) was lowered by approximately 70%. Moreover, three different LA columns reduced Lp(a) efficiently, with a preserved ratio between apo(a) isoforms[33].

In conclusion, it is reasonably well-established that Lp(a) is a cardiovascular risk factor, which is independent from total cholesterol, LDL-C, apolipoprotein B, hypertension, diabetes, obesity and smoking. Lp(a) level predicts the development of CVD and its prognostic weight is relevant when its levels are high. Lp(a) levels are not modulated by diet or exercise, since they appear to be largely genetically determined. Currently, plasma Lp(a) levels are not measured routinely in patients with CVD and genetic studies are not performed. However, monitoring and screening for this specific metabolic disorder could be considerably helpful in patients with a personal or family history of premature CAD, dyslipidaemia or hyperlipidaemia refractory to therapy. The European Atherosclerosis Society (EAS) Consensus Panel recommended that Lp(a) should be measured in patients with an intermediate or high risk of CVD or CHD. In particular, they suggested screening subjects presenting with:

- premature CVD;
- familial hypercholesterolaemia;
- a family history of premature CVD and/or elevated Lp(a);
- recurrent CVD despite statin treatment;
- a ≥3% 10-year risk of fatal CVD according to the European guidelines, and
- a ≥10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines[34].

A novel approach in order to promote early diagnosis in immunohaematology and transfusion medicine centres would be desirable. Evaluation of Lp(a) should be recommended not only in already diagnosed CVD patients for better clinical management, but also in healthy donors. Early diagnosed patients, without complications, would benefit from prompt treatment to increase life expectancy, while improving the quality of the public health service, and preventing the development of new CVD events.

Finally, novel therapies, which are biological drugs in most cases, may be used in the future treatment of hyperLp(a). Given the critical role of Lp(a) synthesis in determining Lp(a) levels, targeting either the synthesis of apo(a) and/or the assembly of Lp(a) would appear helpful[35]. Antisense oligonucleotides and thyroid hormone analogue therapies directed at apo(a) synthesis may be the promises for the future[36,37]. However, it must be acknowledged that, at least for now, the most effective and safe treatment available is LA.

The Authors declare no conflicts of interest.

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