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EDITORIAL
Coronary artery disease

Lipoprotein(a): the enemy that we still don't know how to defeat

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This editorial refers to 'Cardiovascular outcomes in patients with coronary artery disease and elevated lipoprotein(a): implications for the OCEAN(a)-outcomes trial population', by A. Shiyovich *et al.*, https://doi.org/10.1093/ehjopen/oead077.

Despite the fact that lipoprotein (a) [Lp(a)] was discovered in 1963, 60 years ago, it still causes many problems, which are associated with awareness, diagnosis, and especially effective therapy.[1] A survey of the European Atherosclerosis Society Lipid Clinic Network (EAS LCN), based on data from 151 centres, showed that the proportion of clinicians who declare that they routinely measure Lp(a) in clinical practice was 75.5%. However, there were dramatical differences between Western countries, where as many as 90% of physicians routinely measured Lp(a) measurements, and Central and Eastern European countries, where Lp(a) measurements were ordered in only 50% of cases. This latter figure may even be overestimated, as it relates to patients treated in LCNs where levels of knowledge and expertise are highest.[2] Poor performance in managing Lp(a) may result from inconsistencies and doubts relating to the diagnosis and management of hyper-Lp(a)-emia.[1] It is generally agreed that a Lp(a) concentration of ≥50 mg/dL (125 nmol/L) is associated with an elevated risk of cardiovascular disease (CVD), however, epidemiological data suggest that risk is increased above 30 mg/dL (75 nmol/L), with a grey zone of Lp(a) concentration (30–50 mg/dL), which may represent moderately increased risk.[3,4] We also know that there is some visit-to-visit variability of Lp(a)—especially in those with elevated levels of Lp(a), and there are some factors and conditions that might affect this, including chronic kidney disease, thyroid diseases, pregnancy, menopause, as well as low carbohydrate diet/ketogenic diet rich in saturated fatty acid. This issue is often recently raised by patients who wish to employ lifestyle measures to reduce Lp(a).[3,5] Similar variabilities may also exist for other lipoproteins, but questions remain around physicians' knowledge on this topic and on the real effect of non-genetic conditions and risk factors.[3,5] An exhaustive attempt to address some of these burning questions has been recently published and should be very useful in every-day clinical practice.[5]

The real problem, however, relates to identifying targeted therapy to lower Lp(a).[1] Statins may even increase Lp(a) levels, however, this is unlikely to have any clinical relevance, and there is no recommendation to discontinue statin therapy in those patients—and statins nevertheless significantly reduce the overall risk of CVD.[3–6] However, there are also some data suggesting (hyper)responsiveness to statin therapy in some individuals, and it seems that this may especially be the case in those with a low molecular weight apo(a) phenotype. In these individuals, a mean absolute increase even >30 mg/dL (>40%) may be observed.[6] The role of pitavastatin in the potential reduction (or maybe lack of increase) of Lp(a) concentration requires further investigation.[4] Ezetimibe seems to be neutral with respect to Lp(a) levels, likewise bempedoic acid.[3–5] Based on the available data, niacin might be beneficial (unfortunately, it is unavailable in Europe). In particular, it may decrease Lp(a) in a dose-dependent manner by ∼30–40% on average, and by ∼20% in those with the highest Lp(a) levels.[4] It is also worth emphasizing that the final response to niacin is associated with the apo(a) isoform size. In those with the highest Lp(a) levels and smallest isoform sizes the smallest percentage reductions, but the highest absolute reductions are observed.[7] However, apart from apo(a) isoform size, niacin also binds to the LPA gene promoter region.[7,8] The above-mentioned indicates that we should recommend genetic/molecular testing for patients with elevated Lp(a) and to consider available therapies (statins, niacin, and PCSK9 inhibitors) based on the patient's genetic profile.[7,8] It is somewhat surprising that there are no recommendations relating to the use of niacin to reduce Lp(a), based on the negative results from the outcomes trials that were not designed to investigate this effect, especially as we have data that demonstrates that extended-release niacin can lower Lp(a) by over 60%.[3,4,7] Finally, in last few years, it has been demonstrated that PCSK9-targeted therapies have a potential added benefit of Lp(a) lowering by 20–30%. Based on the available data from the FOURIER and ODYSSEY OUTCOMES sub-analyses, this resulted in an absolute CVD risk reduction from 2.4% to 3.7%.[9] However, we face with the problem of very limited reimbursement for this indication (available in only a few European countries), and the fact that PCSK9 inhibitors are not licenced for Lp(a) lowering.[3,4]

However, in order to increase awareness of Lp(a), and to encourage its routine measurement, targeted therapy is necessary. Only then we

