Atherosclerosis 288 (2019) 166–167

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

EAS Updates

Novel therapeutics specific to lipoprotein(a)

Jane Stock

European Atherosclerosis Society, World Trade Center Göteborg, Mässans Gata 18, SE-412 51, Göteborg, Sweden

ARTICLE INFO

Keywords:
Novel therapeutics
Lipoprotein (a)

Novel therapeutics specific to lipoprotein(a) are now available and offer the means to test the 'lipoprotein(a) hypothesis.' However, it is essential to clinical trial design to estimate how much lipoprotein(a) lowering is required for meaningful clinical benefit in a representative high-risk patient population. A recent Mendelian randomization analysis provides new insights highly pertinent to this question.

Testing the lipoprotein(a) hypothesis: how much to lower for clinical benefit?

In the last 20 years, opinion about lipoprotein(a) [Lp(a)] as a cardiovascular risk factor has changed [1]. The European Atherosclerosis Society (EAS) Consensus Panel statement on Lp(a) helped to catalyse this reversal [2]. Indeed, evidence from mechanistic, epidemiological, and genetic studies showing that Lp(a) was a causal mediator of cardiovascular disease and calcific aortic valve disease [3–6], with effects that were consistent across a broad spectrum of subjects, risk factors, and concomitant therapies. Moving forward, Lp(a) measurement is now recommended in both European and USA lipid management guidelines [7,8]. These initiatives are highly relevant given that high Lp(a) is prevalent; in North American or European Caucasian subjects, one in five have an Lp(a) level > 50 mg/dL. Prevalence does, however, vary according to ethnicity, being higher in Africans and lower in Asians [9,10].

Conclusive testing of the association between high Lp(a) and cardiovascular risk awaits a large randomized controlled trial. Until recently, this has been the major stumbling block, with the lack of therapeutics that specifically target Lp(a). Options were limited; PCSK9 inhibitors and lipoprotein apheresis both lower Lp(a) but are costly, and the former is predominantly prescribed for lowering low-density lipoprotein cholesterol (LDL-C). This scenario has now changed with the advent of novel antisense oligonucleotides targeting apolipoprotein(a) that lower Lp(a) production by up to 90% [11]. Recent reports of phase 2b data also showed reduction of Lp(a) in patients with established cardiovascular disease (the majority on a statin and 21% on a PCSK9 inhibitor), by more than 70% when given every 4 weeks, and 80% when given weekly (*American Heart Association Scientific Sessions late breaker, Chicago, November 2018*).

Essential to the planning of this major outcomes study is an estimate of the Lp(a) lowering required to achieve a clinically meaningful reduction in cardiovascular events. Unlike the situation for LDL-C, however, measurement of Lp(a) is fraught with problems. Together with the recognized need for standardization of assay methodologies, there is also lack of agreement regarding the threshold for elevated risk, particularly among individuals with established cardiovascular disease on intensive LDL-C lowering therapy [10].

The use of a Mendelian randomization approach is appropriate to address this question, given that elevation in Lp(a) is almost completely genetic in origin. As allocation of variants in the *LPA* gene, which encodes apolipoprotein(a), a determinant of Lp(a) levels, is random there are no external influences that can affect Lp(a) levels. Using this approach, a recent meta-analysis [12] showed that Lp(a) would need to be lowered by 100 mg/dL to achieve the same benefit as seen with lowering LDL-C by 1 mmol/L (38.7 mg/dL). Others have suggested less Lp(a) lowering is required, ranging from 50 to 60 mg/dL [13]. These differences may relate to the extent of heterogeneity of Lp(a) values in the different cohorts studied; addressing this discrepancy is critical to planning trials to test the 'Lp(a) hypothesis'.

A very recent report by the Lp(a)-GWAS-Consortium provides new insights into this question [14]. This Mendelian randomization analysis used data from 13,781 individuals in 5 primarily population-based studies. Lp(a) measurement was performed by a single central laboratory using a standardized, well-validated assay, with median Lp(a) values across all studies of 11–12 mg/dL. Analysis was restricted to 27 *LPA* variants with a minor allele frequency of at least 1%, to estimate the contribution of low, intermediate, and high numbers of Lp(a) variants to the Lp(a) level. Odds ratios for these variants associated with coronary heart disease (CHD) risk were derived from a subsample of the

E-mail address: office@eas-society.org.

https://doi.org/10.1016/j.atherosclerosis.2019.06.902
Received 7 June 2019; Accepted 12 June 2019
Available online 21 June 2019

Box 1
Testing the Lp(a) hypothesis: unresolved questions

- Does Lp(a) have a cumulative chronic effect on CHD risk?
- What is the contribution of prothrombotic and proinflammatory effects to CHD risk associated with high Lp(a)?
- What is the variability in the reduction in CHD risk with Lp(a) lowering?
- What reduction in Lp(a) is required in other ethnic groups?
- What is the risk reduction associated with Lp(a) lowering in very high risk individuals with cardiovascular disease, especially in those with very low LDL-C levels?

