Study.[52] While MESA participants with both high CAC score and elevated Lp(a) were at the greatest ASCVD risk, a trend of increased risk was observed in participants with high Lp(a) but CAC score of 0 (HR 1.31 [95 % CI 0.73–2.35]). In addition to promoting atherosclerosis, elevated Lp(a) is purported to increase CVD risk through other mechanisms, such as being prothrombotic and proinflammatory. In addition, elevated Lp(a) is not consistently associated with baseline CAC and CAC progression,[53] implying a distinct underlying pathobiology. Thus, a CAC score of 0 does not eliminate the risk associated with elevated Lp(a), particularly in younger adults, in whom a CAC score of 0 may underestimate the lifetime risk of ASCVD and provide false reassurance.

What recommendations should be offered to patients?

Lifestyle modification

Adoption of a healthy lifestyle is the foundation of all prevention guidelines. Although diet and physical activity have minor and variable impacts on Lp(a) concentrations, a healthy lifestyle is clearly associated with reduced vascular risk and should be recommended for all adults and children, particularly high-risk patients, such as those with elevated Lp(a). In a large prospective observational study, individuals with elevated Lp(a) ($\geq\sim$125 nmol/L) but otherwise optimal cardiovascular health scores had lower risk of incident CVD compared with individuals with lower Lp(a) levels but poor cardiovascular health.[54]

Statins

Across all professional society guidelines, statins remain first line-therapy for mitigating LDL-C–driven ASCVD risk in both secondary and high-risk primary prevention patients.[55] Although statins do not lower Lp(a) and may slightly increase Lp(a), statins clearly lower ASCVD risk, reducing major adverse cardiovascular events (MACE) by approximately 22 % for each 1-mmol/L (38.7 mg/dL) reduction in LDL-C.[56] In the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), median Lp(a) was not affected by rosuvastatin treatment, but Lp(a) distribution was shifted toward higher percentiles; patients with Lp(a) level above or below the median had similar benefit with rosuvastatin, and risk for MACE was increased in patients with higher baseline or on-treatment Lp(a) levels.[18] The Lp(a)-raising effects of statins are minimal on average, with an approximate 1.1-mg/dL increase or 0.1 % relative increase in Lp(a) on statin treatment as seen in a large meta-analysis.[57] Although some individuals may have greater increases, especially after high-intensity statin therapy, concerns about Lp(a) elevation should not be a reason to discourage or discontinue statins. Of note, ongoing clinical trials of targeted Lp(a) therapeutics in high-risk ASCVD patients are all being conducted on a background of statin therapy, as statin therapy remains the standard of care for secondary prevention patients.

Ezetimibe and bempedoic acid

Ezetimibe does not affect Lp(a) levels appreciably. A statistically significant 7.1 % Lp(a) reduction in one meta-analysis (including 7 trials and 2337 patients with primary hypercholesterolemia) was not considered clinically significant by the investigators,[58] and another meta-analysis (including 10 trials and 5188 patients with primary hypercholesterolemia) showed no effect on Lp(a) level with ezetimibe as monotherapy or in combination with statin.[59] Bempedoic acid also does not affect Lp(a) level.[60]

PCSK9-directed therapies

PCSK9 inhibitors, including monoclonal antibodies (evolocumab and alirocumab) and small interfering RNAs (siRNAs; inclisiran), can lower Lp(a) by approximately 20–30 %,[19,61,62] although they are not approved for this indication. Moreover, in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial in stable ASCVD patients, evolocumab conferred a greater relative risk reduction among individuals with elevated Lp(a) compared with those without elevated Lp(a), another indication that higher risk patients derive more benefit from intensive LDL-C/apoB–lowering therapy, which may include benefit from Lp(a) lowering.[19] The reduction in MACE with evolocumab was 25 % in patients with baseline Lp(a) above the median (120 nmol/L; HR 0.75 [95 % CI 0.64–0.88]) vs 11 % in those with baseline Lp(a) at or below the median (HR 0.89 [95 % CI 0.79–1.01]; p-interaction = 0.096), and the reduction in MACE appeared proportional to Lp(a) level achieved. Similarly, in ODYSSEY Outcomes, each 1-mg/dL reduction in Lp(a) with alirocumab was associated with HR of MACE of 0.994 (95 % CI 0.990–0.999; $p = 0.0081$).[63] Thus, if a high-risk patient needs additional LDL-C lowering after maximally tolerated statin therapy and also has elevated Lp(a), a PCSK9 inhibitor may be a good choice to address residual risk from both LDL-C and Lp(a).

Niacin

Niacin may lower Lp(a) concentration by decreasing apo(a) production rate. In a meta-analysis of 14 randomized placebo-controlled trials of extended-release niacin (including a total of 9013 patients), niacin was associated with a significant 23 % reduction in Lp(a) levels.[64] Although niacin monotherapy provided ASCVD benefit in men in the secondary-prevention Coronary Drug Project,[65,66] more recent studies of statin combined with niacin as an HDL-C–raising agent did not show clinical benefit despite ~20 % reductions in Lp(a) level.[67,68] Therefore, niacin is not recommended for Lp(a) lowering.

Aspirin

Although aspirin remains a class I recommendation for the secondary prevention of ASCVD, its use is less well established for primary prevention, with recent clinical trials suggesting more harm than benefit. As such, the 2019 ACC/AHA Guideline on the Primary Prevention of CVD