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Carotid Intima-Media Thickness: Can It Close the "Detection Gap" for Cardiovascular Risk?

Given the high morbidity and mortality and the large societal burden imposed by cardiovascular (CV) disease, there have been many strong interdisciplinary efforts to identify at-risk patients during the past decades. The Framingham study and other population-based studies of CV risk, outcomes, and the effect of therapeutic interventions on both have identified what are now considered the "traditional" modifiable CV risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, smoking, obesity, and sedentary lifestyle. However, approximately one-third of CV events are not readily attributed to these traditional CV risk factors.[1,2] This finding, often called the *detection gap*, suggests that other nontraditional or "novel" conditions may cause or contribute to CV disease. At the same time, the trend toward lower definition thresholds for traditional CV risk factors (eg, the change in criteria for what constitutes "low" protective high-density lipoprotein levels, from previously less than 0.91 mmol/L (<35 mg/dL) to more recently less than 1.03 mmol/L (<40 mg/dL) for men and less than 1.29 mmol/L (<50 mg/dL) for women has created an additional problem with specificity in that only a comparatively small fraction of patients who have 1 or more "traditional" CV risk factors ultimately develop overt CV disease during their lifetime. Thus, a refined strategy for accurately identifying patients who are at greatest risk of future CV disease and who could most benefit from risk factor modification is needed.

The 2 key approaches to the refinement of CV risk stratification are as follows: (1) blood serum-based biomarkers of atherosclerosis and inflammation, such as C-reactive protein, interleukin 6, or matrix metalloproteinase 1, might reflect the activity of CV disease better than or provide incremental predictive value to the risk factor–related processes that can affect the vessel wall; and (2) imaging of subclinical atherosclerosis by visualizing nonobstructive, clinically silent plaque directly (eg, measuring carotid intima-media thickness [CIMT]) or indirectly by detecting and quantifying the calcified components of plaque (eg, coronary artery calcium [CAC] scanning) might provide evidence for a genetic susceptibility to clinical CV disease. Recent studies have also examined the annualized progression of morphological markers of subclinical atherosclerosis as an independent indicator of CV disease activity and risk.[3] Severity and progression of subclinical atherosclerosis in the form of vascular calcification are indeed regulated by, in part, genetic factors.[4,5]

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Evidence of functionally active atherosclerosis or the presence of the morphological substrate of subclinical atherosclerosis might allow identification of "vulnerable" patients at a time when appropriate management can slow or halt the atherosclerotic process and reduce the risk of progression to the stage of symptomatic disease. This approach could in theory allow targeted, cost-effective, aggressive risk factor modification in patients who would benefit the most. However, in an era that focuses on cost containment and on the examination of the comparative effectiveness of diagnostic and therapeutic techniques, the cost-to-benefit relationships of these modalities require careful evaluation.

In this issue of *Mayo Clinic Proceedings*, Adolphe et al[6] report the findings of a descriptive cross-sectional study that examined the association of components of the metabolic syndrome with CIMT as a marker of subclinical atherosclerosis in a cohort of 2268 men and women, 17% of whom met the 2001 National Cholesterol Education Program Adult Treatment Panel III definition of the metabolic syndrome. Intimal thickening is among the early

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microscopically recognizable morphological changes related to atherosclerosis, but the thickness of the vascular intima by itself cannot reliably be measured by any current noninvasive imaging technology. B-mode ultrasonography is a relatively inexpensive and safe technique that can noninvasively visualize the lumen and walls of selected arteries, including the carotid, aorta, and femoral.[7] This technique can be used to determine CIMT, a measurement that combines the thickness of the tunica intima and media and that is accurate and reproducible.[7] The metabolic syndrome, assessed in the Adolphe et al report, is a clinically useful but not universally recognized concept of clustering of traditional CV risk factors.[8]

Adolphe et al[6] found that the mean CIMT increases as the number of individual metabolic syndrome components increases. This finding confirms prior reports that examined the association of other markers of subclinical atherosclerosis such as CAC with the metabolic syndrome. The findings of the Adolphe et al study are also consistent with the prevailing understanding that the diagnosis of metabolic syndrome has no more than modest incremental value over the predictive value for CV risk provided by the individual components of the metabolic syndrome alone.

