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## Indices of Subclinical Atherosclerosis: Signposts on the Highway to Disease

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Cardiovascular events are the leading cause of mortality and morbidity worldwide; so it is not surprising that over the past 3 decades there have been many attempts to identify groups of persons at higher risk than others and to refine individual risk prediction. The Framingham Heart Study Risk Scores for predicting coronary artery disease and stroke have been widely used, are recommended by the American Heart Association, and have been integrated into a global cardiovascular disease (CVD) risk score.<sup>1-3</sup> Most recently they formed the basis for the AHA/ACC guidelines for CVD risk assessment. These risk scores use levels of risk factors at the time of risk prediction (current exposure) to predict risk, however, the duration and severity of exposure to a risk factor prior to the time of risk prediction (remote exposure) also determines risk, as has been demonstrated for the association of hypertension with stroke risk.<sup>5</sup> Measures of subclinical disease are useful markers of past exposure to risk and pre-existing injury, signposts as it were of how far along an individual might be on the highway to disease. Incorporating such measures into purely risk factor based prediction algorithms might, therefore, be expected to improve risk prediction.

Coronary artery disease has been associated with an increased risk of stroke. Mechanisms likely include an increased risk of cerebral emboli from a mural thrombus secondary to infarction or a low ejection fraction and an increased susceptibility to atrial fibrillation (AF). However coronary artery disease is also a marker of systemic atherosclerosis, which is why presence of documented coronary artery disease (angina or myocardial infarction) is an important component of the Framingham Stroke Risk Profile (FSRP).<sup>1</sup> As early as 1971, William B. Kannel, a founder of the Framingham Study made the observation that whereas presence of a carotid bruit was associated with a doubling of the risk of stroke, more often than not, the brain infarction occurred in a vascular territory different from that supplied by the carotid with an audible bruit.<sup>6</sup> This observation suggested that the carotid bruit was an indicator of increased risk of stroke but largely as a marker of severity of systemic vascular disease and not necessarily as a direct effect of the local stenosis. The same logic explains

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why incorporating a marker of peripheral artery disease in the CHADS-VaSC score improves prediction of stroke risk in persons with atrial fibrillation. Thus, although genetic, anatomical, environmental and other unknown factors do result in some heterogeneity in inter-individual patterns of progression of atherosclerosis in cerebral, coronary and peripheral arterial beds, overall measures of atherosclerosis in any one vascular bed reflect extent of atherosclerosis in other regions in the same person.

Measures of coronary artery calcium load, assessed using electron-beam CT or multi-detector CT are known to be strongly correlated with presence of coronary atherosclerosis, hence they are a robust marker of subclinical coronary heart disease and systemic atherosclerosis. Such imaging modalities also have the advantages of being non-invasive, objective, quantifiable and repeatable. The possible advantages, or lack thereof, of adding CAC to clinical risk prediction scores in designing primary prevention strategies for coronary artery disease have been explored in some detail and were debated in a recent issue of *Circulation Cardiovascular Imaging*.<sup>7</sup> However, the value of CAC as a stroke risk predictor has been previously addressed in only one study on a German cohort.<sup>8</sup>

In this issue of *JACC Imaging*, nearly 6800 persons of diverse race/ethnic backgrounds, aged 45-84 years, from the Multi Ethnic Study of atherosclerosis (MESA) who had baseline assessment of vascular risk factor levels and of CAC were followed for nearly a decade for the development of new onset strokes or transient ischemic attacks (TIAs). CAC scores, assessed as a continuous measure, or as a score above or below the ACC/AHA recommended cut off of a >300 Agatston score, were predictive of incident stroke risk even after adjustment for age, sex, race/ethnicity, body-mass index, systolic and diastolic blood pressure, blood pressure medication use, total and HDL cholesterol, statin use, cigarette smoking and interim atrial fibrillation. There was a 70% higher risk of stroke/TIA and 60% higher risk of stroke in persons with a positive CAC status. CAC was an independent predictor of stroke risk and improved discrimination when added to the full model described above (c statistic: 0.744 vs. 0.755) or when added to the FSRP (c statistic: 0.664 versus 0.706;  $p < 0.01$ ). The improvement in risk prediction was greatest for persons at intermediate *a priori* risk of stroke. Measures of reclassification and number needed to screen were not reported. Also not discussed was whether the absence of CAC can be used to downgrade stroke risk and defer preventive interventions such as aspirin or anti-coagulants. A strength of this paper is its affirmation of the value of CAC as a marker of stroke risk in a geographically and ethnically diverse sample. MESA participants were 38% white, 28% black, 22% Hispanic and 12% Chinese and lived in different parts of the East and West Coast of the US; however MESA does not include other ethnic groups such as American Indians and South Asians who are high-risk groups for stroke. Also, the study design of MESA excluded persons with prevalent CVD, hence this sample had a lower stroke risk than average. A further caveat is that the full model described here did not adjust for prior coronary heart disease or heart failure, and the FSRP does not take into account lipid levels or measures of obesity. Neither of the two models presented accounted for peripheral vascular disease or physical activity, and including those simple clinical measures might have reduced the incremental predictive utility of CAC. What are the clinical implications of this study? Should CAC scores be incorporated in stroke risk prediction models? CAC is

only one of many markers of longstanding exposure to stroke risk factors such as hypertension, and of severity of systemic atherosclerosis. Other measures, that do not involve exposure to radiation, include retinal examination, urinary (micro) albumin levels, echocardiographic left ventricular mass, tonometric assessment of arterial stiffness, carotid intimo-medial thickness and white matter hyperintensity volumes on brain magnetic resonance imaging, each of which has been shown to be independently associated with stroke risk and several of which have been shown to improve risk prediction over models that only consider baseline levels of risk factors. There has, to date, been no direct comparison of these various markers of subclinical disease in prediction of stroke and total CVD risk. Further, the incremental predictive value of subclinical measures added to risk prediction algorithms that also include multiple circulating biomarkers (such as B-type natriuretic peptide, BNP) remains unclear.<sup>9</sup> Finally, CAC is an imperfect measure of even coronary artery disease since it cannot assess ‘vulnerable’ plaque characteristics. In one study non-invasive assessment of carotid plaque characteristics improved estimation of coronary risk!<sup>10</sup> Needless to say CAC scores cannot substitute for clinical risk prediction scores; they remain promising but unproven adjuncts to clinical prediction algorithms. The authors suggest that clinical trials evaluating the effect of statins on reducing stroke (as well as myocardial infarction) risk in individuals without clinical cardiac disease but positive CAC are needed, and indeed such studies would clarify if CAC will prove useful in risk stratification for primary prevention of stroke.

This study does strengthen the overall message that vascular neurologists and internists both need to think of atherosclerosis as the underlying disease with diverse clinical manifestations, other manifestations besides the presenting one are ignored at peril to the physician and patient.

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