Apolipoprotein B vs Low-Density Lipoprotein Cholesterol and Non–High-Density Lipoprotein Cholesterol as the Primary Measure of Apolipoprotein B Lipoprotein-Related Risk

The Debate Is Over

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In 1979, Avogaro et al reported that apolipoprotein B (apoB) was a more accurate marker of the risk of a myocardial infarction than total cholesterol. In 1980, Sniderman et al reported that low-density lipoprotein (LDL) apoB was a more accurate marker of the risk of angiographic coronary lesions than LDL cholesterol (LDL-C). They inferred that the mass of cholesterol per apoB particle could vary and they speculated that the number of apoB particles mattered more than the cholesterol they contained because it was the particle that entered and was deposited within the arterial wall. Since then, there has been considerable debate whether apoB, LDL-C, or non–high-density lipoprotein cholesterol (non-HDL-C) should be the primary measure of apoB lipoprotein-related risk. The debate is over.

In this issue, Marston and colleagues supply decisive evidence from a large, prospective observational study, UK Biobank, and 2 clinical trials, FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and IMPROVE-IT (Improved Reduction of Outcomes With Vytorin Efficacy International Trial), that apoB should be the primary marker to assess the cardiovascular risk due to the apoB lipoproteins.

This line of thought has been driven as much by advances in basic science as by epidemiology and clinical trials. The discovery of cholesterol ester transfer protein by Patska et al uphoulds the work by Krauss et al, which showed that the cholesterol content of LDL particles varied. By contrast, each apoB lipoprotein particle always has only a single apoB molecule; therefore, apoB equals atherogenic particle number. Because the mass of cholesterol per particle is variable, LDL-C and non-HDL-C can differ significantly from apoB. Because non-HDL-C and LDL-C are physiologically related and highly correlated with apoB, many have argued that LDL-C and non-HDL-C are “good enough” to measure lipoprotein-related risk. Meanwhile, evidence from prospective observational studies, including discordance analyses, mendelian randomization studies, and studies in statin-treated patients, has mounted steadily in favor of using apoB over LDL-C and non-HDL-C to measure atherogenic risk of apoB lipoproteins.

Not only does apoB better predict risk than LDL-C or non-HDL-C, it also better predicts benefit from lipid-lowering therapy. The landmark study by Ference et al, who applied mendelian randomization to simulate randomized clinical trials, demonstrated that reduction of equal numbers of very LDL and LDL particles produced equivalent clinical benefit. Johannessen et al recently demonstrated that apoB was a more accurate marker of cardiovascular risk in statin-treated patients than LDL-C or non-HDL-C. The present analysis by Marston et al should provide a final coup de grâce for LDL-C and non-HDL-C.

Marston et al confirm that the hazard ratios of LDL-C, non-HDL-C, and apoB per standard deviation increase are virtually identical in UK Biobank. That the hazard ratio is similar does not mean they are equally useful in predicting risk. When cholesterol-depleted particles are present, the risk predicted by apoB will be higher than the risk predicted by LDL-C or non-HDL-C. The converse will be true when cholesterol-rich particles are present. In their study, LDL-C and non-HDL-C become nonsignificant markers of risk when apoB is taken into account, demonstrating that the risk of LDL-C and non-HDL-C is fully captured by the number—not the cholesterol content—of the apoB-containing particles. These findings are further supported by data from IMPROVE-IT, which randomized the addition of ezetimibe to statin therapy, and FOURIER, which randomized the addition of a PCSK9 inhibitor to maximally tolerated statin therapy in patients with preexisting cardiovascular disease. That show apoB is a more accurate predictor of cardiovascular risk than LDL-C or non-HDL-C. Thus, there is now broad and consistent evidence from observational studies and post hoc analyses of randomized clinical trials, in both primary and secondary prevention, supporting the superiority of apoB.

But there is another, just as critical, argument for apoB: apoB is far less prone to measurement error than LDL-C or non-HDL-C. The European Atherosclerosis Society/European Federation of Laboratory Medicine consensus report states that apoB can be measured inexpensively, and more accurately, than LDL-C or non-HDL-C, using standardized, automated, widely available methods that produce results as rapidly as a conventional lipid panel. In contrast, accurate, standardized LDL-C measurement remains elusive, as evidenced by ongoing efforts to develop new equations to estimate LDL-C from a traditional lipid panel. How can the decision about who to treat and how aggressively to treat be based on anything but the most reliable and accurate test available? What is the argument for selecting patients for therapies based on a less reliable and less accurate test when a superior alternative is available?

Yes, LDL-C has been the primary marker of clinical effectiveness reported in the major randomized controlled clinical trials of lipid-lowering therapy. But statins and PCSK9 inhibitors lower very LDL apoB particles as well as LDL apoB particles. Therefore, LDL-C is an incomplete marker of the benefit of statin, ezetimibe, or PCSK9 therapy. Others have proposed using non–HDL-C instead of LDL-C. But non-
HDL-C is simply a surrogate marker of particle number, is less accurate in predicting risk compared to apoB, and is not measured as reliably.\textsuperscript{3,7,9} If the paradigm is to shift, why not shift to the best marker?

Does measuring apoB mean abandoning the conventional lipid panel? No. Together, apoB and a conventional lipid panel allow accurate diagnosis of all the clinically significant dyslipoproteinemias, including type III hyperlipoproteinemia. To assess the adequacy of therapy for the atherogenic dyslipoproteinemias except type III, apoB is all that needs to be measured, a change that would simplify and improve care. Some claim that transitioning to apoB from LDL-C would be too difficult as health care professionals are so accustomed to LDL-C. We do not agree. Physicians adapt to change and innovation all the time. ApoB would certainly be easier for patients to understand than non-HDL-C: rather than discussing “bad cholesterol,” we shift to discussing the “number of bad cholesterol particles.”

Changes in physician practices regarding measurement and monitoring of apoB can be catalyzed by increased emphasis of apoB in the guidelines. The 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines have already stated unequivocally that apoB was the best marker of the atherogenic lipoproteins.\textsuperscript{7} Other major guidelines should endorse apoB for routine clinical care and encourage health care professionals to transition from LDL-C to apoB in clinical practice. To support health care professionals in this transition, guidelines should provide the reference ranges to trigger initiation or augmentation of lipid-lowering therapy, just as they presently do with LDL-C.

It is now more than 40 years since the first articles demonstrating the potential clinical utility of apoB were published.\textsuperscript{1,2} LDL-C does predict the atherogenic risk of lipoproteins because it is highly correlated with the number of apoB particles. Trapping of apoB particles is the fundamental cause of atherosclerosis and the number of apoB particles in plasma is the most important driver of this trapping within the arterial wall.\textsuperscript{6} ApoB can be measured directly and accurately, and better predicts risk than LDL-C or non-HDL-C. Accordingly, apoB should be the primary measure of the atherogenic risk of the apoB lipoproteins and the primary measure of the adequacy of therapy to lower the apoB lipoproteins. Using apoB is not the last step to improve clinical care, but it is an important next step. Given the totality of the evidence, to further delay introducing apoB into routine clinical care would break faith with our commitment to practice evidence-based medicine.