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Editorial

Therapeutic lowering of lipoprotein(a): How much is enough?

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The way of lipoprotein(a) [Lp(a)] into the cardiovascular disease (CVD) arena is long and bumpy [1], and the lack of an optimal animal model to perform extended basic research might have contributed to delays in the journey [2]. Starting with association studies in the 1970s, the first Mendelian randomization studies provided a strong support for a causal association between high Lp(a) concentrations and cardiovascular outcomes [3], which were confirmed by most but not all later studies [1]. A meta-analysis including 7382 CVD cases and 8514 controls identified a 2.08-fold increased risk for carriers of small apolipoprotein(a) [apo(a)] isoforms who have on average markedly elevated Lp(a) concentrations [4]. This strong association makes Lp(a) probably one of the most important genetic risk factors for CVD, if we keep the high frequency of small apo(a) isoforms in the population in mind [1]. Some investigations, including patients in the secondary prevention setting [5,6], were not always in line with population-based studies for various reasons, as previously discussed by Boffa and colleagues [7].

Until recently, all interventions with drugs, as well as lipid apheresis that resulted in a lowering of Lp(a), changed also other lipoproteins such as LDL-C, HDL-C or triglycerides. This did not allow to clearly disentangle the effects of the various changes of lipoproteins on clinical outcomes. One of the best examples is lipoprotein apheresis, in which both LDL-C and Lp(a) are reduced by 60–70%, as well as a massive decrease in CHD events. One of these studies included a subgroup of patients with Lp(a) concentrations above the 90th percentile, in whom the amount of Lp(a)-corrected LDL-C was already very low before the onset of apheresis. Interestingly, the reduction in CHD events was about the same as in the other group in which LDL-C could additionally be lowered by apheresis. This means that, in the first group with the "Lp(a) alone elevation", the reduction of CHD events is probably due to the decrease in Lp(a) concentrations [8].

A recently introduced antisense oligonucleotide drug targets apo(a), the characteristic apolipoprotein of the Lp(a) particle, and thereby directly and only influences the production of Lp(a) without an influence on any other lipoprotein [9]. This drug is game-changing since it allows to study the isolated change of this atherogenic lipoprotein. After successful phase 1 and 2 studies, the field is eagerly awaiting phase 3 trials for this type of drugs.

One of the burning questions for the planning of upcoming phase 3 trials is how strong has Lp(a) to be lowered to result in clinical benefits. This can only be roughly estimated by various approaches, which are all characterized by uncertainties. Therefore, the field is grateful for any piece of observation, which might help improve the predictions. In the present issue of *Atherosclerosis*, Ray and colleagues performed a *post-hoc* analysis of data pooled from 10 controlled phase 3 ODYSSEY trials with the PCSK9 inhibitor alirocumab, in 4,983 patients characterized by established CVD or the presence of CVD risk factors without established CVD or heterozygous familial hypercholesteremia, and in whom LDL-C concentrations were not yet sufficiently controlled at the time of enrollment [10]. Besides the expected LDL-C reductions, Lp(a) was significantly reduced by 20–25%. The authors calculated that a 25% reduction in Lp(a) was associated with a 12% relative risk reduction ($p = 0.0254$), which was no longer significant after adjustment of LDL-C changes. However, this association remained significant in a fully adjusted model when only study participants with Lp(a) concentrations ≥50 mg/dL were considered with a relative risk reduction of 40% ($p = 0.0201$) compared to 6% in patients with Lp(a) below 50 mg/dL ($p = 0.3837$) (Table 1).

Similar observations have been made by a recent analysis from the FOURIER Trial: the PCSK9 inhibitor evolocumab reduced the risk of CVD outcomes by 23% in patients with a baseline Lp(a) > median of 37 nmol/L (≈15 mg/dL), and by 7% in those ≤ median (p-value interaction = 0.07). The conclusion was the same when 120 nmol/L (≈50 mg/dL) instead of the median was used as grouping threshold. The study observed a significant relationship with a 15% lower risk (95%CI, 2%–26%; $p = 0.0199$) per 25 nmol/L (≈10 mg/dL) reduction in Lp(a) after adjusting for the change in LDL-C [11]. This would mean that even relatively low changes of Lp(a) should result in a clinical benefit.

