Is LDL-C Passed Its Prime?
The Emerging Role of Non-HDL, LDL-P, and ApoB in CHD Risk Assessment
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Recently, my son, an internal medicine resident of a major academic medical center, called to ask my advice about a patient in the hospital. The case involved a 52-year-old female with type 2 diabetes mellitus, cigarette smoker with an LDL-C of 95 mg/dL, an HDL of 32 mg/dL, and triglycerides of 300 mg/dL. He wanted to initiate statin therapy, but both his senior residents and attending physician were adamant that pharmacological therapy was not indicated because her LDL-C was already below the 100 mg/dL goal according to the ATP III guidelines. This case, along with the tragic death of Tim Russert with an "optimal level" of LDL-C of 68 mg/dL (but a low HDL and elevated triglycerides), highlight the need for a different paradigm to better assess CHD risk and guide treatment.

Targeting LDL-C as the primary goal of therapy was established by the NCEP ATP I guidelines and reinforced in ATP II and ATP III.1 ATP III added non–HDL-C as a secondary goal in patients at their LDL-C target with triglycerides ≥200 mg/dL, but according to surveys, non-HDL goal achievement has significantly lagged behind that of LDL-C goals.2 The recommendation to focus on LDL-C has been largely successful with a marked improvement in goal achievement over the past several years that has led to a significant reduction in CHD mortality in the United States.3 However, two major trends are affecting the ability of LDL-C to serve as the best lipoprotein to target for CHD risk reduction. First, the U.S. population is becoming more obese, with the prevalence of mixed dyslipidemia associated with metabolic syndrome increasing dramatically.4 In patients with metabolic syndrome, the discrepancies between LDL-C and other lipoprotein measures such as apoB, LDL-particle number (LDL-P), or non-HDL are much greater, resulting in a loss of CHD risk predictors for LDL-C in this population.5 Secondly, recent large trials have shown that for patients on statin treatment, non-HDL, apo, and LDL-P are better than LDL-C at predicting cardiovascular outcomes.6 Because the majority of patients on statin therapy have either diabetes or some component of the metabolic syndrome, there is an increasing need to identify in these patients the degree of residual CV risk that warrants further intervention. Therefore, the need to address the increase in residual CV risk on statin therapy has led to increased efforts to move beyond LDL-C to focus goals of therapy on non–HDL-C, apoB, and LDL-P. Recently, a consensus statement from the American Diabetes Association and the American College of Cardiology on lipoprotein management in patients with cardiometabolic risk recommended more prominent roles for non–HDL-C and apoB as targets of therapy.7

To add to the support for LDL-P as a target of therapy, published in this issue of Atherosclerosis, Thrombosis, and Vascular Biology by Hsia et al is an analysis of the Women’s Health Initiative (WHI) Hormone Trial.8 This trial determined two important points: LDL-P predicts risk better than LDL-C and estrogen therapy, whereas lowering LDL-C does not lower LDL-P. This lack of benefit for LDL-P reduction with estrogen therapy may explain the reason oral conjugated estrogen does not reduce CVD in postmenopausal women. Oral estrogen therapy, lacking a reduction in LDL-P but potentially increasing thrombosis and inflammation, results in a net hazard ratio of 1.81 in year one of the estrogen/progestin arm and a relative hazard of 2.3 in four months of the HERS study.9 The mechanism by which oral estrogen does not lower LDL-P is unclear, but a potential hypothesis is that VLDL secretion is increased causing the production of more small dense LDL particle. In addition, oral estrogen increases LDL-receptor upregulation enhancing clearance, resulting in a net no change in the LDL-P (Figure).

The lack of CV benefits for estrogen therapy, despite a reduction in LDL-C, is often used by critics of the LDL hypothesis as an example of an LDL-C lowering treatment that does not improve outcomes. Another example has been torcetrapib, which also lowered LDL-C and increased mortality.10 It is now clear that although both drugs lower LDL-C,11 they do not lower LDL-P and, therefore, the LDL-lowering hypothesis remains valid as long as LDL-P or apoB are adequately lowered without adversely affecting other CV risk factors. In addition to LDL-P, Hsia et al report that VLDL-P and triglycerides were significantly higher in CHD patients compared to controls. Because oral estrogen raises VLDL-P and triglycerides, this may also explain the lack of benefit for hormone therapy for postmenopausal women.8

For clinicians, regulatory authorities, and national guideline committees, this most recent information should help guide implementation of new targets for therapy. An LDL-C focus has worked well in the past, but to address residual CV risk on statin therapy, the recent trials support a more significant role for non–HDL-C, apoB, and LDL-P.1 Although apoB and LDL-P appear to outperform non–HDL in most trials for CHD risk prediction,12 because of the increased cost associated with these tests, there needs to be more information regarding discordance between non–HDL and these advanced measurements. Regulatory authorities have raised concerns about therapies that raise LDL-C in patients with hypertriglyceridemia but decrease LDL-P (for example, fibrates and omega-3 fatty acids). Based on the most recent data, these concerns do not appear to be

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justified, and perhaps a rethinking of a pure LDL-C focus would lead to the approval of novel compounds or combination products with enhanced effects on LDL-P or apoB without LDL-C reduction. As new national guidelines are proposed based on evolving clinical trial data, an expanded focus beyond LDL-C appears warranted.

Disclosures

None.

References

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