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Fellow's Voice

Precise versus pragmatic - a perspective and evaluation of Lipoprotein(a) testing recommendations: A fellow's voice

My interests and passion in preventive cardiology began as a third-year medical student on clinical rotations at Tulane University School of Medicine (New Orleans, LA), as many of the patients I helped care for had cardiovascular disease caused by modifiable risk factors which are especially prevalent in the Southeastern United States. As I have continued through training, I have at times drawn analogies from patient encounters and scientific questions in preventive cardiology to my background and participation on sports teams.

Watching me play from the sidelines, my dad would always emphasize the importance of making the simple pass on the soccer field. His coaching wisdom was complimentary to my playing style, the latter of which involved me trying to place a long ball in stride to a forward teammate from my position of outside defense a few times per game. As I developed into a more mature soccer player, I grew to simplify my style of play and appreciate the fine balance between the short versus attempted long ball passes each game. Both types of passes were useful depending on the game situation. The soccer pass analogy may draw parallels to the equilibrium between precision versus pragmatism related to guidelines and consensus involving lipoprotein(a) [Lp(a)] testing.

Over the past half decade, the integration of Lp(a) testing within major societal statements in North America and Europe has become increasingly prominent. Most recently, a 2022 European Atherosclerosis Society (EAS) consensus statement suggested that Lp(a) be measured at least once in all adults, preferably with the first lipid panel. The EAS also recommends measuring Lp(a) in youth with a family history of premature atherosclerotic cardiovascular disease (ASCVD) (<55 years in men, <65 years in women) or elevated Lp(a) and no other known risk factors [1]. Similarly, the 2021 Canadian Cardiovascular Society dyslipidemia guidelines recommend once-per lifetime Lp(a) testing as a part of an initial lipid screening [2]. These newer recommendations contrast with the 2018 Multi-Society Cholesterol guidelines [3] that consider Lp(a) as a risk enhancer and the 2019 National Lipid Association (NLA) scientific statement [4] on Lp(a), which provide more refined Lp(a) testing criteria predominantly focused on those who have first-degree relatives with premature ASCVD. The 2018 Multi-Society Cholesterol guidelines also provide a relative indication for considering Lp(a) measurement in the setting of a personal or family history of ASCVD not explained by risk factors [3]. Additionally, the 2019 NLA scientific statement states that Lp(a) testing may be reasonable for those with: 1) a personal history of premature ASCVD, 2) LDL-cholesterol ≥190 or suspected familial hypercholesterolemia (FH), 3) 10-year ASCVD risk between 5 and 7.5 % to facilitate discussions involving initiation of statin pharmacotherapy, 4) less-than-anticipated LDL-cholesterol lowering on evidence-based lipid lowering therapy, 5) family members with severe hypercholesterolemia, and 6) those at risk for severe of progressive valvular aortic stenosis [4].

An analysis of major guidelines and consensus regarding Lp(a) testing may help to contextualize the balance between precision and pragmatism in preventive cardiovascular care. Most recent Lp(a) guidelines in the United States favor precision, and align with broader research efforts, including the FIND Lp(a) initiative led by the Family Heart Foundation to develop machine learning models to identify patients at-risk for elevated Lp(a) in electronic health records nationwide. Discoveries from the FIND Lp(a) project and similar implementation science related advances may be important to help overcome the current challenges with Lp(a) testing. Although an estimated one in five United States adults have elevated Lp(a), one recent study from a large academic medical center in California reported that Lp(a) testing was performed in less than 1 % of all patients and in less than 4 % of patients with clinical ASCVD between 2012 and 2021 [5]. However, the prevalence of guideline/consensus-indicated testing for Lp(a) in the entire United States is unknown. Several barriers have been previously reported as potential contributors for the disproportionately low level Lp (a) testing, including unawareness of Lp(a) testing guidelines and/or Lp (a) as a risk factor itself, insurance coverage/cost concerns related to lab testing, lack of currently approved pharmacotherapy for Lp(a) reduction, and a limited number of implementation programs [5]. Completion of ongoing phase 3 cardiovascular outcome trials involving pelacarsen (Lp(a)HORIZON: NCT04023552) and olpasiran (OCEAN(a): NCT05581303) may help increase Lp(a) testing and may lead to revised recommendations for testing modified according to Lp(a)HORIZON (estimated completion date: May 2025) and OCEAN(a) (estimated completion date: December 2026) eligibility criteria. However, inclusion criteria for these trials are relatively strict (HORIZON: clinical ASCVD and Lp(a) ≥175 nmol/L; OCEAN(a): history of myocardial infarction or percutaneous coronary intervention with a high-risk condition and Lp(a) ≥200 nmol/L) given study designs and power calculations from these trials. Other Lp(a) lowering agents are also being tested in phase 2 and phase 3 trials.

