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EDITORIAL COMMENT

Carotid Intima-Media Thickness, Plaques, and Cardiovascular Disease Risk

Implications for Preventive Cardiology Guidelines*

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Carotid ultrasound has been used as a research tool in epidemiology and in clinical trials of cardiovascular disease interventions for nearly 3 decades. Since 2000, 7 guidelines or consensus statements have recommended measuring carotid intima-media thickness (CIMT) and/or carotid plaque detection as clinical tools to assist with cardiovascular disease risk prediction (1). In 2008, the American Society of Echocardiography (ASE) published a consensus statement on the clinical use of carotid ultrasound for cardiovascular disease risk assessment (1). This statement addressed standardization of imaging and measurement protocols as well as training, instrumentation, and quality control. It also defined appropriate patients for whom carotid ultrasound could be considered as a clinical tool for risk prediction.

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However, the United States Preventive Services Task Force (USPSTF) recently recommended against measurement of anatomic markers of atherosclerosis, including CIMT (2,3). The USPSTF based its negative recommendation regarding CIMT, in part, on the absence of specific data regarding the independent predictive value of CIMT for patients at intermediate coronary heart disease (CHD) risk and on concerns about this test's ability to reclassify such patients into lower or higher risk categories, therefore altering their clinical management (2,3). They also criticized the evidence base supporting CIMT as a risk prediction tool since some studies associating CIMT with CHD risk included patients with pre-existing CHD or risk equivalent conditions, were of relatively short duration, and had few CHD events.

Carotid Ultrasound as a Risk Prediction Tool—in Context

The report by Nambi et al. (4) in this issue of the *Journal* provides the best evidence, to date, demonstrating the ability of carotid ultrasound data to improve CHD risk prediction. These findings have direct clinical implications for the use of CIMT and carotid plaque detection in CHD risk prediction, and they address several of the USPSTF's concerns (2,3). Nambi et al. (4) studied 13,145 subjects who were free of prevalent CHD or stroke at the inception of the ARIC (Atherosclerosis Risk In Communities) study (4). After a mean of 15.1 years follow-up, participants had 1,812 CHD events, the majority of which were "hard" events such as coronary death or myocardial infarction. The authors evaluated the additional predictive value of CIMT, plaque presence, or both carotid ultrasound findings to CHD risk prediction. They found that the area under the receiver-operating characteristic curve (AUC) for traditional risk factor prediction of CHD events (0.742) was significantly increased by the addition of increased CIMT (0.750) or carotid plaque presence (0.751), and that the combination of risk factors, CIMT, and plaque yielded the highest AUC (0.755) (4). These findings support the ASE's recommendation of combining CIMT and carotid plaque data for optimal risk prediction (1).

For men, adding carotid plaque presence to models that incorporated CIMT did not improve discrimination, whereas for women, adding CIMT to models that included plaque was not helpful (4). Because atherosclerosis is relatively uncommon among middle-aged women, the authors suggested that its presence indicated more advanced atherosclerosis and therefore higher CHD risk (4). This is a plausible explanation, consistent with the observation that carotid plaque presence generally is more predictive of CHD risk than CIMT (1), and that coronary calcification, a marker of more advanced atherosclerosis than increased CIMT, is more predictive of CHD (but not stroke) (5). However, the apparent sex difference in risk prediction also may reflect the carotid imaging protocol, which included measurement of CIMT not only in the common carotid artery, but also in the bulb and internal carotid artery segments, where plaques form earliest. Nearly two-thirds of patients with increased CIMT had carotid plaques, so it is likely that the predictive information contained in the CIMT measurements overlapped with plaque presence (4). The fact that bulb and internal CIMT contain redundant information with carotid plaque presence explains why the greatest increment in predictive accuracy was seen when either CIMT or plaque was added to the traditional risk factor model, but adding the other carotid ultrasound measure only increased its predictive value modestly. It also

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emphasizes why CIMT scanning protocols that focus only on the common carotid artery must incorporate scanning the remaining segments of the carotid arteries for plaques, to avoid missing "upstream" advanced atherosclerosis (1).

