EDITORIAL COMMENT

Carotid Ultrasound, Coronary Calcium, and Dyslipidemia Patterns in the MESA (Multi-Ethnic Study of Atherosclerosis) Cohort*

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In this issue of the Journal, Paramsothy et al. (1) relate coronary artery calcium (CAC) scores and intima–media thickness (IMT) measurements to patterns of dyslipidemia. Because much of current practice is dictated by such patterns, the authors did not attempt to take into account family history, physical findings, apolipoproteins, and other tests to determine specific diagnoses such as heterozygous familial hypercholesterolemia or familial combined hyperlipidemia. Instead, the paper used operational definitions based on the dominant lipid abnormality (in order of severity: a combination of high triglycerides [TG] and high low-density lipoprotein cholesterol [LDL-C], isolated high LDL-C, increased TG with low high-density lipoprotein cholesterol [HDL-C], termed dyslipidemia of metabolic syndrome, isolated hyper-TG, and isolated low HDL). The cohort is both contemporary and large (n = 4,792), has an optimal proportion of women (53%), and substantial ethnic diversity. Confounding of lipid patterns and imaging measurements as a result of variability in duration, intensity, or type of lipid therapy was avoided by excluding pre-treated patients. Patients with diabetes mellitus were also excluded, thereby avoiding confounding by type and/or duration of diabetes and avoiding controversies about vascular effects of hypoglycemic agents. Furthermore, the study provides an opportunity to compare 2 distinctly different and topical imaging methods for assessing vascular damage, namely, CAC scores and measures of IMT. Because the main goal of the study was to determine the relationship of the dyslipidemic patterns per se and the imaging measurements of vascular disease, the authors adjusted for multiple, important confounders. Thus, analysis in this large and important cohort is methodologically sound. The main result, based on either CAC or IMT, suggests that elevation of LDL-C is indeed the dominant determinant of vascular damage and isolated hyper-TG is not.

The ARIC (Atherosclerosis Risk in Communities) study showed that hyper-TG was, at least in women, a predictor of heart disease (2). The NOMAS (Northern Manhattan Study), however, failed to associate hyper-TG with carotid plaque formation (3). In the current paper, the categorization process for assigning patients to only 1 of the dyslipidemia patterns created a group of hyper-TG patients with relatively high HDL of 54 mg/dl, which may have played a role in failing to show vascular damage. The dyslipidemia of metabolic syndrome group represents the more commonly seen pattern of high TG and low HDL-C. The CAC scoring in this group showed an increased relative risk of prevalent CAC compared with normal subjects, whereas IMT was indistinguishable from normal. In the isolated low HDL group, however, CAC scores were not abnormal, whereas the IMT of the common carotid was thicker when compared with that of normal subjects. The contribution of the differential sensitivity of the 2 methods, which is currently unresolved, to these discrepant findings cannot be properly assessed because IMT was based on continuous measurements whereas CAC analyses were dichotomous, using a single Agatston cut-off score (4,5). At most, the paper suggests that vascular effects of either isolated low HDL-C or the dyslipidemia of metabolic syndrome are not major.

Despite the cohort’s ethnic diversity and the large proportion of women, it is surprising that results failed to show any effect of these critical factors. The current analysis suggests that vascular damage is more the result of the confounding effects of other risk factors and clinical features than of biological differences in dyslipidemia-induced vasculopathy in men versus women or in differing ethnic groups. Even so, current guidelines mandate interpretation of IMT measurements with respect to sex and encourage consideration of race/ethnicity (6). The MESA (Multi-Ethnic Study of Atherosclerosis) program is expected to help us understand these effects more fully in future analyses (6).

The authors chose a limited number of dyslipidemic patterns. Analyses of concomitant high LDL-C, low HDL-C and high-TG, or elevated non-HDL or elevated ratios (i.e., LDL-C/HDL-C, total cholesterol/HDL-C, and TG/HDL-C) might have been valuable (7,8). Additionally, a prior publication from the MESA cohort has already provided a more detailed analysis of the effects of

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LDL on IMT measures of vascular damage with emphasis on the mechanistic role of LDL-C particle subclasses and size (9). So the expectation that only simple lipid measurements might clarify mechanistic linkage with vascular damage may have been overly optimistic.

The dyslipidemia of metabolic syndrome was not limited to patients meeting the formal criteria for the syndrome (10). Although waist circumference, fasting glucose, blood pressure and blood pressure therapy were used to adjust results, they were not used to identify a subgroup truly meeting metabolic syndrome criteria. Such an analysis would have been instructive to evaluate whether the constellation of lipid and nonlipid features have a synergistic, adverse impact on vascular disease or merely an additive one (11).

Lipid guidelines are very heavily focused on treatment of LDL-C, and this analysis suggests that this remains appropriate (12). Framingham risk scoring, reflecting relatively short-term risk, is currently used to determine the need for and aggressiveness of LDL-C lowering. Determination of appropriate therapy in patients with low or moderate risk is a common problem for which imaging studies are often used to help formulate a treatment plan. The Framingham risk scores in this cohort were generally low (average of 7.8% to 11.3% for Framingham-National Cholesterol Education Program coronary heart disease risk per 10 years for all groups). While the value of IMT and CAC scoring in refining risk remains controversial (13), analysis of Framingham risk and imaging findings with respect to the dyslipidemic patterns would have been useful. Indeed, prior work from this group and others has highlighted the importance of short-term versus long-term risk on detection of vascular damage (14).

The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial forces reevaluation of lipid-centric risk stratification (15). While the current paper suggests that high-sensitivity C-reactive protein (hs-CRP) did not modulate the relationship between the dyslipidemic patterns and the measures of vascular damage, no comparison was undertaken between patients who would have been eligible for the JUPITER trial and 2 important groups not represented in the JUPITER study, namely, subjects with high LDL-C and low hs-CRP, and subjects with high LDL-C and high hs-CRP.

Carotid ultrasound for the purpose of risk stratification and for assessing drug intervention is handicapped by diversity of methodologies (16,17). These methods range from those that make measurements of near and far walls in the common, internal, and external carotids and the bulb to those that make measurements only in the far wall of the common carotid; and diffuse IMT is not always distinguished from focal plaque (18–23). Thus, the term IMT represents imprecise jargon. Focal plaque formation, when present, is likely the most important vascular abnormality. When not present, only the measurement of diffuse IMT is available to phenotype a given patient. Both measurements, therefore, are important to record but may differ in the presence of diverse cardiovascular risk factors. Figure 1 of Paramsothy et al. (1) shows that the IMT of the common and internal carotid generally track each other. However, the confidence intervals for measures of the common carotid are consistently and markedly tighter than for the internal carotid. This variance may be due either to greater measurement difficulties or to greater heterogeneity of phenotypic findings (i.e., presence or absence of focal plaques) in that bed. Thus, insights into the relationship of plaque formation versus diffuse IMT with respect to the dyslipidemic patterns would have been instructive.

In conclusion, the MESA study investigators provide reassuring evidence that LDL-C is the dominant lipid determinant of vascular damage. This rich database will provide further insights into controversial issues of vascular health pertaining, for example, to the interplay between dyslipidemia and factors such as sex, ethnicity, hs-CRP, and metabolic syndrome.

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