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EDITORIAL COMMENT

Seeing Is Knowing

Noninvasive Imaging Outperforms Traditional Risk Assessment

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Primary prevention guidelines for atherosclerotic cardiovascular disease (ASCVD) recommend screening for risk factors then initiating preventive interventions. Various risk assessment tools have been developed for this purpose using data from population-based cohort studies.[1,2] These tools have been criticized for overestimating and underestimating risk.[3,4]

Reliance solely on cardiovascular risk factors and population-based risk equations may miss asymptomatic individuals with subclinical disease.[5] Rather than assessing a person's risk based strictly on risk factors derived from studying populations, imaging atherosclerosis itself may be a better way to determine risk. It is in this context that the BioImage Study was designed.

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In this issue of *JACC*, Fuster et al[6] present an analysis from BioImage, an elegant prospective study of asymptomatic adults free of clinical ASCVD showing the association between atherosclerosis as measured in 2 vascular beds on all-cause mortality. Carotid plaque burden (CPB) was measured with vascular ultrasound and repeated 8.9 years later in a subset to assess the relationship between CPB progression and all-cause mortality. Subclinical coronary atherosclerosis was measured with gated noncontrast computed tomography. Nearly 90% of the 5,716 participants (average age 69 years) had subclinical atherosclerosis. There was a higher prevalence of subclinical carotid disease than coronary artery calcium (CAC) in the lower risk group as assessed by the Framingham Risk Score.

After a median follow-up of 12.4 years, baseline CAC, CPB, and CPB progression were all significantly associated with all-cause mortality beyond traditional risk factors. Surprisingly, CPB was superior to CAC in predicting all-cause mortality in BioImage. The MESA (Multi-Ethnic Study of Atherosclerosis) found that CAC score was a better predictor of cardiovascular events than CPB.[7] The Agatston score is a standardized method to measure CAC, whereas there is no standardized method to measure CPB. MESA derived a total carotid plaque score (range 0-12) allocating 1 point per plaque for the near and far walls of each of 12 segments interrogated. BioImage calculated CPB as the sum of plaque areas from all images in cross-sectional sweeps of both carotid arteries, yielding a quantitative metric of total plaque area (mm^2). This novel continuous volumetric measurement, which provides significantly more data than a score from 0 to 12, may help explain why CPB was superior to CAC in predicting mortality in this study. Others have shown that progression of carotid stenosis is associated with cardiovascular mortality after adjusting for traditional risk factors.[8] The present study extends this finding to demonstrate that progression of carotid plaque is associated with all-cause mortality.

This important study should be interpreted in the context of several limitations. First, the average participant age of 69 years at enrollment limits generalizability of these findings to patients we typically encounter for primary prevention. Second, the outcome of this study was all-cause mortality. Understanding cardiovascular disease-specific outcomes remains important, particularly when comparing these imaging studies to the traditional

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risk prediction equations designed to predict ASCVD events. Third, detailed discussion of how medical therapy may have altered progression of CPB and outcomes is lacking.

The practical implications of this study are many. First, the findings demonstrate that screening individuals for the presence of atherosclerosis is a more precise method to determine mortality risk than screening for traditional population-based risk factors. Patients deemed high risk with traditional risk factors may have no disease, and patients at low risk using traditional risk models may have severe disease.[5] This supports screening for subclinical atherosclerotic disease in the at-risk population. Second, this study indicates that measurement of carotid plaque area as performed in BioImage is at least as strongly associated with all-cause mortality as CAC. This raises the question whether we should we use this measure of subclinical atherosclerosis to guide personalized treatment decisions. The advantages of using gated noncontrast computed tomography to measure CAC are the standardized method for calculating the Agatston score and the huge evidence base that supports its predictive ability. The disadvantages are exposure to radiation (however mild), inability to detect noncalcified plaque, and difficulty in interpreting repeat scans for progression when the prior score is >0. The latter is problematic because with aggressive lowering of low-density lipoprotein cholesterol, plaque calcium density increases—thought to be a sign of healing—which increases the Agatston score. Therefore, repeat measurements are rarely recommended because it is difficult to know if a rise in the Agatston score reflects progression of disease caused by an increase in calcified plaque volume or healing of plaque characterized by increased calcium density. The advantages of vascular ultrasound include the ability to assess multiple vascular beds (carotid arteries, femoral arteries, abdominal aorta) at one sitting, ability to detect noncalcified plaque (opening the door to screening younger adults), ability to interpret serial imaging, and no radiation. The disadvantages of vascular ultrasound are operator variability, lack of a standardized assessment method, and the relatively small evidence base as compared with CAC. Neither modality has a Class 1 recommendation or Medicare coverage for screening because neither has clinical trial evidence to demonstrate that noninvasive imaging of subclinical atherosclerosis improves clinical outcomes. A third implication is the extremely high prevalence of subclinical atherosclerosis in this population with an average age of 69 years. This suggests that we should start screening at a younger age, as in the PESA (Progression of Early Subclinical Atherosclerosis) study.[9]

Last, if a baseline carotid ultrasound has been performed, this study raises the question of whether imaging should be repeated to monitor response to therapy and to intensify therapy if progression is demonstrated. The interval between repeat carotid imaging was nearly 9 years in BioImage. Other investigators have detected progression with shorter intervals.[8] The optimal timing to repeat testing is unknown.

In summary, our ability to identify asymptomatic people with atherosclerosis based on traditional risk factors is imprecise. We have noninvasive imaging tools, as demonstrated in BioImage, that are superior to traditional risk factors in assessing the risk of death. It is time for a randomized controlled trial that compares treating asymptomatic individuals based on population-derived traditional risk factors with treatment based on an individual's personal burden of atherosclerosis to prove that image-guided therapy is superior to the status quo.

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