Recently, data from the ODYSSEY OUTCOMES Trial have been presented at the American Colleague Cardiology Session (March 2019) (https://www.acc.org/latest-in-cardiology/clinical-trials/2018/03/09/08/02/odyssey-outcomes). The authors showed that Lp(a)-lowering by alirocumab contributes to a reduction of major adverse cardiovascular

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Table 1
Calculations from *post-hoc* analyses from PCSK9 trials as well as Mendelian randomizations studies to estimate the effect of Lp(a)-lowering on clinical outcomes.

Publication	Study description	Main findings
***Post-hoc* analyses**		
Pooled data from 10 controlled phase 3 ODYSSEY trials [10]	4,983 patients with established CVD or presence of CVD risk factors without established CVD or heterozygous familial hypercholesteremia	Relative risk reduction per 25% reduction of Lp(a) adjusted for LDL-C changes: for group with Lp(a) ≥50 mg/dL: HR = 0.60 (95%CI 0.39–0.92), $p = 0.0201$ for group with Lp(a) < 50 mg/dL: HR = 0.94 (95%CI 0.81–1.09), $p = 0.3837$
FOURIER trial [11]	Intervention study of 25,096 patients treated by evolocumab *vs.* placebo in patients with established CVD	Lp(a) > median of 37 nmol/L: HR = 0.77 (0.76–0.88) *vs.* ≤median: 0.93 (0.80–1.08) Lp(a) > 120 nmol/L: HR = 0.75 (0.64–0.88) *vs.* ≤120 nmol/L: 0.89 (0.79–1.01)
ODYSSEY OUTCOMES Trial[a]	18,924 patients with recent acute coronary syndrome and LDL-C ≥70 mg/dL despite intensive or maximum tolerated statin treatment	Proportion of MACE reduction attributable to changes in Lp(a) increased from 4% to 11% to 27% for Lp(a) levels at the 25th, 50th, and 75th percentiles, respectively. Lowering of Lp(a) by 42% would be required to lower the MACE rate by 22%
Mendelian randomization studies		
Burgess et al. [12]	5 population-based prospective cohort and case-control studies including 20,793 individuals with CHD and 27,540 controls. Lp(a) concentration was measured in 34,276 individuals using various assays	A 101.5-mg/dL change (95%CI, 71.0–137.0) in Lp(a) concentration had the same association with CHD risk as a 38.67-mg/dL change in LDL-C level
Lamina & Kronenberg [14]	13,781 individuals from the Lp(a)-GWAS-Consortium from 5 primarily population-based studies in whom Lp(a) was measured with the same assay in a single laboratory.	A 65.7 mg/dL change (95%CI 46.3–88.3) in Lp(a) concentration had the same association with CHD risk as a 38.67-mg/dL change in LDL-C level
Kamstrup & Nordestgaard[b]	2,527 individuals from the Copenhagen General Population Study with a history of CVD.	Using data from a secondary prevention setting revealed that a ≈55 mg/dL change in Lp(a) concentration is required to have the same association with CHD risk as a 38.67-mg/dL change in LDL-C level

[a] Presented at the American Colleague Cardiology Session (March 2019) (https://www.acc.org/latest-in-cardiology/clinical-trials/2018/03/09/08/02/odyssey-outcomes).
[b] Presented during the Congress of the European Atherosclerosis Society and the satellite meeting "The imminent danger of Lp(a): Time to face the challenge" in Maastricht 2019.

events (MACE) independently of LDL-C-lowering in 18,924 patients with recent acute coronary syndrome and LDL-C ≥70 mg/dL despite intensive or maximum tolerated statin treatment. Most importantly, the proportion of MACE reduction attributable to changes in Lp(a) caused by alirocumab treatment increased from 4% to 11% to 27% for Lp(a) levels at the 25th, 50th, and 75th percentiles, respectively. From these data, it has been calculated that a lowering of Lp(a) by 42% would be required (but with very wide confidence intervals) to lower the MACE rate by 22%.

Most importantly, all these studies have in common that they were not designed to target a population with high Lp(a) concentration but to target patients with CVD and or high-risk equivalents without any selection criterion on Lp(a) concentrations. Therefore, the median Lp(a) concentrations were far below the values one would use for selecting patients to specifically study the effect of Lp(a)-lowering on MACE reduction. Nevertheless, these *post-hoc* analyses support the idea that lowering Lp(a) will have an effect on clinical outcomes.

