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Editorial

Lipoprotein(a) and familial hypercholesterolemia: Partners in crime in heritable hyperlipidemia

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Familial hypercholesterolemia (FH), affecting an estimated 1 in 200–250 individuals globally, represents a well-known, heritable hyperlipidemia characterized by lifelong elevations in low-density lipoprotein (LDL) cholesterol levels and a concomitant markedly increased risk of premature atherosclerotic cardiovascular disease (ASCVD) [1]. In contrast, genetically determined high lipoprotein(a) (Lp(a)) levels represent a somewhat less known heritable hyperlipidemia despite high prevalence and increased attention in recent years [2–4]. Lp(a) consists of a cholesterol-laden LDL-like particle identified as a unique lipoprotein by the addition of the plasminogen-like glycoprotein, apolipoprotein(a) (apo(a)) [5]. Lp(a) levels vary widely between individuals and are primarily genetically determined by variation in the *LPA* gene coding for apo(a). Approximately 20% of European descent populations thus have genetically determined high Lp(a) levels (>42 mg/dL, >88 nmol/L), with levels in the top 10% of the concentration distribution associating with (and likely causally) two-to threefold increases in risk of coronary heart disease and aortic valve stenosis, but also increased risk of peripheral artery disease, ischemic stroke, and heart failure [4,6]. Accordingly, "hyper-Lp(a)-emia" may be considered the most common heritable hyperlipidemia affecting >1 billion individuals worldwide, although a substantially higher Lp(a) level than that found in 20% of the population is needed to equate the risk of heterozygous FH [7]. Further, as the Lp(a) cholesterol content is included in LDL cholesterol measurements, regardless of LDL cholesterol levels being measured directly or calculated from total and HDL cholesterol measurements, high Lp(a) levels may contribute to clinically diagnosed (using scoring systems) FH through points given based on LDL cholesterol levels, as well as through points for index patient and/or family history of premature ASCVD [2,8,9]. Indeed, on this background variation in the *LPA* gene causing high Lp(a) has previously been suggested as the second most frequent cause of genetic FH, with the most frequent being mutations in the LDL receptor gene, *LDLR* [8].

The question of how high Lp(a) levels may contribute to a clinical diagnosis of FH is examined in the paper published by Tromp et al. in this issue of *Atherosclerosis* [17]. Tromp et al. used genetically estimated Lp(a) levels to evaluate the contribution of high Lp(a) levels to the FH phenotype in a large, contemporary, Dutch, nation-wide referral population of clinical FH. The study included 1504 patients referred for genetic testing for FH who also had Lp(a) levels estimated based on genotyping for two *LPA* single-nucleotide polymorphisms (SNP), rs10455872 and rs3798220, in previous studies shown to explain >30% of the total variation in Lp(a) levels [10,11]. Based on data from the UK Biobank, patients carrying one risk allele were assigned an Lp(a) level of 146 nmol/L (approx. 64 mg/dL), and patients carrying two risk alleles, an Lp(a) level of 262 nmol/L (approx. 114 mg/dL) [3]. The association of the *LPA* SNP genotypes with Lp(a) levels was in the study by Tromp et al. confirmed in a small subgroup of patients (N = 54) re-invited for Lp(a) measurements. Genetic testing for FH was performed by next generation sequencing of 29 lipid related genes including the *LDLR*, *APOB*, and *PCSK9* genes, where patients carrying a likely pathogenic or pathogenic variant in either of these three genes were diagnosed with mutation-positive FH.

The main finding in the study by Tromp et al. was that the use of Lp(a)-cholesterol-corrected LDL cholesterol levels, calculated by subtracting 17% of genetically estimated Lp(a) total mass from LDL-cholesterol, resulted in a downward reclassification of clinical FH category [17]. Thus, up to 9% of patients lost the clinical FH diagnosis based on a modified Dutch Lipid Clinic Criteria Network (DLCN) score. Further, genetically estimated high Lp(a) was more prevalent among FH mutation-negative than FH mutation-positive patients and of 30 patients reclassified to "unlikely FH", only one carried a pathogenic FH variant. The authors suggest that routine Lp(a) measurements in patients with clinical suspicion of genetic FH, could thus be used to guide for whom costly FH genetic testing should be withheld, where currently 85% of patients tested lack an FH mutation. Finally, the authors showed that the addition of Lp(a) levels to 10-year ASCVD risk prediction leads to risk reclassification, confirming previous findings from other study populations [4]. Thus, approximately 3% of patients without prior ASCVD and 19% of patients with prior ASCVD were reclassified towards a higher ASCVD risk category using, respectively, the SCORE or the SMART risk calculator in this selected referral population and including only mutation-negative patients.

