small dense LDL-C has been shown in several large epidemiologic studies to be more closely related to ASCVD risk than LDL-C.

Lipoprotein (a) [Lp(a)] is a class of lipoprotein that is structurally related to LDL and contains apoB-100, as well as apolipoprotein(a) [apo(a)]. It represents a specific class of atherogenic particles and is an independent risk factor for ASCVD. The clinical utility of Lp(a) was recently reviewed in a recent statement from the NLA[58] Lp(a) elevations are for the most part genetically determined, but can also be elevated with low estrogen levels, severe hypothyroidism, and chronic kidney disease.[58] Lp(a) assays are not well standardized and information on the analytical accuracy and precision of Lp(a) assays used in patient care is limited. Lp(a) particles are typically heterogeneous due to remarkable interindividual variation in the size of the defining apo(a) lipoprotein, and some assays have limitations as measurements are based on an assay calibrator of fixed size. Except for a few research laboratories, many commercial methods continue to use different calibrators with values traditionally assigned in mg/dL that may not accurately reflect the number of Lp(a) particles. Some experts have suggested that measuring Lp(a) or apo(a) molarity may provide greater accuracy.[59,60] For the measurement of Lp(a) the NLA specifically recommends use of an immunochemical assay that is calibrated against the WHO/IFCCLM secondary reference material. The preferred reporting measurement is in nmol/L.[58]

According to data from the 2018 College of American Pathologists ABL-B laboratory survey, Lp(a) assay variability, expressed as coefficient of variation, can be as high as 26% CV. The precision of most Lp(a) assays ranges between 10% to 12% and appears to be independent of TG levels.[61] Despite deficiencies in Lp(a) measurement accuracy, a recent NLA scientific statement that focused on Lp(a) and its clinical utility concluded that Lp(a) levels could help guide clinical management of patients.[58] The 2018 AHA/ACC Multi-Society Cholesterol Guideline classified Lp(a) measurement as a risk enhancer that could help to guide care for persons at intermediate ASCVD risk. Measuring Lp(a) may also be valuable in patients with a strong family history of ASCVD, patients who do not fully respond to statin therapy, or those who go on to have an ASCVD event while on evidence-based lipid-lowering therapy.[58]

Specific considerations for traditional and advanced lipid testing

Question: *For high-risk patients with LDL-C below 70 mg/dl on treatment, which lipid/lipoprotein measures are most appropriate to assess residual atherogenic burden?*

For patients at high ASCVD risk with LDL-C < 70 mg/dl, the current threshold for potential further intervention, residual atherogenic burden may be ascertained by assessing measures of other lipid measurements beyond LDL-C. The three most widely used assays to assess this residual burden are non-HDL-C, apoB and LDL-P. In general, these measurements are more likely to be discordant from LDL-C in the presence of elevated plasma TG and/or low HDL-C. In patients with hypertriglyceridemia, there is elevation of triglyceride-rich lipoproteins, which contain both cholesterol and apoB. The cholesterol within triglyceride-rich lipoproteins has been given various names, such as VLDL-C or REM-C, where (REM-C) = (Total-C)- (HDL-C) – (LDL-C). Perhaps the most accurate designation for the mechanistically active component is triglyceride-rich lipoprotein cholesterol (TRL-C). These measurements are not synonymous, but pragmatically represent equivalent levels of atherogenic cholesterol that are elevated in patients with hypertriglyceridemia. There is increasing evidence that TRL-C is at least equivalent in atherogenicity to LDL-C, but interventional trials that target lowering this cholesterol moiety are lacking. An ongoing clinical trial (PROMINENT) that assesses pemafibrate to reduce cardiovascular outcomes by reducing TG in patients with diabetes may provide evidence to further lower TRL-C when LDL-C is well controlled. A level of TRL-C < 30 mg/dl is considered desirable. Since non-HDL-C represents [(LDL-C) + (TRL-C)] a desirable level would be < 100 mg/dl once LDL-C is less than 70 mg/dL.

In the presence of hypertriglyceridemia apoB is elevated not only due to the presence of apoB on triglyceride-rich lipoproteins, but also because of CETP mediated exchange of triglyceride for cholesterol with LDL. During this process, LDL particles become triglyceride enriched and after further hydrolysis by lipases, they become smaller and denser. Since each LDL particle contains one apoB molecule, the more abundant smaller LDL particles result in a significant elevation of total apoB. Therefore, measurements of apoB or LDL-P may effectively identify a patient with an increased ASCVD risk due to a higher atherogenic lipoprotein burden. These patients may benefit from additional therapy to lower apoB/LDL-P by taking higher doses of statins, adding ezetimibe or PCSK9 inhibitors, but data from clinical trials are lacking on this topic. Quantile levels for the United Kingdom Biobank and the Framingham Heart Study are shown in **Table 6** for LDL-C, Non-HDL-C, and apoB.[62,63]

Question: *What is the utility of non-HDL-C measurement?*

Increased concentrations of non-HDL-C, which is simply the difference between the concentration of total cholesterol and HDL-C, are highly associated with the development of ASCVD events when evaluating persons at screening.[20] Measurement of non-HDL-C is not affected by fasting status and at low concentrations of atherogenic lipids this moiety can be readily estimated from results of the standard lipid panel. Several meta-analyses support both the superiority of non-HDL-C and apoB over LDL-C for both ASCVD risk assessment and for on-treatment risk assessment. One meta-analysis compared the standardized relative risk ratios for a standard deviation increment of the ASCVD risk hazard ratio for apoB, LDL-C and non-HDL-C. The investigators reported that apoB was the most potent marker of relative risk reduction (RRR) for ASCVD (RRR, 1.43; 95% CI, 1.35 to