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EDITORIAL
Epidemiology and prevention

New data allow to better understand the secrets of lipoprotein(a): is that for sure?

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Elevated lipoprotein(a) [(Lp(a)] is more and more commonly recognized and diagnosed independent cardiovascular disease (CVD) risk factor, affecting even 1.5 billion people worldwide (more common than hypertension, diabetes, or obesity).[1] Its concentration is largely associated with genetic factors (≥90%) including *LPA* kringle IV-2 domain size and single-nucleotide polymorphisms. In last few years, however, we have had more and more knowledge on the environmental risk factors, conditions, and therapies that may significantly affect Lp(a) levels, what can be responsible for observed visit-to-visit Lp(a) level variability (*Figure 1*).[2] Additionally, Lp(a) values can fluctuate by about ±25%, as observed in serial blood sample measurements from placebo groups in randomized trials aimed at lowering Lp(a).[5] The above has been a reason that more and more experts and recommendations suggest a need to have more than one Lp(a) measurement, emphasizing also the importance of the first measurement in people under 18 years of age for risk assessment, cascade screening, monitoring, and lifestyle modification.[2]

The abovementioned has been recently extensively discussed in a study by Harb *et al.*,[6] published in *European Heart Journal Open* (*EHJ Open*) simultaneously with the European Society of Cardiology (ESC) Congress 2024 presentation in London. The authors aimed to determine, in a retrospective analysis with 609 individuals in the Nashville Biosciences database, the intraindividual variability of Lp(a) and whether a repeated measure (within median 1.07 years) reclassified Lp(a)-specific CVD risk. Lp(a) concentrations changed by >10 mg/dL (~25 nmol/L) in 38.1% (95% CI 34.2–42%) and in 40.5% (95% CI 36.6–44.3%) by >25% of the individuals. Levels and the changes were greater in women compared to men and in Black individuals compared to White individuals. A total of 53% of participants classified at the beginning for the intermediate grey zone category transitioned to either the low (20%)- or high (33%)-risk category. Lp(a) variability was assessed in individuals undergoing lipid-lowering treatments. The initial median Lp(a) level was higher among those treated with niacin or a PCSK9 inhibitors (57 [21–92] mg/dL) compared to those not treated (26.5 [11–64] mg/dL, $P < 0.01$). Additionally, the median absolute change in Lp(a) was greater in the treated (9 [3–21] mg/dL) than in the untreated group (5 [2–12] mg/dL, $P < 0.01$). A change of ≥10 mg/dL (~25 nmol/L) occurred in 48.5% of the treated group vs. 31.8% of the untreated group ($P < 0.01$). Interestingly, no significant differences in Lp(a) levels were observed between patients on statin therapy and those without. Despite evident limitations (retrospective nature of the analysis, and some incomplete/inaccurate data on patients' characteristics and therapy), the results of this study again indicate that a repeat Lp(a) measure may allow for more precise Lp(a)-specific CVD risk prediction.[6]

In Europe, depending on the investigated population and the CVD risk, as many as 20% of people have Lp(a) level ≥ 50 mg/dL (125 nmol/L) and 25–30% ≥30 mg/dL (75 nmol/L).[7] Elevated Lp(a) levels are significantly associated with the risk of CVD risk and all-cause (ACM) and CVD mortality. It was shown that for the top vs. bottom tertile of Lp(a) levels, the ACM risk was 1.09 (95% CI: 1.01–1.18) in the general population and 1.18 (95% CI: 1.04–1.34) in CVD patients. The risk for CVD mortality was 1.33 (95% CI: 1.11–1.58) in the general population, 1.25 (95% CI: 1.10–1.43) in CVD patients, and 2.53 (95% CI: 1.13–5.64) in patients with diabetes mellitus (*Figure 1*).[8] One should also always think about elevated Lp(a) levels in patients with premature atherosclerotic cardiovascular disease (ASCVD), specifically with premature myocardial infarction (MI).[9] This link was investigated in a recent meta-analysis by Tian *et al.*,[10] including 51 studies with 100 540 participants, that summarized the impact of Lp(a) levels on the risk of various ASCVDs. Higher Lp(a) in young was significantly associated with the composite ASCVD (odds ratio [OR] 2.15; 95% CI: 1.53–3.02), coronary artery disease (OR 2.44; 95% CI: 2.06–2.90), and peripheral arterial disease (OR 2.56; 95% CI: 1.56–4.21), as well as in those with familial hypercholesterolaemia and diabetes (OR: 3.11 and 2.23, respectively), regardless of study design, gender, population characteristics (community or hospitalized), different premature ASCVD definitions, and various Lp(a) measurement approaches.[10] Despite the study did not confirm the significant association with the