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Some limitations of the study by Tromp et al. should be noted, as also described by the authors. Most importantly, plasma Lp(a) levels were not available in the large majority of the referral population and in lieu, levels were estimated based on genotyping for 2 *LPA* SNPs and data from the UK Biobank on median levels in minor allele carriers [3]. However, Lp(a) levels vary widely, even within specific *LPA* SNP genotype groups [12], as also demonstrated in the present study with a Lp(a) plasma level interquartile range for *LPA* SNP minor allele carriers of approx. 70–140 mg/dL. Further, the cholesterol content of the Lp(a) particle was not measured directly (not surprisingly, given that no commercial assays are available) and is currently a point of debate, with estimates of the Lp(a) particle cholesterol content ranging from 17% (used in the present study) to 45% dependent on the studied population and the applied methodology [9]. These two limitations of the study by Tromp et al. have likely resulted in inaccuracy in the correction of LDL cholesterol levels for the Lp(a) cholesterol contribution and may partly explain the smaller fraction of patients downward reclassified in clinical FH category compared to reclassification estimates of up to 23% reported in previous studies using measured and not estimated Lp(a) levels [8]. Additionally, a number of patients may have been incorrectly downward reclassified based on an overestimation of true plasma Lp(a) levels, which may potentially explain the reclassification of one FH mutation positive patient to "unlikely FH". A further limitation of the study by Tromp et al. although not discussed by the authors, is that the use of genetically estimated and not measured Lp(a) levels, prevented observations regarding possible effects of mutations in *LDLR*, *APOB*, or *PCSK9* genes on Lp(a) levels independent of *LPA* gene variation, a question examined in previous studies and with somewhat inconsistent findings but with the majority of data pointing to negligible effects [8,13,14]. Nonetheless, the study by Tromp et al. is timely and clinically relevant and adds considerably to the growing evidence base demonstrating that a clinical diagnosis of FH may in fact reflect hereditary "hyper-Lp(a)-emia", and not true hereditary LDL hypercholesterolemia, in a substantial proportion of patients diagnosed with clinical FH. It is therefore of particular importance for Lp(a) measurements to be performed in all patients suspected of FH with the aim of identifying not only those clinically "mis"-diagnosed with FH, but also to identify patients at very high risk of ASCVD due to the co-existence of both FH and high Lp(a) levels, as demonstrated in previous studies [8]. The differentiation may have clinical implications as high Lp(a) is resistant to statin treatment, the cornerstone in FH treatment, while more novel lipid lowering treatment in the form of PCSK9 inhibitors in addition to markedly lowering LDL cholesterol levels also lower Lp(a) levels by up to 30% [2]. Clinically, it is also important to note that in contrast to what is true for LDL cholesterol, where a similarly elevated LDL cholesterol level in two individuals may reflect quite different cumulative atherogenic burdens, and thus risk of ASCVD, dependent on the presence or absence of FH gene mutations, a Lp(a) plasma measurement may more accurately capture the lifelong cumulative burden of high Lp(a) without the need for *LPA* genotyping. This, as Lp(a) plasma levels are primarily genetically determined, reaching adult levels early in life, and minimally influenced by lifestyle factors in contrast to LDL cholesterol levels [5,15]. Accordingly, genotyping of *LPA* genetic variants does not substantially improve ASCVD risk prediction beyond inclusion of information on Lp(a) plasma levels [16], and *LPA* genotyping should be considered a research tool, as in the present study where information on plasma Lp(a) levels was unavailable, and not a diagnostic test to be implemented in clinical practice.