CHD Exome + consortium. Using these data, the authors reported that Lp(a) would need to be lowered by 65.7 mg/dL (95% CI, 46.3–88.3 mg/dL) for a comparable 22% risk reduction associated with lowering LDL-C by 1 mmol/L (38.7 mg/dL) over 5 years in a randomized controlled trial. Thus, when considering the design of future trials aimed at testing the 'Lp(a) hypothesis', Lp(a) in the patient cohort would need to exceed 75 mg/dL to achieve the required magnitude of Lp(a) reduction. It is pertinent that in the recent phase 2b study of a specific Lp(a) therapeutic, median Lp(a) levels at baseline exceeded 80 mg/dL and the absolute Lp(a) reduction achieved was 75 mg/dL with a weekly dosing regimen (*American Heart Association Scientific Sessions late breaker, Chicago, November 2018*). Thus, collective findings bode well for the design of a major outcomes study to test the Lp(a) hypothesis.

Results from the current study are also strengthened by 1) the use of a central laboratory using a validated standardized assay, and 2) a cohort with less heterogeneity in Lp(a) values than in precious reports. Yet, a number of outstanding questions remain (Box 1) [15]. First, it is recognized that this is an estimate of the required Lp(a) reduction, and baseline Lp(a) values may need to be higher if an upper limit of the confidence interval for this estimate is more appropriate. On the other hand, emerging evidence that Lp(a) also has prothrombotic and proinflammatory effects that are likely to contribute to pathophysiological mechanisms [6], suggest that a lower baseline Lp(a) value may be adequate. And finally, there remains uncertainty in translating the CHD risk reduction associated with lifelong exposure to genetic variants conferring lower Lp(a) values, with short-term exposure to Lp(a) lowering therapies in clinical trials.

Irrespective of these uncertainties, this analysis provides further information critical to informing the design of clinical trials of novel Lp(a) lowering treatments. The forthcoming years could represent the pinnacle of the Lp(a) renaissance, in very much the same way as genetic data for PCSK9 was the driver for development of highly efficacious LDL-C lowering therapies that reduce cardiovascular events.

Conflicts of interest

The author declared she does not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

[1] B. Gencer, F. Kronenberg, E.S. Stroes, Mach F. Lipoprotein(a): the revenant, Eur. Heart J. 38 (2017) 1553–1560.
[2] B.G. Nordestgaard, A. Langsted, Lipoprotein(a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology, J. Lipid Res. 57 (2016) 1953–1975.
[3] P.R. Kamstrup, A. Tybjaerg-Hansen, R. Steffensen, B.G. Nordestgaard, Genetically elevated lipoprotein(a) and increased risk of myocardial infarction, J. Am. Med. Assoc. 301 (2009) 2331–2339.
[4] B.G. Nordestgaard, A. Langsted, Lipoprotein(a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology, J. Lipid Res. 57 (2016) 1953–1975.
[5] P.R. Kamstrup, A. Tybjærg-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.
[6] S. Tsimikas, A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies, J. Am. Coll. Cardiol. 69 (2017) 692–711.
[7] A.L. Catapano, I. Graham, G. De Backer, et al., ESC/EAS guidelines for the management of dyslipidaemias, Eur. Heart J. 37 (2016) 2999–3058 2016.
[8] S.M. Grundy, N.J. Stone, A.L. Bailey, et al., AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol, 2018, Circulation (2018), https://doi.org/10.1161/CIR.0000000000000625 ([Epub ahead of print]).
[9] S. Varvel, J.P. McConnell, S. Tsimikas, Prevalence of elevated Lp(a) mass levels and patient thresholds in 532 359 patients in the United States, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 2239–2245.
[10] S. Tsimikas, S. Fazio, K.C. Ferdinand, et al., NHLBI working group recommendations to reduce lipoprotein(a)-mediated risk of cardiovascular disease and aortic stenosis, J. Am. Coll. Cardiol. 71 (2018) 177–192.
[11] 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.
[12] S. Burgess, B.A. Ference, J.R. Staley, et al., European Prospective Investigation into Cancer and Nutrition–Cardiovascular Disease (EPIC-CVD) Consortium. 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. Parish, J.C. Hopewell, M.R. Hill, et al., HPS2-THRIVE Collaborative Group. Impact of apolipoprotein(a) isoform size on lipoprotein(a) lowering in the HPS2-THRIVE study, Circ Genom Precis Med 11 (2) (2018) e001696.
[14] C. Lamina, F. Kronenberg, for the Lp(a)-GWAS-Consortium, Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes: a mendelian randomization analysis, JAMA Cardiol (2019), https://doi.org/10.1001/jamacardio.2019.1041 ([Epub ahead of print]).
[15] G. Thanassoulis, Using genetics to plan future randomized trials of lipoprotein(a) lowering—how much reduction, for how long, and in whom? JAMA Cardiology (2019), https://doi.org/10.1001/jamacardio.2019.1107 ([Epub ahead of print]).