QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES   **Editorial Comment**

Selective Use of Coronary Artery Calcium Screening

Worth the Cost?*

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Coronary artery disease (CAD) is the principal cause of morbidity and mortality in industrialized nations. In approximately one-half of the individuals, the initial presentation of CAD is either myocardial infarction (MI) or sudden death. Unfortunately, conventional risk factor assessment only predicts 65% to 80% of future cardiovascular events, leaving many middle-aged and older individuals to manifest a major cardiovascular event despite being classified as low risk by the Framingham risk estimate.

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One landmark study showed that just 25% of patients who presented with an MI before the age of 65 would have qualified for pharmacotherapy with a statin the day before their MI based on their Framingham risk profile (1). The percentage of women qualifying for aspirin and statin therapy before their MI is even lower, because women younger than 70 years of age are very unlikely to reach the 10% risk of a hard event threshold (2). Considering the limits of current screening strategies based on traditional risk factors, clinicians need to explore other strategies to more accurately capture this vulnerable population and reduce the likelihood of downstream adverse events.

Many noninvasive imaging tests have emerged as candidates for further refining our ability to detect those patients harboring advanced subclinical atherosclerosis. Among these, coronary artery calcification (CAC) testing has convincingly been demonstrated to provide additional prognostic information over office-based CAD risk assessment, and there has been a trend in recent years toward the acceptance of a role for selective use of CAC testing in "intermediate-risk" adults (3).

The authors of a recent meta-analysis (4) demonstrated that patients without any CAC (approximately 50% of individuals screened) are extremely unlikely to have significant CAD, have myocardial perfusion abnormalities, or develop an acute coronary syndrome; they are deemed to be at negligible risk for a CAD event over the next 5 years.

Selective use of CAC testing may, thus, be helpful to identify those requiring more aggressive pharmacotherapy and, perhaps more important, to identify the larger subset of individuals at very low risk for whom further cardiac testing and pharmacotherapy with aspirin and statin may be safely be avoided in the short term (5).

From a societal standpoint, it is not only important to establish the ability of CAC testing to predict future CAD outcomes but also vital to demonstrate that the use of atherosclerosis imaging for adults will not lead to a cascade of costly downstream testing (6). In addition to the monumental rate of morbidity and mortality that is directly related to atherosclerotic vascular disease, the total economic cost of cardiovascular disease is already estimated to be >$475 billion (7). This issue becomes even more relevant in the current economic climate, and there are active governmental efforts to curtail health care expenditures.

Does atherosclerotic testing significantly impact downstream cost? In this issue of the *Journal*, Shaw et al. (8) present the results of the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study, a timely and landmark investigation that attempts to address this question by examining the downstream effect of screening for subclinical atherosclerosis. The authors sought to determine how CAC testing affects the economics of resource consumption and procedural costs.

In this study, the majority of individuals had either no CAC (57%) or minimal CAC scores of 1 to 10 (21%), with very few individuals with advanced atherosclerosis (CAC 401 to 1,000: 6%; CAC >1,000: 2%). The study is unique in that for the first time, costs incurred from downstream noninvasive and invasive procedures (as well as treatment costs, including medications, revascularization, and hospitalization) were examined.

The results were reassuring in that the likelihood of pursuing further testing given no or minimal coronary atherosclerosis was negligible. Most of the downstream resource utilization (whether appropriate by current guidelines or not) was in the presence of very high CAC scores. Importantly, invasive procedures were not performed immediately after CAC testing, and they were performed in a stepwise manner preceded by functional imaging with either exercise stress testing or stress myocardial perfusion imaging.

The study findings also may provide fuel to critics who fear that those with significantly increased CAC scores will be sent for more testing without any indication that this would have a positive impact on saving lives (9). Although current guidelines recommend managing these patients aggressively with pharmacotherapy and more intensified lifestyle modification, the results of the EISNER study demonstrate a greater likelihood of these individuals undergoing noninvasive studies leading to invasive coronary angiography (ICA) and ultimately costly revascularizations.

This is a concern in light of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial results, in which aggressive medical and lifestyle management in patients with advanced stable CAD led to similar outcomes compared with an interventional plus optimal medical and lifestyle approach (10,11). However, the costly procedures were primarily limited to the group with a CAC score of >400 (8% of population screened). In addition, although abnormal findings resulted in more testing, the absolute increase in testing is not high when the overall population is taken into account.