In summary, the study by Tromp et al. stresses the importance of measuring Lp(a) to correctly identify and characterize individuals at high risk of ASCVD due to common heritable dyslipidemia be it FH, "hyper-Lp(a)-emia", or a combination of both. While international guidelines and consensus reports are increasingly recommending once-in-a-lifetime Lp(a) measurement in all adults [1,3], currently routine Lp(a) measurements are not widely implemented in clinical practice. A good place to start would be at lipid clinics or referral centers with an opportunity to perform cascade screening in relatives of patients with high Lp(a) levels to promote identification of individuals with high Lp(a), particularly as potent and specific Lp(a) lowering treatments are on the horizon pending results from on-going cardiovascular outcome trials [2].

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PRK reports lecture honoraria or consultancies from Physicians' Academy for Cardiovascular Education, PCSK9 Forum, Silence Therapeutics, and Novartis.

References

[1] F. Mach, C. Baigent, A.L. Catapano, et al., ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk, Eur. Heart J. 41 (2019) 111–188, 2020.
[2] G. Reyes-Soffer, H.N. Ginsberg, L. Berglund, et al., Lipoprotein(a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American heart association, Arterioscler. Thromb. Vasc. Biol. 42 (2022) e48–e60.
[3] F. Kronenberg, S. Mora, E.S.G. Stroes, et al., Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement, Eur. Heart J. 43 (2022) 3925–3946.
[4] P.R. Kamstrup, Lipoprotein(a) and cardiovascular disease, Clin. Chem. 67 (1) (2021) 154–166.
[5] K. Schmidt, A. Noureen, F. Kronenberg, G. Utermann, Structure, function, and genetics of lipoprotein (a), J. Lipid Res. 57 (2016) 1339–1359.
[6] B.J. Arsenault, P.R. Kamstrup, Lipoprotein(a) and cardiovascular and valvular diseases: a genetic epidemiological perspective, Atherosclerosis 349 (2022) 7–16.
[7] B.S. Hedegaard, C.S. Bork, M. Kaltoft, et al., Equivalent impact of elevated lipoprotein(a) and familial hypercholesterolemia in patients with atherosclerotic cardiovascular disease, J. Am. Coll. Cardiol. 80 (2022) 1998–2010.
[8] A. Langsted, P.R. Kamstrup, M. Benn, A. Tybjaerg-Hansen, B.G. Nordestgaard, High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective cohort study, Lancet Diabetes Endocrinol. 4 (2016) 577–587.
[9] F. Kronenberg, Lipoprotein(a) measurement issues: are we making a mountain out of a molehill? Atherosclerosis 349 (2022) 123–135.
[10] R. Clarke, J.F. Peden, J.C. Hopewell, et al., Genetic variants associated with Lp(a) lipoprotein level and coronary disease, N. Engl. J. Med. 361 (2009) 2518–2528.
[11] P.R. Kamstrup, A. Tybjaerg-Hansen, B.G. Nordestgaard, Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population, J. Am. Coll. Cardiol. 63 (2014) 470–477.
[12] P.R. Kamstrup, B.G. Nordestgaard, Elevated lipoprotein(a) levels, LPA risk genotypes, and increased risk of heart failure in the general population, JACC Heart Fail 4 (2016) 78–87.
[13] M. Trinder, M.L. DeCastro, H. Azizi, et al., Ascertainment bias in the association between elevated lipoprotein(a) and familial hypercholesterolemia, J. Am. Coll. Cardiol. 75 (2020) 2682–2693.
[14] H.G. Kraft, A. Lingenhel, F.J. Raal, M. Hohenegger, G. Utermann, Lipoprotein(a) in homozygous familial hypercholesterolemia, Arterioscler. Thromb. Vasc. Biol. 20 (2000) 522–528.
[15] N. Strandkjaer, M.K. Hansen, S.T. Nielsen, et al., Lipoprotein(a) levels at birth and in early childhood: the COMPARE study, J. Clin. Endocrinol. Metab. 107 (2022) 324–335.
[16] P.R. Kamstrup, A. Tybjaerg-Hansen, B.G. Nordestgaard, Extreme lipoprotein(a) levels and improved cardiovascular risk prediction, J. Am. Coll. Cardiol. 61 (2013) 1146–1156.
[17] Tycho R. Tromp, Shirin Ibrahim, Nick S. Nurmohamed, et al., Use of Lipoprotein(a) to improve diagnosis and management in clinical familial hypercholesterolemia, Atherosclerosis (2022). In press.

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