JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 73, NO. 9, 2019

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

In Search of Patients With Elevated Lp(a)

Seek and Ye Shall Find*

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Following a long latent period of controversy since lipoprotein(a) [Lp(a)] was discovered in 1962, it is now generally agreed that Lp(a) is an independent, genetic, and likely causal risk factor for cardiovascular disease (CVD) and calcific aortic valve stenosis (AS), both in primary care populations and in patients on statins (1). A confluence of divergent sources of evidence have contributed to this conclusion, including improved diagnostic assays, epidemiological studies, Mendelian randomization, and genome-wide association studies (2,3). In concert, the first demonstration of a specific therapy to lower Lp(a) was demonstrated in 2011 using an antisense oligonucleotide that substantially lowered Lp(a) (4). Refinements in antisense technology have progressed the clinical development of these compounds to phase 2B, showing a mean reduction in Lp(a) of 80% (5), that will allow testing of the Lp(a) hypothesis in the near future (6).

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Despite these advances, the identification of patients with elevated Lp(a) at the bedside is significantly lacking. In this issue of the *Journal*, Ellis et al. (7) provide evidence for the efficiency and high yield of cascade screening of relatives of patients with genetically diagnosed, pathological mutations in the low-density lipoprotein (LDL) receptor (LDLR) leading to familial hypercholesterolemia (FH) derived from the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) registry. The authors screened 2,927 family members from 755 index cases of FH enrolled in the SAFEHEART study to identify subjects with elevated Lp(a). The patients with FH were relatively young (mean age in the 40s) but had significantly elevated LDL-cholesterol (LDL-C) (mean 175 mg/dl) despite 94% receiving a statin/ezetimibe for a mean of 15 years, and 18% had CVD. The relatives of the probands were of similar age, had slightly lower LDL-C (mean 166 mg/dl) with >59% receiving lipid-lowering therapy, and 9% had CVD. Mean Lp(a) levels were higher in the probands (22.3 vs. 18.6 mg/dl), but 39.3% of relatives had Lp(a) >30 mg/dl and 25.1% had Lp(a) >50 mg/dl.

They showed that systematic screening from index cases with both FH and elevated Lp(a) identified 1 new case of elevated Lp(a) for every 2.4 screened, and that screening from index cases with FH, but without elevated Lp(a), identified 1 individual for 5.8 screened. Importantly, over a 5-year follow-up period, relatives with only elevated Lp(a) had a higher hazard ratio (HR) (HR: 3.17) of a CVD event or death than FH (HR: 2.47) without elevated Lp(a), but the greatest risk was observed in relatives with both FH and elevated Lp(a) (HR: 4.40).

What are the pathophysiological and clinical implications of this study? First, similar to cascade screening of FH, it was demonstrated that a high yield of finding elevated Lp(a) was achieved by screening close relatives of subjects with FH and elevated Lp(a). Of 2,927 family members, 1,413 had FH only, 531 had FH plus elevated Lp(a), 203 had elevated Lp(a), and 780 had neither. Thus, of the FH patients, 27.3% had elevated Lp(a) >50 mg/dl. If one used >30 mg/dl, which is more strongly supported by epidemiological data where risk accrues (8), rather than >50 mg/dl, which is an arbitrary cutoff based on population cutoffs (9), the percentage would have been higher, perhaps closer to 40%.

Second, it is becoming increasingly clear that patients with FH have elevated levels of Lp(a) compared

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2018.12.036

with the general population reflected in epidemiological (9) and laboratory databases (10), where ~20% of the population have levels >50 mg/dl. The prevalence of elevated Lp(a) in the SAFEHEART study is consistent with prior data in 382 patients with either homozygous or heterozygous FH showing a prevalence of 57% and 44% for Lp(a) levels >30 mg/dl and >50 mg/dl, respectively (11). These data suggest that elevated Lp(a) at an atherogenic level is a concomitant risk factor in FH patients in almost one-half of the patients. Additionally, in view of Lp(a)'s role in AS, elevated Lp(a) also contributes to the higher risk of AS in patients with FH, as suggested recently with aortic valve calcification (12). Anecdotal and case report data exist for AS in FH, particularly in patients with homozygous FH who are characterized by supravalvular AS due to insudation of lipids in the aortic root (13). However, formal, systematic studies of the role of Lp(a) in clinically manifest AS of the aortic valve leaflets in FH patients have not been performed to date.