Adolphe et al[6] propose a revised definition of the metabolic syndrome that includes an increase in CIMT that is greater than or equal to 1 SD of the population mean as a component, based on their finding that this new definition can reclassify patients from the low (1%-10% risk of CV events over 10 years) to the intermediate (11%-20%) Framingham risk category. However, the reclassification rate is low at 3.4% (1 in approximately 30 patients), which suggests that using such a new definition of metabolic syndrome would have a low overall impact on therapeutic decision making and presumably on CV outcomes (which were not addressed in their study) in a typical patient population.

The article by Lester et al[9] in this issue of *Mayo Clinic Proceedings* raises the important question of whether "screening" for subclinical coronary artery disease with more than 1 imaging test provides concordant or incremental information. Among a population of men and women aged 36 to 59 years, 47% of patients with no CAC (low risk) had evidence of atherosclerosis in the form of carotid plaque or a CIMT greater than the 75th percentile for age, sex, and race (increased risk). Conversely, only 15% of those with a CIMT lower than the 50th percentile (low risk) had CAC (increased risk). Thus, the authors suggest that CIMT may be more sensitive than CAC scanning for determination of CV risk related to subclinical atherosclerosis in young to middle-aged patients.

The association between CIMT and CAC has been studied previously. The ongoing National Institutes of Health–supported Multi-Ethnic Study of Atherosclerosis (MESA)[10] is examining in more than 6000 patients the predictive value of various markers of CV disease activity and subclinical atherosclerosis and their relationship to patient outcomes for a period of 10 years. On the basis of initial results, CIMT is less predictive of overall CV events than CAC, but it is a better predictor of stroke than of cardiac events.[11] Conversely, the Cardiovascular Health Study (a population sample older than that in MESA) found similar predictive value for CIMT and CAC.[12] Measurements of CIMT and CAC are often discordant and, in direct comparison, CIMT is a better predictor of the relative progression of CAC over time than of the absolute value of CAC at a single point in time.[13]

Given these facts, the prognostic information provided by CIMT and CAC measurements may well be incremental, and carefully matching the correct type of examination to the correct patient becomes part of practicing preventive medicine rationally. On the basis of current data and recommendations, CIMT measurements might indeed be best used in younger patients in an office-based outpatient care environment[7,14] because CIMT can be determined in all patients (as opposed to CAC, which has low prevalence in younger patients) with easily portable devices and without exposure to ionizing radiation.[15] Conversely, CAC measurement might be most appropriate in older patients (>50 years) with intermediate risk of CV events based on Framingham criteria.[16] Certainly, no data suggest that an individual patient should have both CIMT and CAC examinations except in the context of rigorously defined research protocols. Such layered testing is much feared by insurance providers because it potentially wastes medical resources without clear clinical gains and may ultimately lead to more restrictive policies for the reimbursement for, and ultimately decreased access to, CV screening.

Although CIMT screening is a technically mature and accurate technology, key data points, such as the net CV risk reclassification rate, its integration into standard risk-screening tools such as the Framingham risk index, and its effect on therapeutic decision making, are needed before it can fully emerge into the clinical mainstream. Randomized clinical trials that define the impact of at least the general paradigm of subclinical atherosclerosis imaging in general, if not of CIMT specifically, on clinical CV outcomes are pivotal. Although the traditional approach to CV prevention of matching the intensity of risk factor modification to the level of perceived risk certainly has its merits, there is no implicit guarantee that adjusting risk factor modification on the basis of identifying evidence for subclinical atherosclerosis will improve patient outcomes.[17] Yes, it intuitively "makes sense" that earlier institution of risk factor modification should delay the time to a first CV event or cardiac death. However, many caveats apply, per-

haps most importantly the concept of "lead-time bias,"[18] which is well-known from the study of some forms of cancer screening: although earlier detection and treatment of disease increase the time span from when a patient's disease is first diagnosed to when the patient dies of the disease, it does not necessarily affect the time from onset of symptoms to death. In that circumstance, early detection of disease does not affect the patient outcome that would have occurred if treatment had commenced at the time the patient first became symptomatic.

More information about CIMT is essential for validating atherosclerosis imaging techniques as a means to close the detection gap for CV risk. Such information should include the association of abnormal CIMT with various risk factors and with the findings of other imaging techniques, as well as the rate by which CIMT allows reclassification of CV risk. Through these efforts we can ensure that future preventive CV practice provides the best value through refined CV risk prediction.

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