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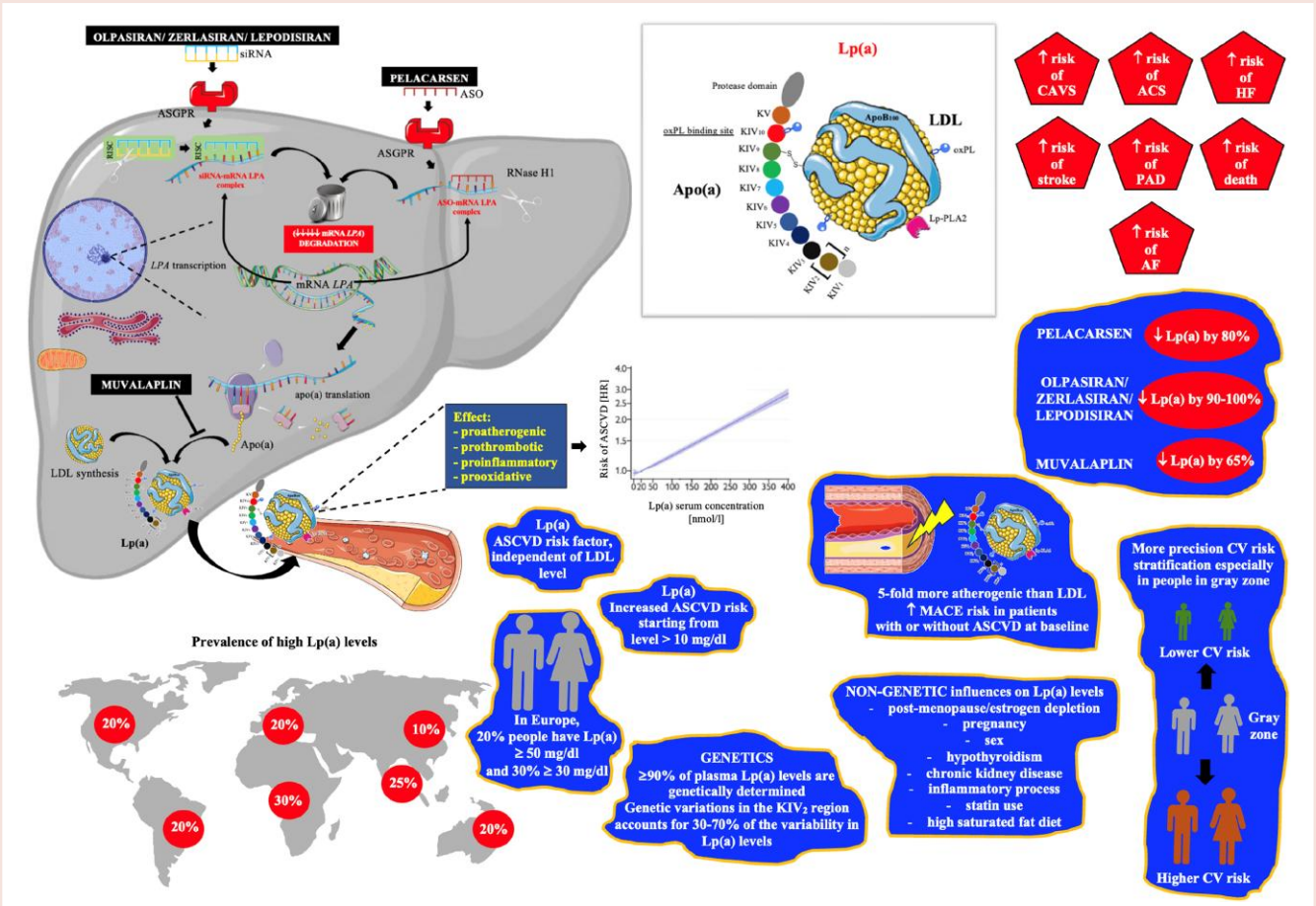

