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Screening for high lipoprotein(a) – the time is now

George Thanassoulis, MD MSc FRCPC

Preventive and Genomic Cardiology, McGill University Health Center and Research Institute, Montreal, QC CANADA

In 1994, the landmark 4S trial reported that lowering low-density lipoprotein (LDL) cholesterol with simvastatin reduced cardiovascular events in patients with coronary artery disease and hypercholesterolemia[1]. This seminal trial crystallized our understanding of the causal role of LDL cholesterol in atherosclerosis and launched the modern era of preventive cardiology. Today, the evidence in favor for LDL cholesterol as a modifiable causal driver of atherosclerosis has never been stronger and current therapies, such as PCSK9 inhibitors (PCSK9i), can now lower LDL cholesterol to levels never previously seen. But, despite achieving very low-levels of LDL cholesterol, many patients continue to have recurrent events. Although the residual risk for cardiovascular (CV) events is likely multifactorial, in certain patients, a key component is a high residual burden of atherogenic lipid particles due to high lipoprotein(a) (Lp[a]).

Lp(a) is a curious lipoprotein particle, first discovered in 1963, that consists of a lipid rich apoB lipoprotein covalently linked to an apo(a) moiety[2]. The apo(a) component is encoded by the *LPA* gene, and levels of Lp(a) are almost entirely explained by genetics. Indeed, elevated Lp(a) is the most common genetic dyslipidemia, with nearly 1 in 5 individuals affected in the US (i.e. based on Lp(a) > 50 mg/dL or >120 nM). Epidemiologic evidence has linked Lp(a) to several CV diseases including myocardial infarction (MI)[3], stroke[3] and aortic valve stenosis[4] and genetic evidence, using Mendelian randomization, have provided supportive evidence that these associations are causal[4, 5]. Causality is a key criterion in evaluating whether circulating biomarkers are possible therapeutic targets and the evidence in support of Lp(a) appears quite favourable. Several agents are currently in development to specifically lower Lp(a), and these appear highly effective in lowering plasma Lp(a) with an excellent safety profile[6]. However, to date, there remains no strong clinical evidence that lowering Lp(a) has any beneficial effects in preventing CV disease. Lp(a) still waits for its "4S" moment – but that moment appears imminent with at least one trial in the final planning stages for post-acute coronary syndrome patients.

In the context of these developments, Lp(a) is experiencing a resurgence in interest by the cardiovascular research community and with good reason; there remain many unanswered questions about Lp(a) and its role in CV disease. In this issue of Circulation, two papers are presented that provide answers to some of these outstanding questions. In the first, Paré et al[7], using data from the large multi-ethnic INTERHEART study evaluate the associations

Address for Correspondence: George Thanassoulis MD MSc FRCPC, Director, Preventive and Genomic Cardiology, McGill University Health Center, 1001 Decarie Boul, D5-5120, Montreal, QC, H4A 3J1, Tel: 514-934-1934 x35465, George.thanassoulis@mcgill.ca, Twitter: @ThanassoulisMD.

between Lp(a) levels and isoform size difference with MI across 7 ethnic groups in 6,086 cases of first MI and 6,857 controls. The authors should be commended for using this rich multiethnic dataset to examine the role of Lp(a) across ethnicities using state-of-the-art methods. The authors used an appropriate isoform independent assay to measure Lp(a) in all participants across ethnicities and also performed western blotting in 4219 participants, a laborious procedure, to estimate the kringle IV type 2 repeats. A minor limitation is that the authors present the Lp(a) concentrations in mass (mg/dL), despite calls for standardization of Lp(a) measurement using molar concentrations (nmol/L)[8]. Nonetheless, the investigators make several important contributions to our knowledge of Lp(a). First, they confirm that Lp(a) levels vary significantly across different ethnicities, with Africans having the highest Lp(a) levels (median 27 mg/dL) while Chinese were observed to have the lowest (7.8 mg/dL). They also demonstrate, as previously shown in Europeans, that Lp(a) concentrations are highly inversely correlated with isoform size, across all seven ethnicities[5]. Importantly, the authors perform a compelling analysis to demonstrate that after accounting for Lp(a) concentrations, isoforms are no longer associated with MI. Second, the investigators confirm the association between Lp(a) > 50 mg/dL and MI, conferring an increased odds of MI of 48% (95%CI 32-67%). More importantly, they demonstrate that this association was more or less consistent (allowing for statistical uncertainty) across several ethnicities indicating that Lp(a) is a risk factor regardless of ethnicity. The only ethnic groups that were heterogeneous were Africans and Arabs, where the association appeared null; however, these were the smallest subgroups and suffered from poor precision. Prior work, in larger samples has confirmed that Lp(a) > 50 mg/dL is a risk factor for CV disease in African-Americans[9] and further work will be needed to better resolve this association in additional cohorts of Arab participants. The investigators also provide some evidence that the population attributable risk of Lp(a) may be greater in South Asians (~9-10%) as compared to Europeans (5%) based on the higher prevalence of high Lp(a). If this result is replicated by others, this would indicate that Lp(a) contributes to a larger proportion of cases among South Asians, a high-risk group based on recent lipid guidelines[10], and would suggest that Lp(a) lowering would have greater population impact among South Asians, which could have important ramifications for global health.

