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Lipid Profiles and Coronary Artery Plaque by CT Angiography: Promise for Translation of Biology to Imaging

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Abnormal lipid levels, particularly elevated low-density lipoprotein (LDL-C) and decreased high-density lipoprotein (HDL-C), are well-established independent risk factors for cardiovascular disease (CVD), including coronary artery disease (CAD).¹ Large scale randomized controlled trials provide strong evidence for net benefits from LDL-lowering drug therapies, such as statins, although available trials to date do not show evidence for a benefit from HDL-raising drug therapy.² However, non-HDL cholesterol has received increasing attention for its potential role in CVD risk.^{3,4} The recognition of the critical role of LDL-lowering is reflected in consensus lipid-lowering guidelines⁵ currently being updated by the National Heart, Lung, and Blood Institute. Atherosclerotic plaques, the hallmark of CAD, are intermediate lesions in clinical CAD and cause progressive vessel narrowing or may rupture, leading to acute coronary syndromes. Because plaque rupture may occur at areas of only modest plaque severity⁶ and the propensity for plaque rupture is associated with plaque morphology,⁷ keen interest lies in non-invasive methods to characterize the presence and location of *high-risk* atherosclerotic plaques beyond simple quantification of lesion presence and severity.

Assessment of coronary calcification and extent of coronary stenosis using coronary computed tomography (CT) and CT angiography (CCTA) have been shown to be associated with and add to prediction of CVD events^{8–10} and may increase the efficiency of diagnosis of significant coronary stenoses in the evaluation of acute chest pain.^{11,12} The use of CCTA to determine atherosclerotic plaque characteristics is still evolving. Numerous studies have evaluated the ability to differentiate plaque composition by Hounsfield units on CCTA.^{13–15} Evidence suggests that partially calcified plaque, consisting of both non-calcified and calcified plaque, on CCTA is associated with CVD events.^{16–18} Given that certain plaque

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characteristics may be associated with worse prognosis, understanding the modifiable risk factor associations of such characteristics may help target areas for prevention and or therapy.

In the current issue, Nakazato et al. describe the association of lipid subtypes with CCTA in the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes) study, an international, multicenter registry. In this study, from 27,125 consecutive patients undergoing CCTA, the investigators identified 4,575 individuals without prevalent CAD and not taking lipid-lowering medication. All patients had fasting lipid profiles available, including LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and total cholesterol (TC). Overall, the prevalence of significant CAD was low: 57% had no CAD and the large majority did not have non-calcified plaque (NCP) or mixed plaque (MP). In multivariable-adjusted analyses, the presence of NCP was associated with elevated TC and non-HDL cholesterol and low HDL-C, with strongest associations between greatest lipid levels and NCP. For both non-HDL-C and LDL-C, results showed modest associations of the greatest lipid level subgroups with calcified plaque (CP), though the strength of associations were less than for NCP. No lipid subtypes were associated with MP. These findings suggest that, in a relatively healthy, statin-naïve referral sample, specific lipid types are associated with particular characteristics of atherosclerotic plaque. This study makes progress towards understanding the connections between lipid biology and clinical manifestations of atherosclerosis, which may have implications for future risk stratification and more personalized medical treatment of individuals with dyslipidemia.

CCTA has a well-established role to evaluate for flow-limiting stenoses of low to intermediate-risk patients with chest pain,¹⁹ and the evaluation of its benefit in long-term outcomes against established functional imaging techniques hopefully will be answered by the ongoing PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) trial. Does evidence suggest utility of assessing atherosclerotic plaque composition in clinical practice? Traditionally, lipid-laden plaque has been considered more prone to rupture while CP may be relatively more stable,⁷ but recent evidence suggests that MP may confer relative instability and a worse prognosis.^{16–18} Nakazato et al. observed associations between lipid subtypes and predominantly NCP, but no association of lipid types with MP. The translation of these findings into clinical practice is not immediately clear, as NCP may be lipid-rich or alternatively fibrous in content. One issue underlying the limited ability to differentiate these plaque types is their considerable overlap in the Hounsfield units both within and between studies.^{13–15} Further investigation into alternative thresholds, new quantitative methods for analyzing plaque, or use of combined molecular imaging to target inflammation, may eventually allow improved recognition of specific and high-risk plaque types. In addition, as CT technology continues to advance rapidly, even greater spatial resolution will improve our ability to image atherosclerotic plaque.

Even with reliable discrimination of plaque composition, however, several remaining factors preclude routine use of CCTA for plaque characterization in clinical practice at present. Beyond the current limited body of evidence,^{16,17,20} independent data are needed to establish that CCTA plaque type independently predicts increased risk for CAD and improves upon currently available strategies such as assessment of coronary artery

calcification. It will be with the understanding of CCTA plaque prognosis that the findings of current study, and other future studies demonstrating associations with CCTA plaque, will be placed in context. Once plaque characteristics and their respective associations by CCTA are able to be reliably identified, the ultimate management, medical and/or procedural interventions tailored to plaque type, will need to be determined. In addition, similarly to the use of CCTA to screen for coronary stenosis, the ideal population to be screened must be defined. A related issue that would need to be addressed is the healthcare expenditures associated with CCTA, with consideration of number needed to screen in cost-effectiveness analyses. Furthermore, with newer tests with increasing sensitivity to detect lesions, there is a potential for greater false positive studies, leading to further interventions which may not be necessary. Lastly, as with any screening strategy, practitioners need to carefully consider the adverse effects from intravenous contrast and radiation exposure, the latter of which has continued to be reduced through newer techniques, as well as the risk of unnecessary procedures. Further investigation in these numerous aspects will be required for a complete evaluation of the use of CCTA to discriminate plaque composition as a potential adjunct in screening. Ultimately, randomized controlled trials will be necessary to demonstrate the additional benefit of assessing CCTA plaque composition.

Lipid levels are modifiable and targetable constituents of atherosclerosis with both genetic and environmental determinants. Indeed, 95 single nucleotide polymorphisms (SNPs), variants of common genetic loci, were found to influence lipid levels.²¹ Of these SNPs, only those associated with LDL have very modest association with coronary artery calcification that is no longer seen after adjustment for LDL levels in a general community sample.²² One possible explanation for these findings is that conventional lipid measures only partially capture the cholesterol or triglyceride content within circulating lipoprotein particles. Thus, a more comprehensive approach to lipid analysis may provide additional insight into disease mechanisms. In a recent study, the 95 SNPs associated with lipid levels were found to have a much stronger association with metabolites involved in lipoprotein metabolism (the “lipome”) rather than the lipid subtype levels themselves, and the SNPs explained a significantly greater variance in metabolite measures than lipid measures.²³ Examination of lipid subfractions is a parallel avenue of study to understand lipid biology and its associations. For example, evidence from large prospective studies suggests that lipid composition may have differential effects in disease processes.^{24,25} While considerable debate remains regarding the utility of lipid subfraction analysis,^{26,27} study of the upstream genetic, metabolic, and proteomic components may reveal mechanisms for the pathogenesis of atherosclerosis.

Investigation in imaging techniques and lipid biology have in parallel made significant advances in the past decade, and the investigation by Nakazano et al. is one of the few studies thus far to examine the translation of the biology into current non-invasive imaging of the coronary arteries. Future work investigating lipid genomics and metabolomics, advances in CCTA imaging technology, assessment of outcomes by CCTA plaque type, and ultimately the demonstration of treatment benefit from CCTA plaque measurements, will be required to clarify the ultimate clinical role, if any, of CCTA in the characterization, prediction, and prevention of CAD.

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