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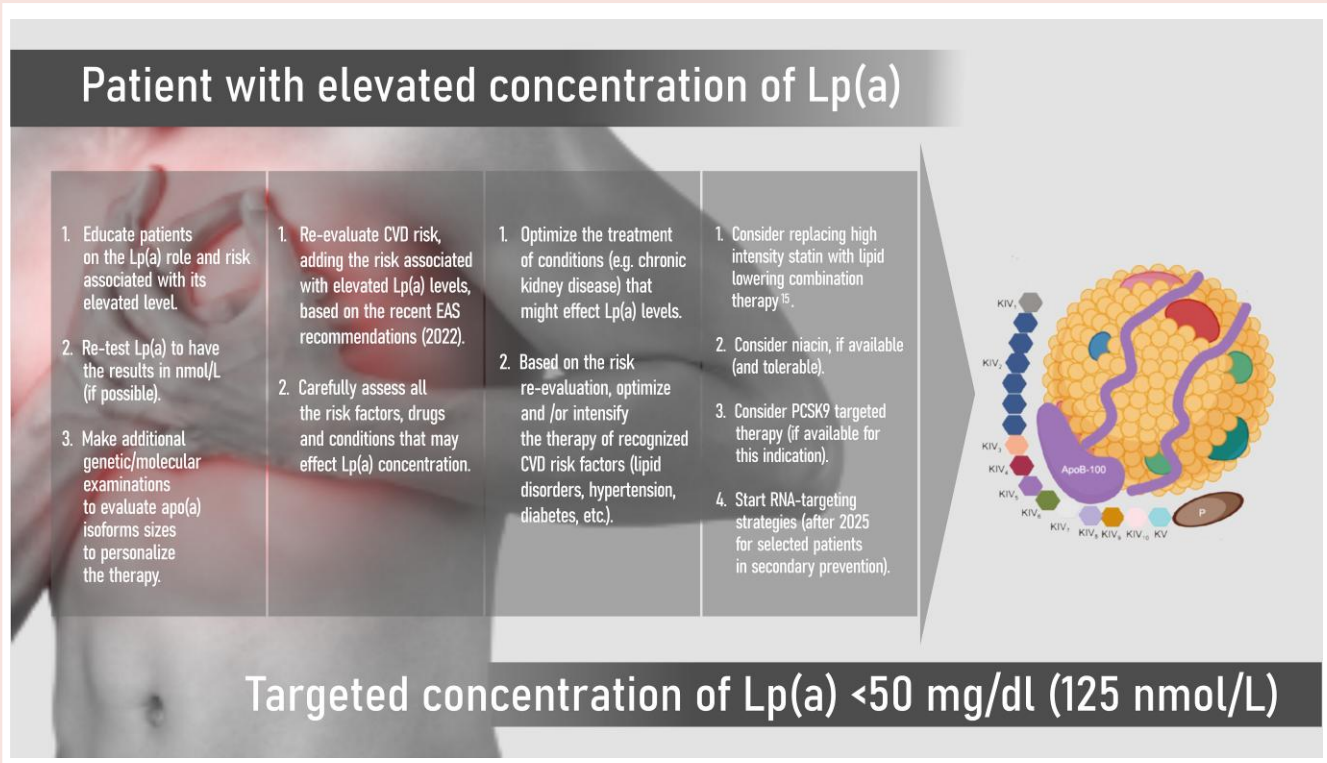

Figure 1 The suggested pathway of management with patients with elevated Lp(a) concentration. *The picture of Lp(a) was reprinted and modified from Liu, T et al. Chonnam Med J. 2021, 57, 36–43[14] (no permission required).

will be able to significantly reduce Lp(a) to very low and extremely low levels, and thereby reduce the Lp(a)-related residual risk of CVD.[1] This can be achieved using specific Lp(a)-lowering drugs, which perturb apolipoprotein(a) [apo(a)] synthesis in hepatocytes using RNA-targeting strategies. Pelacarsen (60–80 mg, administered subcutaneously every 4 weeks) is a single-strand antisense oligonucleotide (ASO) that binds to the RNA for apo(a) resulting in even 80% reduction in Lp(a) plasma concentrations.[1] Another RNA-targeting strategy uses small interfering RNA (siRNA) with three agents in development (olpasiran, SLN360, and new LY-3819469—now in phase 2 trials).[1,3] Based on the available data, these drugs (administered subcutaneously every 3–6 months) lead to Lp(a) reduction by as much as >90%. However, we need to wait for the results from the CVD outcomes studies that are expected to be released in 2025 [Lp(a)HORIZON for pelacarsen] and 2026 [OCEAN(a) study for olpasiran].[1,3,5]