Among every 100 individuals screened for CAC, only 8 would have CAC scores >400, with the majority undergoing stress echocardiograms or myocardial perfusion testing (5 to 7 individuals) and nearly one-half undergoing ICA (approximately 4 individuals). In comparison, only 14 individuals of the 78 of 100 screened with CAC scores of 0 to 10 would undergo some sort of stress imaging, and only 1 will proceed with ICA in 6 years of follow-up. For the majority of individuals with no or low CAC (78% of those screened with CAC), the median costs were minimal ($25 to $35), mostly incurred by ECG testing, which is often part of the initial assessment of individuals with hypertension (a feature observed in nearly 60% of this low-risk group).

Overall, of all individuals undergoing CAC testing, nearly 20% had some form of stress imaging performed, whereas 7% had an ICA. An interesting question not addressed by EISNER is whether these procedures would have taken place even in the absence of CAC testing. For example, it is unclear whether atypical anginal symptoms prompted some of these individuals to undergo further testing, an outcome that might have occurred even without a priori CAC testing. In addition, the study does not provide any comparison with other well-established CAD screening tools such as carotid intima-medial thickness or measurements of biomarkers such as high-sensitivity C-reactive protein. Future studies also are needed to show whether various imaging/nonimaging risk-stratifying strategies produce comparable downstream outcomes.

However, the EISNER study is a starting point in our efforts to understand how best to use limited resources for CHD prevention. From a national health care expenditures standpoint, it may well provide justification for restricting aggressive CAD management to those with at least moderate subclinical atherosclerosis, which is observed in approximately 10% to 15% of middle-aged adults. In MESA (Multi-Ethnic Study of Atherosclerosis), only 9% of total events occurred over a median of 4 years in 50% of individuals who had no detectable CAC, whereas 91% were seen in the other one-half having varying degrees of CAC (12). Similar findings were reported by Blaha et al. (5) in which during a follow-up of 13 years, only 6% of all deaths were recorded among those with an absence of CAC. Many physicians tend to overtreat patients in this "intermediate-risk" group because of their uncertainty about future cardiovascular events.

In ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), in which hypertensive individuals with at least 3 CAD risk factors were randomized to statin or placebo, 93 persons had to be treated for a mean of 3.3 years to prevent a single cardiac event (13). Thus, treating all intermediate-risk persons is highly cost-inefficient, and these patients tend to have poor long-term compliance with therapy. On the basis of the MESA study, if we narrow our focus to those with a CAC >100 (only 25% of the population), we can identify a subgroup in whom 63% of all coronary heart disease (CHD) events would occur in short-term follow-up (13). Separating the subset of individuals with absent or low CAC and, thus, a very low risk of CHD events and focusing on those individuals with a high atherosclerotic burden may in the end limit an unsustainable health care cost spiral.

Of all tests available for risk stratification, CAC superiorly divides patients into 2 clear subgroups of high and low future CHD risk than carotid intima-media thickness testing (14). The results of the EISNER study alleviate the fear that such a strategy will inevitably lead to high downstream costs. In light of this, we hope that the various stakeholders in determining health care resource allocation will move in the direction of addressing whether selective use of atherosclerosis imaging should play any role in halting the epidemic of atherosclerotic vascular disease by better refining which middle-aged and older adults are truly at relatively high risk versus very low risk for a CVD event during the next 5 to 10 years.

The EISNER study provides further evidence for the urgency of a randomized trial that compares the current traditional risk factors-based approach with one supplemented by subclinical atherosclerotic screening to determine whether this approach can save lives in a manner that is at least moderately cost effective. This study does show that screening costs will beget more costs; testing produces more than the upfront cost of a procedure. In this regard, we applaud the recent efforts of the National Heart, Lung, and Blood Institute to initiate a dialogue on how to assess the societal utility of such screening tests and look forward to the outcome of these discussions. How best to deploy CAC screening, more intensive lifestyle changes, earlier initiation of aspirin, and statin therapy is quickly approaching a trillion-dollar question! The sooner we find the answer, the better.

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