Figure 1 Key facts about lipoprotein(a). Based on information from Sosnowska *et al.*,[1] Ziogos *et al.*,[3] and Moriarty *et al.*[4] ASGPR, asialoglycoprotein receptor; ASO, antisense oligonucleotides; siRNA, small interfering; LPA, lipoprotein(a) gene; LDL, low density lipoprotein; ASCVD, atherosclerotic cardiovascular; RNA, ribonucleic acid; LPA, lipoprotein(a) gene; LDL, low density lipoprotein; ASCVD, atherosclerotic cardiovascular disease; Lp(a), lipoprotein(a); apo(a), apolipoprotein(a); RICS, RNA-induced silencing complex; $ApoB_{100}$, apolipoprotein B_{100}; oxPL, oxidized phospholipids; Lp-PLA2, lipoprotein-associated phospholipase A2; CAVS, calcific aortic valve stenosis; ACS, acute coronary syndrome; HF, heart failure; PAD, peripheral artery disease; AF, atrial fibrillation; MACE, major cardiovascular event.

risk of stroke, other studies yielded opposite results,[1,2,11] suggesting that elevated Lp(a) concentration is also a significant risk factor for ischaemic stroke (1.60-fold risk), but also aortic valve stenosis (2.90-fold risk), heart failure (1.79-fold risk), and acute coronary syndrome (2.47-fold risk—what was also observed in the above study[10] for both stable angina and ACS [OR: 2.95], ACS only [OR: 2.70], and MI [OR: 1.88]).[10,11] It should be emphasized that Lp(a) is five times more atherogenic compared to LDL and increases the risk of major cardiovascular event independently of LDL levels in patients with or without ASCVD at baseline.[12,13]

The pro-atherogenic effect of Lp(a) is also related to its prothrombotic and pro-inflammatory effects (oxidized phospholipid content, cytokine, and interleukin release and monocyte chemotaxis).[1,2] There has been also a discussion whether Lp(a) might be an acute phase reactant (APR). Ziogos *et al.*[3] have recently investigated the changes in serum lipoprotein(a) levels in individuals with ACS within 24 h of hospital admission and six months following the event. Median Lp(a) levels increased from 53.5 nmol/L (19, 165) during hospital admission to 58 nmol/L (14.8, 176.8; 8.4% increase; absolute median increase by 4.5 nmol/L) six months after the acute MI ($P = 0.02$). Lp(a) levels increase by at least 25 nmol/L in >20% of patients. This pattern differs from that of hsCRP, indicating that Lp(a) does not act as an APR during AMI. However, in the available literature, Lp(a) was found as an APR and was observed to be significantly elevated in patients with sepsis, after surgery, viral infections, and MI.[4,14] A total of 51% of patients in the Ziogos *et al.* study were not taking statins or were on low-dose statin therapy at baseline, while after 6 months, 95% were taking moderate- or high-intensity statins what could have led to Lp(a) elevation by ~6–10%.[2] However, a linear regression model analysing the difference in Lp(a) levels showed that neither initial statin therapy nor changes in statin therapy during the study influenced Lp(a) levels between baseline and follow-up.[3] A more detailed analysis would be of interest as some available data suggest different effect of different statins (hydrophilic vs. lipophilic, and especially of pitavastatin), and different statins' effect in relation to apo(a) isoforms.[1,2,11] A limitation of this study is no information on the study participants' Lp(a) levels before MI, therefore, it is unknown whether the higher levels observed in the follow-up were a long-term consequence of the infarction or a return to lower, earlier infarction values. But in fact, the main question is on the clinical relevance of this increase, as it is only 4.5 nmol/L median absolute increase (~1.8 mg/dL). Similar changes in Lp(a) levels after ACS were found in another study where Lp(a) levels were measured

immediately after the intervention, 1 and 2 days later, and during a follow-up visit 3–6 months after the ACS. The median Lp(a) levels increased from mean 7.9 mg/dL at hospital admission to 8.4 mg/dL the next day, then to 9.3 mg/dL on the second day ($P < 0.001$) and reached 11.2 mg/dL at the follow-up visit ($P < 0.001$).[15] The above results suggest that repeated Lp(a) measures are useful, however, considering these small differences, the measurement during the hospitalization seems to be sufficient for the risk stratification and prediction.

The recently published studies on Lp(a) in *EHJ Open* bring us some new information on Lp(a) predictive role, risk stratification, and management, however still a lot of questions exist, mainly in relation to individual Lp(a) variability and recommendations on repetitive measurements, the patients populations that should be recommended to have Lp(a) measured, and especially on the management with the elevated Lp(a) levels. Most of the existing questions might be resolved with real-life data, when more patients will have Lp(a) measurements (it is still only few per cent) and when the results from randomized controlled trials with new drugs are available. But with the increasing number of patients with known Lp(a) levels, we finally need to have effective therapeutic tools, and not only in those at very high risk in secondary prevention (for whom new targeted drugs will be mostly recommended), but especially in primary prevention, to avoid ASCVD occurrence and the first cardiovascular event (*Figure 1*).

Data availability

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