EDITORIAL COMMENT

Indexes of Subclinical Atherosclerosis
Signposts on the Highway to Disease*

Sudha Seshadri, MD

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 (1-3). Most recently, they formed the basis for the American Heart Association/American College of Cardiology guidelines for CVD risk assessment (4). 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 before the time of risk prediction (remote exposure) also determines risk, as has been demonstrated for the association of hypertension with stroke risk (5). 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 the presence of documented coronary artery disease (angina or myocardial infarction) is an important component of the Framingham Stroke Risk Profile (FSRP) (1). As early as 1971, William B. Kannel, a founder of the Framingham Study, made the observation that although the 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 artery with an audible bruit (6). This observation suggested that the carotid bruit was an indicator of an 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 why incorporating a marker of peripheral artery disease in the CHADS-VASc (Congestive Heart Failure, Hypertension, Age, Diabetes, Sex and Vascular Disease) score improves prediction of stroke risk in persons with AF. Thus, although genetic, anatomic, environmental, and other unknown factors do result in some heterogeneity in interindividual patterns of progression of atherosclerosis in cerebral, coronary, and peripheral artery beds, overall measures of atherosclerosis in any 1 vascular bed reflect the extent of atherosclerosis in other regions in the same person.

Measures of coronary artery calcium (CAC) load, assessed using electron-beam computed tomography or multidetector computed tomography are known to be strongly correlated with the 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 noninvasive, 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* (7). However, the value of CAC as a stroke risk predictor has been previously addressed in only 1 study of a German cohort (8).

In this issue of *iJACC*, nearly 6,800 persons of diverse race/ethnic backgrounds, 45 to 84 years of age, from the MESA (Multi-Ethnic Study of Atherosclerosis) 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 (9). CAC scores, assessed as a continuous measure or as a score above or below the American College of Cardiology/American Heart Association recommended cutoff of an Agatston score >300, 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 high-density lipoprotein cholesterol, statin use, cigarette smoking, and interim AF. There was a 70% higher risk of stroke/transient ischemic attack 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 earlier (C statistic: 0.744 vs. 0.755) or when added to the FSRP (C statistic: 0.664 vs. 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 anticoagulant agents.

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. In MESA, there were 38% white participants, 28% black, 22% Hispanic, and 12% Chinese who lived in different parts of the East and West Coast of the United States; however, MESA does not include other ethnic groups such as Native Americans and South Asians who are groups at high risk of 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 previous coronary heart disease or heart failure, and the FSRP does not take into account lipid levels or measures of obesity. Neither of the 2 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 1 of many markers of long-standing exposure to stroke risk factors such as hypertension and of the severity of systemic atherosclerosis. Other measures that do not involve exposure to radiation include retinal examination, urinary (micro) albumin levels, left ventricular mass on echocardiography, tonometric assessment of arterial stiffness, carotid intima-medial thickness, and white matter hyperintensity volume 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. To date, there has been no direct comparison of these various markers of subclinical disease in the 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,) remains unclear (10). Finally, CAC is an imperfect measure of even coronary artery disease because it cannot assess "vulnerable" plaque characteristics. One study found that noninvasive assessment of carotid plaque characteristics improved the estimation of coronary risk (11)! Needless to say, CAC scores are not a 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 whether 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—manifestations other than the presenting one are ignored at peril to the physician and patient.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Sudha Seshadri, Boston University School of Medicine, 72 East Concord Street, B602, Boston, Massachusetts 02118. E-mail: suseshad@bu.edu.

REFERENCES

1. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991; 22:312-8.

2. Wilson PW, Castelli WP, Kannel WB. Coronary risk prediction in adults (the Framingham Heart Study). Am J Cardiol 1987;59:91G-4G.

3. D'Agostino RB Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-53.

4. Goff DC Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2935-59.

5. Seshadri S, Wolf PA, Beiser A, et al. Elevated midlife blood pressure increases stroke risk in elderly persons: the Framingham Study. Arch Intern Med 2001;161:2343-50.

6. Wolf PA, Kannel WB, Sorlie P, McNamara P. Asymptomatic carotid bruit and risk of stroke. The Framingham study. JAMA 1981;245: 1442-5.

7. Andersson C, Vasan RS. Is there a role for coronary artery calcium scoring for management of asymptomatic patients at risk for coronary artery disease? Clinical risk scores are sufficient to define primary prevention treatment strategies among asymptomatic patients. Circ Cardiovasc Imaging 2014;7:390-7; discussion 397.

8. Hermann DM, Gronewold J, Lehmann N, et al. Coronary artery calcification is an independent stroke predictor in the general population. Stroke 2013;44:1008-13.

9. Gibson AO, Blaha MJ, Arnan MK, et al. Coronary artery calcium and incident cerebrovascular events in an asymptomatic cohort: the MESA study. J Am Coll Cardiol Img 2014;7:1108-15.

10. Kara K, Gronewold J, Neumann T, et al. B-type natriuretic peptide predicts stroke of presumable cardioembolic origin in addition to coronary artery calcification. Eur J Neurol 2014;21:914-21.

11. Ibrahimi P, Jashari F, Nicoll R, Bajraktari G, Wester P, Henein MY. Coronary and carotid atherosclerosis: how useful is the imaging? Atherosclerosis 2013;231:323-33.