A completely different approach has recently been performed by a Mendelian randomization examination using genetic data from association studies on Lp(a) and LDL-C concentrations, as well as association studies on CHD analysis, to estimate the required Lp(a)-lowering effect size to show the same association with CHD risk-lowering as a 38.67-mg/dL (1 mmol/L) therapeutic reduction in LDL-C. This intriguing idea revealed that Lp(a) would have to be lowered by 101.5 mg/dL to show the same effect as lowering LDL-C by 38.67 mg/dL [12]. This number was probably markedly overestimated since the main study on which these results are based on had median Lp(a) concentration 2-fold–3-fold higher compared to other studies of the same ethnicity. We therefore repeated these calculations using the same approach and the same data basis except for the estimates of various SNPs on Lp(a) concentrations. For these, we used our own data from almost 14.000 individuals in whom Lp(a) was measured within one laboratory and with median Lp(a) levels in the range of expectations for typical Caucasian populations [13]. We calculated that an Lp(a)-lowering of roughly 65 mg/dL would be required instead of more than 100 mg/dL [14]. These data were mainly based on population-based data and it is not clear whether these holds also true for secondary prevention patients. Exactly this situation has been tested by the Copenhagen General Population Study and the authors, represented by Pia Kamstrup and Borge Nordestgaard, showed first results during the Congress of the European Atherosclerosis Society and the satellite meeting "The imminent danger of Lp(a): Time to face the challenge" in Maastricht 2019. They calculated that even a smaller Lp(a)-lowering is required (≈55 mg/dL) when the data are used from a secondary prevention setting, a setting that will probably be used in the first phase 3 trials. For all these studies, it has to be added that the comparison with an LDL-lowering of 38.67 mg/dL was only used as benchmark, which results in a 22% lowering of MACE for LDL-C [15]. Of course, even smaller lowering might be beneficial as it has been demonstrated for LDL-C.

Limitations for this Mendelian randomization approach come from various assumptions, which have to be considered with cautions: first, it is unclear whether Lp(a) and LDL-C particles have a similar cumulative effect on CVD over time, or in other words, whether they have the same atherogenic potential? This is not necessarily the case since there is some evidence that even Lp(a) particles of different apo(a) isoforms have different atherogenic potential [16,17]. Second, besides an atherogenic nature of Lp(a), some data point also to a thrombogenic nature [18,19]. If this is also the case *in vivo*, the pathogenic mechanism of Lp(a) might even be stronger than for LDL-C and the lowering of Lp(a) would have an additional benefit on the thrombogenic axis.

All the available observations - independent of whether they are coming from *post-hoc* analysis of intervention studies or from Mendelian randomization studies - can only be supporting tools for the planning of future trials. These trials will have to consider the uncertainties connected with these data, such as more or less wide confidence intervals of the estimates. One of these uncertainties are introduced by the insufficiently standardized Lp(a) assays used in the various studies. This became obvious when looking at the data presented by Burgess et al. with the above mentioned very high Lp(a) concentrations in their main cohort [12]. An overestimation of the Lp

(a) concentration by an insufficiently standardized assay might result in a misclassification of patients to be at high risk and an enrollment of patients, which would otherwise not be appropriate for the study. Therefore, major efforts should be invested in the screening phase for suitable study patients to avoid misclassification of patients by inappropriate Lp(a) assays.

In summary, the causal association between high Lp(a) concentrations and CVD is strongly supported by genetic studies. *Post-hoc* analyses following intervention studies with PCSK9-inhibitors that targeted primarily LDL-C, but additionally lower also Lp(a) as done by Ray and colleagues, provide some evidence that an additional lowering of Lp(a) besides LDL-C is beneficial. However, these studies were not designed to target patients with high Lp(a) levels and are therefore limited. Mendelian randomization studies provide further strong support that lowering Lp(a) might be beneficial, but the estimates of how much is enough are wide. Combining all these observations supports the idea to include, in first phase 3 trials, patients with Lp(a) concentrations above 100 mg/dL and not patients with Lp(a) concentrations close to 50 mg/dL. Patients with concentrations between 50 and 100 mg/dL could be studied after the first phase 3 results are available, which will specify the potential of these drugs on clinical outcomes more precisely. Even if the current observations are associated with some uncertainties, the Lp(a) field is in a luxury position compared to the HDL field two decades ago: if the genetic data on HDL-C and the Mendelian randomization experience had been already available at that time, drugs that increase HDL-C such as CETP inhibitors would probably not have been developed or such drugs would have targeted other proteins or lipids of the multifaceted HDL particles [20,21]. With the evidence we have now for Lp(a), it is better justified to get phase 3 trials running and to plan the inclusion criteria in a way to be on the safe side concerning a beneficial outcome.