Simplified recommendations involving once-per-lifetime testing may help overcome certain barriers to clinical Lp(a) testing, as well as enhance identification of individuals who have a higher inherited risk for ASCVD or aortic stenosis. This pragmatic approach may be helpful for implementation by simplifying testing recommendations communicated to primary care clinicians and cardiologists. Additionally, once-per-lifetime Lp(a) testing may be useful to guide cascade screening in families when elevated Lp(a) is detected, similar to the cascade screening in FH. Given that an Lp(a) level of 175 mg/dL (378 nmol/L)

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confers equivalent risk of ASCVD to that of genetically diagnosed FH [6] and that *LPA* genotype influences the clinical diagnosis of FH [7], broadened and simplified Lp(a) testing may be justifiable. While once-per-lifetime Lp(a) testing may lead to identification of a larger number of individuals with elevated Lp(a) in the general population, outcome data on the potential benefit from direct therapeutic lowering of Lp(a) are unknown at this time. Importantly, specific trials in primary prevention populations have yet to be initiated. Such trials in primary prevention are likely to be initiated after secondary prevention trials involving Lp(a) are completed; of note, a prespecified analysis from the ORION-11 trial including a subset of individuals without clinical ASCVD demonstrated that subcutaneous inclisiran administered on day 1, day 90, and every 6 months thereafter for up to 1.5 years lowered Lp(a) by 28.5 % [8]. However, it is uncertain whether this magnitude of lowering is sufficient, as it is thought that ≥70 % reduction in Lp(a) will be needed to have significant impact. As well, the phase 2 Lp(a)FRONTIERS CAVS Trial (NCT05646381) involving pelacarsen as a potential agent to slow the progression of calcific aortic valve stenosis (outcomes: aortic jet velocity and aortic valve calcium score) will begin enrollment. Currently the potential benefit of increasing the identification of individuals with elevated Lp(a) with expanded, simplified testing criteria is limited by the lack of evidence involving Lp(a)-specific-lowering pharmacotherapies, especially among those without clinical ASCVD.

Additional challenges shared by both precise and pragmatic Lp(a) testing approaches are lack of standardization across assays, thresholds for the consideration of elevated Lp(a), and temporal variability. Evidence suggests that one in ten individuals with borderline high Lp(a) (75 nmol/L or 30 mg/dL) have normal levels upon retesting and that two in five individuals have >25 % variation in Lp(a) over a 30 to 190-day retesting period [9]. The potential for longer term intraindividual increases in Lp(a) related to the development of chronic kidney disease and menopause are also important to note while determining thresholds and implementing testing guidelines. The new American Heart Association PREVENT (Predicting Risk of CVD EVENTS) risk equations incorporate estimated glomerular filtration rate in base models and urine albumin-creatinine ratio in optional models. Early menopause (age <40 years old) is considered a risk-enhancing factor [3] that may influence Lp(a) measurement and decisions regarding recommended initiation of statins. Statins can increase Lp(a) levels by 10–20 % [10], therefore clinical consideration of potential background statin therapy when interpreting Lp(a) results may be necessary, especially if being used to guide the initiation of Lp(a)-lowering therapies in the future.

As efforts to improve personalized medicine in ASCVD prevention are investigated, the broader public health implications should not be forgotten. In the setting of Lp(a) testing, efforts to identify those most likely to benefit from screening will be of value. Similar to balancing the situational benefits of accurately placed long passes and sensible short passes when playing soccer, Lp(a) testing guidelines will require a combination of precision and pragmatism to determine net clinical benefit, initiation of preventive therapies, and cost effectiveness. This will depend on the clinical context and population being considered.

CRediT authorship contribution statement

Alexander C. Razavi: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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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