In the current issue of *European Heart Journal Open*, Shiyovich *et al.* aimed to evaluate the association of elevated Lp(a) with CVD outcomes in an observational cohort from the large Mass General Brigham (MGB) Lp(a) Registry, adapting the same main enrollment criteria as the ongoing OCEAN(a)-Outcomes trial.[10,11] The study included patients with a history of myocardial infarction (MI) or percutaneous coronary intervention (PCI) and elevated Lp(a) levels ≥ 200 nmol/L (≥93.5 mg/dL); patients with severe kidney dysfunction (eGFR < 15 mL/min/m^2) and those with a renal transplant, or on dialysis, were excluded. The primary outcome was a composite of death from coronary heart disease (CHD), MI, or coronary revascularization [despite the fact that in the OCEAN(a) trial, the main composite endpoint is defined as a time to CHD death, MI, or urgent coronary revascularization].[10,11] Of the 16 821 patients in the registry, 3142 (18.7%) met the eligibility criteria and were included in the study. The study population had a median age 61 years, 28.6% were women, and 12.3% had elevated Lp(a). About 90% received statin therapy in both groups, however, those with elevated Lp(a) had a higher prevalence of non-statin lipid-lowering therapies (24.9% vs. 14.4%, $P < 0.001$). Over a median follow-up of 12.2 years, the primary composite outcome occurred more frequently in patients with elevated Lp(a) (46.0% vs. 38.0%, HR = 1.30; 95%CI: 1.09–1.53, $P = 0.003$), and elevated Lp(a) remained independently associated with the primary outcome after adjustment for multiple measured confounders (adjHR = 1.33; 95%CI: 1.12–1.58, $P = 0.001$). Elevated Lp(a) was also associated with increased risk for all secondary outcomes, including MI (adjHR: 1.40; 1.11–1.78, $P = 0.005$), coronary revascularization (1.42; 1.14–1.75, $P = 0.001$), CHD death (1.52; 1.16–2.01, $P = 0.003$), and CV death (1.39; 1.10–1.74, $P = 0.005$), except ischaemic stroke and all-cause mortality.[10]

First of all, I would like to congratulate the authors for this important analysis, but especially for their well-designed Lp(a) registry. We should all follow their lead in order to increase the knowledge of Lp(a) in different regions in the world. These are indeed important results, once again, showing that elevated Lp(a) may additionally and independently increase risk in those already being at a very high or even extremely high risk, already treated with statin therapy and combination lipid-lowering therapy.[10] Obviously, we do not have any knowledge on the use of high intensity statins (HIS) in both groups, or which non-statin therapies were applied. Therefore, it is unclear whether we would see the same results with optimally treated post-MI patients, with an upfront lipid lowering therapy combination therapy of HIS and ezetimibe, with bempedoic acid and/or PCSK9-targeted therapy approach (which by itself may significantly reduce Lp(a) levels). Another open question is how and when new therapy will be administered, and which patients will be indicated first, considering drug licencing and indications based on forthcoming recommendations and

reimbursement criteria. Based on the hitherto knowledge, we may recommend the following pathway of management (*Figure 1*). If we consider the inclusion criteria in CVD outcomes trials, the registration/indication for pelacarsen and olpasiran is likely to be for very high risk or extremely high risk patients with the history of atherosclerotic cardiovascular disease (ASCVD), defined as MI and/or coronary revascularization with PCI and at least one additional risk factor or [based on Lp(a)Horizon trial] with ischaemic stroke (≥3 months from screening) or clinically significant symptomatic peripheral artery disease, and elevated Lp(a) levels ≥ 70–93.5 mg/dL (175–200 nmol/L).[11,12] This means that a very selected group of patients after the study will be released, and assuming their positive results, will benefit from these highly effective therapies. Taking into account, e.g. Polish population with ∼80 000 acute coronary syndromes per year, abovementioned criteria suggest that a maximum of 6400 patients annually might benefit from these drugs [assuming 8% of those with per criteria elevated Lp(a) levels].[3,13] What about those from the grey zone of Lp(a) concentrations between 50 and 70 mg/dL (125–200 nmol/L) or even 30–70 mg/dL (75–200 nmol/L)? What about those with established ASCVD and elevated Lp(a) levels in order to prevent the first event of MI or stroke? Finally, what about those at high and very high CVD risk in primary prevention, for whom elevated Lp(a) level ≥ 50 mg/dL additionally increases the risk? Those questions cannot stay unanswered, especially when new drugs become available.

Data availability

No new data were generated in support of the article.

Conflict of interest: (36 months) Maciej Banach: speakers bureau: Amgen, Daiichi Sankyo, Kogen, KRKA, Polpharma, Novartis, Novo-Nordisk, Pfizer, Sanofi, Teva, Viatris, Zentiva; consultant to Adamed, Amgen, Daichii Sankyo, Esperion, NewAmsterdam, Novartis, Novo-Nordisk, Sanofi; grants from Amgen, Daiichi Sankyo, Sanofi, and Viatris, CMDO at Longevity Group; CMO at Nomi Biotech Corporation.

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