ment, including lifestyle modification and lipid-lowering drug therapy in high-risk individuals, primarily to reduce low-density lipoprotein cholesterol (LDL-C) levels. The U.S. Food and Drug Administration approved an indication for lipoprotein apheresis (which reduces both Lp(a) and LDL-C) in high-risk patients with familial hypercholesterolemia and documented coronary or peripheral artery disease whose Lp(a) level remains ≥60 mg/dL [∼150 nmol/L)] and LDL-C ≥ 100 mg/dL on maximally tolerated lipid-lowering therapy. Although Lp(a) is an established independent causal risk factor for cardiovascular disease, and despite the high prevalence of Lp(a) elevation (∼1 of 5 individuals), measurement rates are low, warranting improved screening strategies for cardiovascular disease prevention.

Introduction (Preface)

The lipoprotein(a) [Lp(a)] field is rapidly evolving on many fronts, warranting this focused update to the 2019 National Lipid Association (NLA) Scientific Statement on Use of Lipoprotein(a) in Clinical Practice.[1] Recent evidence has influenced our understanding of whom should have Lp(a) levels measured, how to interpret Lp(a) levels for use in risk assessment, and clinical management of patients with elevated Lp(a). The NLA now recommends: (1) measurement of Lp(a) levels at least once in every adult; (2) classification of individuals with Lp(a) levels <75 nmol/L (30 mg/dL) as low risk, individuals with Lp(a) levels ≥125 nmol/L (50 mg/dL) as high risk, and individuals with Lp(a) levels between 75 and 125 nmol/L (30–50 mg/dL) as intermediate risk; and (3) use of lipoprotein apheresis as now indicated by the U.S. Food and Drug Administration (FDA) in high-risk patients with familial hypercholesterolemia (FH) and documented coronary or peripheral artery disease whose Lp(a) level remains ≥60 mg/dL [∼150 nmol/L)] and low-density lipoprotein cholesterol (LDL-C) ≥100 mg/dL on maximally tolerated lipid-lowering therapy. This statement expands on new and emerging evidence supporting these recommendations (Table 1).

A. What new evidence has emerged regarding Lp(a) as a cardiovascular risk factor since the last NLA scientific statement?

Accumulating data from large, population-based studies indicate that elevated plasma Lp(a) is an important independent, causal risk factor for atherosclerotic cardiovascular disease and calcific aortic valve stenosis

The most notable of these studies are two analyses of the UK Biobank.[2,3] Their enormous sample sizes ($n = 460{,}506$ and 413,734, respectively) allowed several key questions to be addressed with unprecedented statistical power.

First, a continuous, log-linear relationship between baseline Lp(a) and risk for atherosclerotic cardiovascular disease (ASCVD) events was observed, with a significant (albeit small) increase in risk at what would usually be considered "low-risk" levels of Lp(a) (25–50 nmol/L).[2,3] This finding should prompt the retirement of the old concept of a dichotomous threshold, i.e., 125 nmol/L or 50 mg/dL. Indeed, the continuous gradient of risk with increased Lp(a) implies that clinical decision-making should be influenced by the degree of Lp(a) elevation and the patient's other risk factors, not the mere presence of elevated Lp(a).

Second, while substantial differences in median Lp(a) levels and the distribution of Lp(a) levels between different racial/ethnic groups were observed in UK Biobank (in accordance with prior research[4]), no impact of race on Lp(a)-attributable risk was found.[2,3] ASCVD risk attributable to elevated Lp(a) was similar for White, South Asian, and Black individuals (hazard ratios [HRs] 1.11, 1.20, and 1.07 per 50-nmol/L increase in Lp(a), respectively).[2] Further, a recent analysis of a large multiethnic US pooled cohort of five prospective studies showed consistent increases in ASCVD risk associated with higher Lp(a) levels by sex and race/ethnicity, with particularly stronger relationships noted in individuals with versus without diabetes.[5] Some (but not all) studies—generally with smaller sample sizes and fewer ASCVD events—have shown similar results.[4,6-8] Accordingly, there is no evidence for the establishment of race-based definitions of elevated Lp(a).

Additional evidence has emerged supporting the unique impact of elevated Lp(a) on multiple cardiovascular diseases

The most consistent and quantitatively substantial associations between elevated Lp(a) and cardiovascular disease (CVD) events are for myocardial infarction (MI) and calcific aortic valve stenosis (CAVS).[2,3,9-11] Higher Lp(a) levels are also associated with a stepwise increase in the risk of peripheral artery disease, abdominal aortic aneurysms, and major adverse limb events.[12] However, in comparison, associations of Lp(a) with ischemic stroke,[2,3,9,10] heart failure,[3,9] and cardiovascular mortality[3,10,13,14] are less strong, and a higher Lp(a) level is required to see a similar increment in risk for these outcomes. For example, in participants of European ancestry in the Copenhagen General Population Study, the Lp(a) level associated with HR of 1.5 for MI was 193 nmol/L (89.5 mg/dL) and for CAVS was 154 nmol/L (71.3 mg/dL), whereas the levels were higher for ischemic stroke (323 nmol/L [150 mg/dL]) and heart failure (261 nmol/L [121 mg/dL]).[9] Recent studies have also