Conflicts of interest

FK has received honoraria related to consulting or speaker activities from: Amgen, Fresenius, Kaneka and Miltenyi Biotech.

References

[1] F. Kronenberg, G. Utermann, Lipoprotein(a) - resurrected by genetics, J. Intern. Med. 273 (2013) 6–30.

[2] K.M. Kostner, G.M. Kostner, A.S. Wierzbicki, Is Lp(a) ready for prime time use in the clinic? A pros-and-cons debate, Atherosclerosis 274 (2018) 16–22.

[3] C. Sandholzer, N. Saha, J.D. Kark, et al., Apo(a) isoforms predict risk for coronary heart disease: a study in six populations, Arterioscler. Thromb. 12 (1992) 1214–1226.

[4] S. Erqou, A. Thompson, A.E. Di, et al., Apolipoprotein(a) isoforms and the risk of vascular disease: systematic review of 40 studies involving 58,000 participants, J. Am. Coll. Cardiol. 55 (2010) 2160–2167.

[5] P. Willeit, P.M. Ridker, P.J. Nestel, et al., Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials, Lancet 392 (2018) 1311–1320.

[6] S. Zewinger, M.E. Kleber, V. Tragante, et al., Relations between lipoprotein(a) concentrations, LPA genetic variants, and the risk of mortality in patients with established coronary heart disease: a molecular and genetic association study, Lancet Diabetes Endocrinol 5 (2017) 534–543.

[7] M.B. Boffa, S. Stranges, N. Klar, et al., Lipoprotein(a) and secondary prevention of atherothrombotic events: a critical appraisal, J Clin Lipidol 12 (2018) 1358–1366.

[8] B.R. Jaeger, Y. Richter, D. Nagel, et al., Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events, Nat. Clin. Pract. Cardiovasc. Med. 6 (2009) 229–239.

[9] N.J. Viney, J.C. van Capelleveen, R.S. Geary, et al., Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials, Lancet 388 (2016) 2239–2253.

[10] K.K. Ray, A.J. Vallejo-Vaz, H.N. Ginsberg, et al., Lipoprotein(a) reductions from PCSK9 inhibition and major adverse cardiovascular events: pooled analysis of alirocumab phase 3 trials, Atherosclerosis 288 (2019) 194–202.

[11] M.L. O'Donoghue, S. Fazio, R.P. Giugliano, et al., Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk, Circulation 139 (2019) 1483–1492.

[12] S. Burgess, B.A. Ference, J.R. Staley, et al., Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a mendelian randomization analysis, JAMA Cardiol 3 (2018) 619–627.

[13] S. Mack, S. Coassin, R. Rueedi, et al., A genome-wide association meta-analysis on lipoprotein(a) concentrations adjusted for apolipoprotein(a) isoforms, J. Lipid Res. 58 (2017) 1834–1844.

[14] C. Lamina, F. Kronenberg, Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes: a mendelian randomization analysis, JAMA Cardiol 4 (2019) 575–579, https://doi.org/10.1001/jamacardio.2019.1041 in press.

[15] C. Baigent, L. Blackwell, J. Emberson, et al., Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, Lancet 376 (2010) 1670–1681.

[16] F. Kronenberg, M.F. Kronenberg, S. Kiechl, et al., Role of lipoprotein(a) and apolipoprotein(a) phenotype in atherogenesis: prospective results from the Bruneck Study, Circulation 100 (1999) 1154–1160.

[17] D. Saleheen, P.C. Haycock, W. Zhao, et al., Apolipoprotein(a) isoform size, lipoprotein(a) concentration, and coronary artery disease: a mendelian randomisation analysis, Lancet Diabetes Endocrinol 5 (2017) 524–533.

[18] M.B. Boffa, M.L. Koschinsky, Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? J. Lipid Res. 57 (2016) 745–757.

[19] R. Romagnuolo, C.A. Scipione, Z.A. Bazzi, M.B. Boffa, M.L. Koschinsky, Inhibition of pericellular plasminogen activation by apolipoprotein(a): roles of urokinase plasminogen activator receptor and integrins aMb2 and aVb3, Atherosclerosis 275 (2018) 11–21.

[20] F. Kronenberg, High-density lipoprotein cholesterol on a roller coaster: where will the ride end? Kidney Int. 89 (2016) 747–749.

[21] F. Kronenberg, HDL in CKD - the devil is in the detail, J. Am. Soc. Nephrol. 29 (2018) 1356–1371.

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