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COMMENTARY

Universal Testing for Lp(a): What Are We Waiting For?

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February 01, 2023

Lipoprotein(a) [Lp(a)] was first identified in 1963, just about the time that my 16-year-old arteries were probably developing fatty streaks. It soon became clear that Lp(a) was associated with atherosclerotic cardiovascular disease (ASCVD), but whether an elevated blood level was a biomarker or a causal factor proved difficult to determine. Studies of inheritance patterns confirmed that blood levels were primarily genetically determined and largely resistant to lifestyle and pharmacologic intervention. Deemed "unmodifiable," it seemed senseless to test for something that wasn't treatable. That label stuck for decades.

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Fortunately, a resurgent interest in molecular pathophysiology this past decade has clarified Lp(a)'s unique contribution to atherothrombotic disease and calcific aortic stenosis. While there remains much to be learned about this complex, highly atherogenic molecule and its role in cardiac disease, it seems shortsighted not to take the simple step of identifying who carries this risk. Why are we not testing everyone for an extremely common and potent risk factor for the most lethal disease on the planet?

Epidemiologic studies project a stunning number of people in the United States to be at increased risk for Lp(a)-mediated coronary and cerebrovascular events. Because the *LPA* gene which codes for the apo(a) component of the Lp(a) molecule is fully expressed at age 2, this is a truly lifelong risk factor for a projected 64 million individuals with blood levels (> 60 mg/dL) high enough to double their risk for ASCVD. Because risk increases linearly, this includes 16 million, like me, with levels > 116 mg/dL, who are at four times the risk for ASCVD as those with normal levels (< 30 mg/dL).

Because Lp(a) level remains relatively constant throughout life, a single blood test would help stratify the risk it confers on millions of people who, under current US guidelines, would never be tested. Until Lp(a) is integrated into its algorithms, the commonly used ASCVD Risk Calculator will substantially underestimate risk in 20% of the population.

A potential barrier to universal testing is that the ideal method to measure Lp(a) has yet to be determined. Lp(a) comprises an apoB particle bonded to an apo(a) particle. Apo(a) is complex and has a number of isoforms that can result in large heterogenicity in apo(a) size between, as well as within, individuals. This contributes to controversy about the ideal assay and whether Lp(a) levels should be expressed as mass (mg/dL) or number of particles (nmols/L). This should not, however, deter universal testing.

One-time Cost, Lifetime Benefit?

Absent universal testing, it's impossible to estimate the economic toll that Lp(a) exacts, but it's surely an extraordinary number, particularly because the highest-risk individuals are prone to recurrent, nonfatal vascular events. The substantial price tag for my personal decade of Lp(a)-induced vascular havoc included four percutaneous coronary interventions with rapid stent restenosis, an eventual bypass surgery, and an aborted left hemispheric stroke, requiring an urgent carotid endarterectomy.

As a frame of reference, US expenditures related to ASCVD are estimated to be $351 billion annually. If everyone in the United States over the age of 18 were tested for Lp(a) at a cost of $100 per person, this would be a $21 billion expenditure. This nonrecurring expense would identify the 20% — or almost 42 million individuals — at high risk for ASCVD, a number of whom would have already had vascular events. This one-time cost would be a foundational step in securing year-after-year savings from enhanced ASCVD prevention and reduction in recurrent vascular events.

Such savings would be significantly enhanced if and when targeted, effective Lp(a) treatments become available, but it seems shortsighted to make this the linchpin for universal testing. It's noteworthy that Canadian and European guidelines already endorse one-time testing for all.

The confirmation of Lp(a)'s causal role in ASCVD remains underappreciated by medical providers across all specialties. Much of the elegant Lp(a)-related science of the past decade has yet to translate to the clinical world. What better way to rectify this than by identifying those with high Lp(a)? Since the advent of the statin era, "good" and "bad" cholesterol values are common conversational fare, in part because virtually every adult has had not one, but many lipid panels. Universal Lp(a) testing would spotlight this pervasive and important risk factor that was referred to as the "horrible" cholesterol in a recent review.

US Guidelines Need Updating

To foster this, US guidelines, which influence every aspect of care, including testing, prevention, treatment, reimbursement, and medical legal issues, need to be simplified. The discussion of Lp(a) testing in the 2018 US guidelines on cholesterol management is already obsolete. The contingencies on when testing is "reasonable" or "may be reasonable" are dated and cumbersome. In contrast, a recommendation to test everyone once, perhaps in adolescence, would be a useful, forward-looking strategy.

To date, trials of an antisense oligonucleotide and a small interfering RNA molecule targeting hepatic *LPA* messenger RNA have confirmed that plasma Lp(a) levels can be significantly and safely lowered. If the ongoing Lp(a) HORIZON and OCEAN(a) phase 3 trials have positive outcomes in patients with known ASCVD, this would spawn a host of clinical trials to explore the possibilities of these therapies in primary prevention as well. These will require tens of thousands of enrollees, and universal testing would expand the pool of potential participants.

The majority of at-risk individuals identified through universal testing would be candidates for primary prevention. This large, currently unidentified cohort should have all coexisting risk factors assessed and managed; lowering elevated LDL-C early and aggressively is paramount. Recent data from the United Kingdom suggest that attainment of specific LDL-C levels may offset the risk for vascular events in those with high Lp(a) levels.

Of note, this was the advice given to the small fraction of high-risk individuals like me, who had their Lp(a) level tested long before its ominous implications were understood. This recommendation was informed mostly by common sense. For any number of reasons, the same might be said for universal testing.

Dennis Leahy, MD, is a retired cardiologist in San Diego. He has an abiding professional and personal interest in Lp(a), which has been responsible for a number of cardiovascular events in his own life over the past two decades. He was a participant in the phase 2 clinical trial of the Lp(a)-lowering antisense oligonucleotide being studied in the Lp(a) HORIZON Trial, funded by Novartis, and is currently undergoing apheresis treatment.

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Cite this: Dennis R. Leahy. Universal Testing for Lp(a): What Are We Waiting For? - *Medscape* - Feb 01, 2023.