Third, this observation suggests pathophysiological implications in the metabolism of Lp(a) that are not explained by *LPA* genetics, as presumably the relatives had similar underlying genetics to the probands. Although kringle repeats were not reported in the current study, prior data have strongly suggested that, for similar isoform size, patients with homozygous FH have 2-fold higher Lp(a) levels, and patients with heterozygous FH, 1.5-fold higher levels than unaffected siblings (14). Although experimental data are controversial, these observations implicate the LDLR and possibly the LRP1 receptors in affecting Lp(a) levels. The data suggest that the normally reduced affinity of Lp(a) for the LDLR, along with the potential competition for such receptors by the large number of circulating LDL particles in FH, mediates higher Lp(a) levels.

Fourth, the HR for CVD events and death were numerically higher for individuals with elevated Lp(a) alone versus elevated LDL-C alone, although formal statistics were not provided for the comparison. In conjunction, individuals with elevated Lp(a) plus a concomitant diagnosis of FH had the highest risk, suggesting that measuring Lp(a) in patients with FH will allow clinicians to identify the patients with the highest risk of CVD events and death.

Finally, the aforementioned findings provide a strong rationale to consider elevated Lp(a) as part of the clinical syndrome of FH, with >30 mg/dl as the pathophysiologically supported cutoff in general populations. In turn, diagnostic criteria for FH may now consider formally incorporating Lp(a) measurements in all patients with a clinical diagnosis of FH, and if levels are elevated, these individuals should be considered at the highest risk category of FH patients.

What can clinicians do with information incorporating Lp(a) in their clinical diagnostic workups? As shown in this study, these patients are at high risk but have suboptimal LDL-C management, and therefore, further reduction in LDL-C is warranted. The lack of optimal LDL-C levels reflects the difficultly in reducing LDL-C in these patients, but they also did not appear to have been treated with maximal LDL-C-lowering therapy during the period of evaluation. For example, it was not reported that any patients were treated with niacin, colesevelam, or PCSK9 inhibitors, and only 3 patients were on apheresis. Higher use of PCSK9 inhibitors would have reduced the treated LDL-C significantly and likely improved outcomes. In particular, apheresis is very effective in reducing LDL-C and Lp(a), and apheresis performed specifically for elevated Lp(a) in the setting of controlled LDL-C has been shown to be associated with a reduction of events while on apheresis compared with pre-apheresis (15), and to reduce refractory angina (16). If approved in the future, bempedoic acid or angiopoietin-like 3 inhibitors (17,18) may address the residual LDL-mediated risk. In addition, it has to be acknowledged that the measure called "LDL-C" contains the content of Lp(a)-cholesterol in it, which can account for 30% to 45% of "LDL-C" (19), and the "LDL-C" levels of patients with elevated Lp(a) cannot be reduced to low levels if the Lp(a) remains elevated (20). Thus, specific therapies to lower Lp(a) in addition to LDL-C are warranted in these patients (7).

It is estimated that Lp(a) levels >50 mg/dl are present in 1.4 billion people (1). It will be imperative to create practice pathways to appropriately screen and identify the most appropriate patients that might benefit from early diagnosis and future therapies. This applies, not only to relatives of subjects with FH, which is a relatively small group, but also to relatives of index cases identified with Lp(a)-mediated CVD. Because Lp(a) is transmitted in a codominant fashion, approximately 0.5 subjects will be identified for every 1 screened, making this a highly successful cascade screening to identify preclinical elevated risk. The European Atherosclerosis Society/European Society of Cardiology (Class IIb, Level of Evidence: C) and Canadian guidelines provide guidance on measuring Lp(a) levels in intermediate- and high-risk patients (21,22). The recent American College of Cardiology/American Heart Association guidelines have also recommended that in patients with 10-year risk (7.5% to 19.9%) and elevated Lp(a), initiation of statin

therapy should be considered (23). A day can be envisioned in the next decade when, in conjunction with a healthy lifestyle and low cholesterol diet, available pharmacological therapies will lower LDL-C and Lp(a) levels to levels similar to the general population to mitigate the excess risk of CVD mediated by these lipoproteins.

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KEY WORDS cascade screening, familial hypercholesterolemia, lipoprotein(a)