

EDITORIAL COMMENT

Cardiovascular Risk Beyond Low-Density Lipoprotein Cholesterol*



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Over the last 50 years, routine lipid parameters for risk prediction of cardiovascular disease (CVD) have not changed: clinical assays still rely on simple biochemical measurements of total triglycerides (TGs), total cholesterol, and high-density lipoprotein cholesterol (HDL-C). Low-density lipoprotein cholesterol (LDL-C) is not always measured but calculated from non-HDL-C. Further, standard lipid tests quantify the cholesterol or TG content of lipoproteins, without providing size-specific lipoprotein particle information. By contrast, nuclear magnetic resonance (NMR) spectroscopy provides a rapid method for distinguishing and quantifying a wide range of lipoprotein subclasses. Upon exposure to a magnetic field, distinct lipoprotein subclasses emit a unique signal that is directly proportional to their concentration. Although NMR spectroscopy lacks sensitivity when compared with mass spectrometry, it can be used to analyze the lipid composition of lipoprotein subclasses (1,2).

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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In this issue of the *Journal*, Holmes et al. (3) present NMR-based findings from the China Kadoorie Biobank study that contribute to refining the quantitative and qualitative features of atherogenic lipid profiles. Very-low-density lipoprotein (VLDL) particle concentrations were at least as strongly associated with myocardial infarction (MI) and ischemic stroke (IS) as were LDL particles. Further, TGs were more consistently related with MI and IS across the entire spectrum of lipoprotein subfractions than cholesterol, and VLDL and remnant cholesterol outperformed LDL-C in CVD risk prediction in this Chinese population characterized with low mean LDL-C levels (85 mg/dl in the control group).

SEE PAGE 620

A causal role for remnant cholesterol in TG-rich lipoproteins such as VLDL has previously been suggested by meta-analysis and large-scale Mendelian randomization studies (4,5). Similarly, mass spectrometry-based proteomics in the Bruneck study ranked 3 VLDL-associated apolipoproteins—apolipoprotein C3, apolipoprotein C2, and apolipoprotein E—as first to third with regard to CVD risk prediction (6). However, these data must be interpreted in the context of the widespread use of statins for primary prevention in this cohort. Emerging studies suggest that cause for MI is shifting from plaque ruptures to plaque erosions, possibly due to the widespread use of LDL-C lowering therapies (7,8). With low LDL-C levels, the relative contribution of TG-rich lipoproteins to CVD risk may increase.

The China Kadoorie Biobank study (3) offers additional remarkable insights. First, the data contradict the conventional, yet outdated view that lipids are predominantly a risk factor for MI and are only a weak predictor for IS. In fact, the associations of lipoprotein particles with MI and IS were highly concordant, and their magnitude was only marginally lower for IS. This is supported by other studies that obtained

similar findings for MI and IS, that is, by measuring the plasma lipidome (9) or apolipoproteins such as lipoprotein (a) (10-12). The most recent meta-analysis of LDL-C lowering therapies yielded a risk reduction of 24% for MI and 19% for overall stroke for more intensive versus less intensive therapy (13). The randomized controlled trials (RCTs) for proprotein convertase subtilisin/kexin type 9 inhibition and ezetimibe therapy but not cholesteryl ester transfer protein inhibition with anacetrapib reported benefits of lipid-lowering therapy for IS similar to or even higher than for MI (14-17). Taken together, these findings are consistent with the notion that lipids promote atherosclerosis systemically and that atherosclerosis is a main underlying cause for IS across its major subtypes. The pathogenetic relevance of lipids is obvious for IS as a downstream manifestation of atherosclerosis in extracranial or intracranial large arteries, one of the main causes of stroke in China. It is also plausible for small-vessel stroke. Small-vessel strokes commonly arise from plaques at the orifice of the penetrating artery rather than from lipohyalinosis. The pathogenic relevance, however, may also extend to cardioembolic stroke and embolic stroke of undetermined source. Stiffening of the aorta due to atherosclerosis and subsequent loss of the Windkessel function may elicit a diastolic backward flow at the upper circumference of the aortic arch redirecting cardiac emboli into the cerebral circulation. A large proportion of embolic stroke of undetermined source may actually be the consequence of fissuring of nonstenotic plaques that escape detection by carotid ultrasound. Further research into the role of lipids in the IS subtypes is required to draw more definitive conclusions.

Second, the Chinese Kadoorie Biobank Study (3) provides clarity as to one of the most controversial topics in stroke medicine—the purported protective role of lipids for intracerebral hemorrhage (ICH). In brief, none of 61 NMR spectroscopy parameters (lipoprotein particle concentrations and composition, particle size, and apolipoproteins) exhibited a significant relationship with ICH despite the high incidence of ICH in the Chinese population and the large number of cases (1,138 ICH patients) included in the analysis. Importantly, there was no signal suggesting that low cholesterol or TG levels confer a higher risk of ICH, as has been suggested by a large-scale meta-analysis of observational studies including 1.4 million participants and 7,960 ICH cases (18). This literature-based meta-analysis might have been confounded by unrecorded comorbidities that alter lipid levels (e.g., liver and renal disease, inflammatory diseases and malignancies), inclusion of high-risk individuals for

CVD who were treated with statins, and other determinants of ICH risk (e.g., alcohol consumption and socioeconomic status) that were not rigorously assessed. This view is corroborated by genetic association studies demonstrating a higher risk of ICH in carriers of variants related to high rather than low cholesterol levels (19). Moreover, the initial finding of the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial that high-dose statin therapy increases the risk for ICH appears to have been an artifact of the intention-to-treat principle and was not confirmed in any other RCT testing lipid-lowering strategies, nor in subsequent meta-analyses (20,21). Even in the setting of stroke thrombolysis, there was no higher risk of ICH among statin users (22). Although it is premature to close this discussion, the study by Holmes et al. (3) in this issue of the *Journal* adds further evidence that the proposed link between low cholesterol and ICH is a misconception.

Third, now that most RCTs on HDL-C raising strategies have failed and Mendelian randomization studies refute a causal role of HDL-C in CVD, research should target HDL composition, functionality (e.g., cholesterol efflux capacity), and other qualitative features. The Chinese Kadoorie Biobank study (3) suggests that the TG rather than the cholesterol content of HDL is a determinant of atherogenicity. Finally, circulating glycoprotein N-acetylglucosamine residues—a glycan biomarker linked to inflammation and aging—showed one of the strongest associations across all 3 main vascular endpoints (MI, IS, and ICH). More studies are required to scrutinize these associations and to further explore cause and effect.

We are entering a new era of lipid management (12,14-16). With a growing armamentarium of lipid-lowering therapies, patients can be more readily treated to achieve the recommended LDL-C target levels. Besides LDL-C, the therapeutic focus may broaden to tackle the residual CVD risk and include VLDL and TGs (3-6,23), as well as fatty acid composition (9,24) and other apolipoproteins, that is, lipoprotein (a) (10-12). It is time to advance NMR spectroscopy and mass spectrometry technologies for lipoprotein and apolipoprotein profiling to meet the high throughput, low cost, and standardization required for potential clinical use (25,26). The application of multiomics technologies may pave the way toward redefining CVD risk (27).

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KEY WORDS apolipoproteins, biomarkers, mass spectrometry, nuclear magnetic resonance spectroscopy, precision medicine