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Understanding the use of lipoprotein (a) in the primary care office for primary prevention: A fellow's voice☆

As I have advanced in my medical training and have been exposed to a variety of diseases and cardiovascular conditions, I have learned that I play a pivotal role in shifting a disease process and impacting my patient's outcomes significantly, but sometimes it might be too late to make a significant difference. Medicine is not only about treating the sick but also about preventing disease. Because of this, I have found passion in helping my patients get the best understanding of their cardiovascular risk early and build together tools to live a healthier life, and that's why I love preventive cardiology.

Let's start with a case: Mr. Jones is a 58-year-old man who came to my office for a primary prevention assessment; notably, his father had a myocardial infarction in his early 50 s. He has a medical history of hypertension, total cholesterol is 220 mg/dL, high-density lipoprotein cholesterol (HDL-C) is 57 mg/dL, and low-density lipoprotein cholesterol (LDL-C) is 100 mg/dL currently with therapy using moderate-intensity statin and ezetimibe. The calculated 10-year atherosclerotic cardiovascular disease (ASCVD) risk, based on traditional risk factors, is 7.4 % and he comes to the clinic to know if there are additional strategies to prevent the same fate as his father. I decided to order a lipoprotein(a) [Lp(a)] and the result surprisingly shows a concentration >700 nmol/L. What is Lp(a)? Is this an alarming number? What are the next steps? How can we interpret that value? Should I refer this patient to a lipid clinic?

Lp(a) is an apo B-containing lipoprotein bound to a hydrophilic, glycosylated protein called apolipoprotein(a). Its importance lies in the association as an independent risk factor for the progression of coronary heart disease, stroke, heart failure, cardiovascular mortality, and aortic stenosis that has been well described [1]. A potential mechanism for this association is thought to be because of monocyte activation that leads to inflammation and endothelial dysfunction [2]. Lp(a) promotes atherogenesis, vascular calcification, valvular calcification, and thrombosis. Different from the regular lipid panel, Lp(a) is mostly genetically determined and has seldom to do with how we eat or exercise. By the time we are 5 years old, the LPA gene has already been expressed and the adult Lp(a) levels have already been reached. A caveat is that after menopause, the Lp(a) can increase slightly in women [3].

There have been different recommendations on what patients to measure this biomarker. The 2022 European Atherosclerosis Society (EAS) consensus statement recommends screening it at least once in adult life [3], whereas US guidelines are more focused on recommending screening in those with a personal or family history of premature ASCVD [4,5]. In my practice, I apply the European consensus, screening all my adult patients, I have found that it gives me a better understanding of what other factors I need to consider in reducing the risk of cardiovascular disease in everyone, and can work towards a personalized plan. If I find a low Lp(a) I can focus on other screening tools like coronary artery calcium score, high-sensitivity C-reactive protein, or other risk enhancers, this piece is not intended to expand on these other strategies but it is worth looking into for your practice. On the other hand, if it is elevated, then that gives me enough evidence to be aggressive with the modifiable risk factors and provides data to talk to my patient to make better decisions.

In general, we can use the values of 50 mg/dL or 125 nmol/L to classify Lp(a) as a risk enhancer, depending on how your laboratory reports it [4]. Although beyond lipoprotein apheresis there are no currently approved therapies to lower high levels of Lp(a), that should not be the reason we don't obtain it. Elevated Lp(a) can identify the high-risk patient such that risk-reducing strategies can be implemented. The idea is to have a comprehensive understanding of the individual risk for CVD and work on the modifiable factors. The HORIZON and OCEAN Outcomes trials investigating whether the Lp(a)-targeted therapeutics of pelarsen and olpasiran, respectively, can reduce cardiovascular events are ongoing and due to be reported in the next few years. There are other novel agents in Phase II trials as well. Once these results are published, we may have other tools in our arsenal to decrease the CVD burden associated with elevated Lp(a). In the meantime, there are plenty of strategies including evidence-based diets like the Mediterranean [6] and DASH [7] diets, physical activity (at least 150 min a week of moderate physical activity), tobacco cessation, and a comprehensive approach to other metabolic risk factors like weight loss, hypertension control, diabetes management, and dyslipidemia that can still apply to our patients [8]. In addition to their potent LDL-C lowering ability, the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), i.e., alirocumab and evolocumab, also have some lowering effect in Lp(a) in the range of 20–30 % [although not specifically approved for Lp(a) lowering], and secondary analyses of the PCSK9i trials suggest that the patients with ASCVD with elevated Lp(a) derived an even greater absolute and relative risk benefit from PCSK9 inhibition [9].

With the increased complexity of risk assessment along with newer therapeutic approaches, an integrative vision of cardiometabolic pathophysiology needs to be developed, supporting a further expansion of the field of preventive cardiology beyond its traditional lipid focus [10].

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However, as primary care clinicians there is a responsibility to be aware of the different options available for our patients, recognize where there can be more answers, and as an additional resource, also recognize when to refer the patients to a cardiologist for more support. Hopefully, these general concepts will be helpful the next time faced with the decision of whether to screen or not your patients and what to do with the results.

Finishing up Mr. Jones's case, we did an additional workup, finding mild aortic stenosis and significant multivessel disease in computed tomographic coronary angiography, which until now has been subclinical. Now, in addition to statin and ezetimibe, he is starting a PCSK9i to achieve a more intensive LDL-C goal, as well as strict lifestyle modifications. He is happy and I am happy that we are doing our best based on the available data for his health benefit.

Author declaration

I wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. I understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

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CRediT authorship contribution statement

Carlos Vergara Sanchez: Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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