Although the 0.008 to 0.013 increments in AUC achieved using the carotid ultrasound data may seem small, they are on the same order of magnitude as the individual contributions of smoking status and systolic blood pressure to the Reynold's Risk Score for women, and greater than the contributions of lipids, family history, and high-sensitivity C-reactive protein (6). Indeed, after age and sex are considered in almost any CHD predictive model, additional risk factors contribute little on an individual basis, but are very important when considered in aggregate. The limitations of the AUC as the sole descriptor of a predictive model's accuracy are well known (7).

Of greater importance to the clinician are indices of reclassification that address how often exceeding a threshold for a risk marker correctly reclassifies a person's predicted risk, and by extension, alters the clinical management. For the carotid ultrasound data presented by Nambi et al. (4), the conclusions are clear. Large numbers of persons in the intermediate-risk classifications were reclassified when CIMT and plaque data were considered. Indeed, 37.5% of patients in the 5% to 10% CHD risk stratum (based on risk factors) and 38.3% of patients in the 10% to 20% risk stratum were reclassified when carotid ultrasound data were considered, with plaque presence being more important than increased CIMT among women (4). Adding either CIMT or carotid plaque presence to traditional risk factors led to net clinical reclassification indices of 16.7% and 17.7%, respectively; 21.7% when used together (4). These findings demonstrate that ultrasound findings of increased CIMT or plaque improve CHD risk prediction among patients at intermediate risk—the very patients for whom risk prediction and subsequent medical management are most challenging. The magnitude of reclassification using carotid ultrasound findings is similar to or greater than that observed with the Reynold's Risk Score (vs. the Framingham Risk Score) and its individual components, including high-sensitivity C-reactive protein (6,8).

Finally, it must be recognized that the majority of reclassified patients moved into a *lower* risk stratum, rather than a higher risk stratum, mitigating some of the concern that testing uncovers disease that may not need to be treated, and raising the intriguing hypothesis that carotid ultrasound could be used to identify persons at lower than apparent risk who might be candidates for *less* intensive interventions.

Atherosclerosis Imaging—the Bigger Picture

Of course, the clinical utility of carotid ultrasound or any atherosclerosis imaging test for CHD risk prediction cannot be demonstrated by observational studies, no matter how large or well conducted they may have been. Demonstrating the utility of these tests is more than an issue of mathematics and requires more than elegant statistical analyses—it requires outcomes research. To convincingly demonstrate the value of atherosclerosis imaging will require prospective, randomized studies comparing a strategy of imaging-guided risk factor modification to risk factor modification alone. This is the standard to which pharmacological agents are held; we should expect no less regarding use of imaging tests that can profoundly affect patient management and health care costs. In this regard, randomized data showing the efficacy of any atherosclerosis imaging strategy are scant. The best data are from the METEOR (Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin) Study, a prospective multicenter clinical trial of middle-aged adults at low to intermediate CHD risk who would not have qualified for lipid-lowering therapy but who had increased CIMT (9). Subjects randomly assigned to statins, as opposed to placebo, had less progression of CIMT; the difference in CIMT progression rates was similar to that observed in secondary prevention trials of statin therapy that were associated with a reduction in CHD events (9,10).

In summary, the report by Nambi et al. (4) provides clear answers to several concerns expressed about CIMT imaging by the USPSTF (2,3), and their findings validate the recent consensus statement recommendations for appropriate patient selection for use of carotid cardiovascular disease risk prediction (1). The National Cholesterol Education Program Adult Treatment Panel IV should carefully consider these findings in their deliberations about use of carotid ultrasound and CHD risk assessment. This paper closes the discussion about the incremental value of carotid ultrasound for CHD risk prediction in patients at intermediate risk, thus opening the door for outcomes research studies that are required to determine if atherosclerosis imaging truly is as helpful as its proponents believe.

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