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EDITORIAL COMMENT

Coronary Artery Calcium Score, Distribution, and Future Revascularization*

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In this issue of *iJACC*, Silverman et al. (1) report the relationship of baseline Agatston coronary artery calcium (CAC) score and coronary calcium distribution with future incident coronary revascularization in 6,540 MESA (Multi-Ethnic Study of Atherosclerosis) participants. The primary findings of this novel analysis is that baseline calcium score and the number of vessels with CAC were each independently predictive of future coronary revascularizations over a median follow-up of 8.5 years.

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Additionally, among subjects who underwent revascularization, those with more diffuse baseline CAC were at higher risk to undergo coronary artery bypass graft (CABG) versus percutaneous coronary intervention (PCI). Specifically, adjusted for overall CAC score, individuals with 3- and 4-vessel CAC were 3 to 4 times more likely to undergo coronary revascularization than were patients with CAC in a single vessel, and ≥3 vessel CAC was strongly predictive of the risk for future CABG, particularly when involving the left main coronary artery. Conversely, the risk of CABG was low in the absence of baseline diffuse coronary calcification (<3 vessels), and, not surprisingly, the absence of CAC was associated with extremely low rates of future revascularizations.

At first glance, the primary findings by the authors appear to be axiomatic. CAC scoring is a well-validated measure of the severity and distribution of coronary atherosclerosis and is a powerful predictor of future major adverse cardiovascular events—events often appropriately treated with coronary revascularization, to include CABG in cases of left main and/or multivessel coronary artery disease. The absence of CAC has been consistently demonstrated to predict an exceptionally good prognosis and probably a low risk for subsequent coronary revascularizations, particularly in an asymptomatic screening cohort. With regard to CAC distribution, a prior study of more than 25,000 asymptomatic subjects demonstrated that those with left main or 3-vessel CAC had significantly higher rates of all-cause death as compared with subjects with no disease or 1- or 2-vessel CAC, independent of total Agatston score (2). It stands to reason, therefore, that patients with high CAC scores and multivessel CAC would be more likely to undergo future coronary revascularization and that those who undergo incident CABG would be more likely to have baseline CAC involving 3 or more coronary arteries (particularly the left main), as compared with subjects who underwent incident PCI. Although numerous studies have convincingly and consistently demonstrated the superior prognostic accuracy of coronary calcium scoring vis-à-vis standard cardiovascular risk variables and other novel risk markers (e.g., high-sensitivity C-reactive protein) for all-cause mortality and coronary heart disease events (3,4), the relationship of total CAC score and distribution with long-term incident coronary revascularizations, and the type of revascularization, was previously largely unknown.

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The results of the current study provide us with important data that further refine the powerful prognostic narrative of CAC testing. The authors should be commended for this contribution. There are, however, several caveats to the current analysis that deserve discussion. Foremost, debate endures as to the wisdom of including coronary revascularization procedures as an outcome in observational studies of cardiovascular prognosis, due to the potential for this outcome to be significantly influenced by referral bias. Such residual bias could occur as a result of the influence of the results of the index test (e.g., CAC score), in which patients with higher degrees of CAC are preferentially referred for additional ischemic testing, which may invariably translate to higher revascularization rates. Additionally, patient variables and provider and regional care variations in coronary revascularization utilization may influence referral patterns for invasive coronary angiography, particularly in patients with stable clinical presentations.

Concerns about the potential for induced procedural costs and resource utilization after CAC screening were directly addressed by the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study, a pivotal randomized, prospective trial that compared CAC testing versus usual care in patients without baseline cardiovascular disease for the primary outcome of change in calculated cardiovascular risk (5). Similar to the MESA study, the care of patients during the 4 years of follow-up after CAC testing was not dictated by investigators but was left to patients and their providers. In an EISNER cohort of 1,381 subjects, additional cardiovascular testing was differentially performed according to CAC severity, primarily in the small percentage of subjects with advanced degrees of CAC. Specifically, noninvasive testing for coronary artery disease was infrequent in patients with minimal or no CAC (CAC <10) but was significantly more frequent among participants with CAC scores ≥400. Similarly, the rate of invasive coronary angiography and coronary revascularizations at 1 year were higher in those with severely elevated CAC scores but was performed exclusively among patients who had first undergone noninvasive testing and was ultimately overall performed in only 19% of subjects with a CAC score ≥1,000. Importantly, the addition of calcium scoring did not significantly increase overall estimated healthcare expenditures because the absence of CAC was associated with significantly lower rates of subsequent cardiovascular testing and costs. CAC scoring was ultimately associated with overall significant improvements in several cardiovascular risk factors (blood pressure, low-density lipoprotein cholesterol, and waist circumference) (6).

Within the current study, because of its observational nature, the "appropriateness" of subsequent coronary revascularizations could not be precisely determined, and the influence of CAC test results on subsequent patient and provider behavior regarding cardiovascular testing and risk factor modification is regrettably unknown. Additionally, the relationship of changes in post-test risk factors to subsequent rates and type of coronary revascularization cannot be elucidated. Furthermore, the clinical outcomes and symptom status of patients after revascularization were not reported. Fortunately, the authors reassuringly demonstrate that very few revascularizations occurred within 90 days of CAC testing (median time to revascularization, 3.6 and 4.0 years for PCI and CABG, respectively) and that the majority of revascularizations (85%) were temporally related to MESA-adjudicated angina or myocardial infarction. The authors also performed a sensitivity analysis evaluating only patients with symptoms/myocardial infarction and reported no overall differences in the primary study findings. While serial CAC scoring was performed in many MESA study participants, with prior reports highlighting the prognostic usefulness of CAC progression on composite coronary outcomes (that included symptom-related revascularization) (7), the relationship of CAC progression to overall long-term rates and type of coronary revascularization and post-revascularization outcomes is of interest and remains unelucidated.

Notwithstanding these limitations, patients, providers, and all imaging stakeholders will undoubtedly appreciate the additional pragmatic prognostic information provided by this pivotal MESA analysis. In fact, one would be remiss by failing to mention the tremendously positive, enduring impact that the MESA study, and its cohort of tireless investigators, has had on the field of noninvasive atherosclerosis imaging and cardiovascular risk prediction. We have learned—and continue to learn—enormously from this seminal National Institute of Health/National Heart, Lung, and Blood Institute–sponsored study.

However, above all, data from MESA have made the following statement nearly indisputable: CAC testing is currently the most accurate noninvasive method for the assessment of individual cardiovascular risk in asymptomatic adults.

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Key Words: cardiac CT ■ coronary artery calcium ■ coronary artery disease ■ revascularization.