In the second paper, O'Donoghue et al[11], provide important new data in a secondary prevention population using the recently completed FOURIER trial data. The secondary prevention setting represents a critical area for study, given the high residual risk observed in these patients and the potential for Lp(a) lowering to reduce this risk in select patients. Unlike statins which have no effect on Lp(a), PCSK9i are among the few drugs with Lp(a) lowering effects. Therefore, the FOURIER trial represents a unique opportunity to further study the role of Lp(a) in secondary prevention and O'Donoghue et al have provided exciting and compelling evidence in favour of the Lp(a) hypothesis. First, they demonstrate that in the well-treated FOURIER cohort, in which over 99% of participants received moderate or low-intensity statins, and in which LDL-C was <100 mg/dL (apoB < 90 mg/dL), higher Lp(a) was associated with major adverse cardiovascular events (MACE; defined as a composite of coronary heart death, MI or urgent coronary revascularization). Both the third and fourth upper quartile of Lp(a) distribution had an increased risk of MACE of 17% and 22%, as compared to the lowest quartile. Results were also largely consistent across all

major individual endpoints. These results are in keeping with several recent studies[12], including a large meta-analysis[13], that demonstrated that despite optimal statin therapy, Lp(a) remains a key component of the residual risk after a first CV event. This is a key observation that addresses a major area of controversy for Lp(a), namely, whether Lp(a) remains relevant as a risk factor after aggressive lipid-lowering. These observations provide critical evidence that trials to lower Lp(a) in secondary prevention are warranted. A second interesting finding, that will nonetheless require further validation, is the role of high Lp(a) in appropriately selecting patients for PCSK9i based on the predicted benefit received from such therapy. In FOURIER, the investigators observed a possibly greater relative risk reduction from PCSK9i among patients with Lp(a) above the median (HR 0.77, 0.67-0.88) as compared to those with Lp(a) at or below the median (HR 0.93, 0.80-1.08). They show that the number needed to treat was substantially lower for individuals with high Lp(a) (40 for individuals with Lp(a) > median vs 105 for those at or below Lp(a) median). Although the p-value for interaction did not reach statistical significance, if this finding is replicated by others, perhaps in other PCSK9i trials, this could have important implications for selecting PCSK9i to those individuals with the most to benefit. Finally, in an additional exploratory analysis, the investigators provide suggestive evidence that Lp(a) lowering may have added benefits over and above LDL-C lowering. Using a meta-regression framework, and after adjustment for change in LDL-C, the investigators demonstrate that for each 25 nM reduction in Lp(a) from PCSK9i, there was a concomitant 15% relative risk reduction (95% CI 2-26%). Although this analysis is subject to several statistical limitations given the observational nature of the data and the correlated nature of the changes in LDL-C and Lp(a), it provides exciting suggestive evidence that Lp(a) lowering may explain some of the benefits of PCSK9i, and adds to the evidence that Lp(a) may be a modifiable causal risk factor for CV disease.

Despite the mounting evidence for the role of Lp(a) in several cardiovascular diseases across ethnicities and the high burden of Lp(a)-associated disease, there remains tremendous clinical inertia for measurement of Lp(a) in North America and worldwide. There are approximately 60 million Americans with high Lp(a) but the majority have not yet been identified. For Lp(a) trials to be successful, proactive screening of patients with myocardial infarction and stroke (especially those with premature events and/or a family history) will be needed, with particular attention placed on screening individuals with recurrent events despite adequate lipid-lowering, who frequently have high Lp(a). Indeed, a compelling argument can be made that all individuals should have Lp(a) measured at least once in their lifetime given that levels remain largely stable throughout life. The most recent version of the US lipid guidelines[10] have newly recommended Lp(a) measurement in select individuals, as a risk enhancer, and this should further raise awareness of Lp(a). Finally, a common misconception among clinicians regarding Lp(a), which may partially drive the clinical inertia and lack of screening, is the perceived lack of therapeutic options for high Lp(a). However, this is not entirely correct. Although there is no targeted therapy for Lp(a) lowering yet, to properly care for our cardiovascular patients requires knowledge of Lp(a). Individuals with high Lp(a) have a higher burden of atherogenic lipoproteins and are therefore at higher CV risk, which can only be detected by Lp(a) measurement. These individuals may obtain significant benefit from more aggressive lifestyle modifications and

the maintenance of optimal risk factors throughout life[14]. Many may also benefit from more aggressive lipid-lowering with statins and perhaps even PCSK9i[15].

Targeted therapy for Lp(a) is around the corner and a test of the Lp(a) hypothesis is imminent, as it was for the LDL hypothesis a few decades ago. The 4S trial catalyzed a new era in cardiovascular prevention and we eagerly wait to see whether Lp(a) lowering will have a similar impact. Until then, we need to manage our patients with high Lp(a) as best we can, and that starts with identifying them first.

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