Arterial Calcification in Cardiovascular Risk Prediction
Should We Shift the Target for Screening Beyond the Coronaries?

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There is considerable controversy regarding the most effective means to reduce the global burden of cardiovascular disease (CVD). Although traditional metrics, such as the Pooled Cohort atherosclerotic cardiovascular disease (ASCVD) risk equation, remains essential in providing a comprehensive assessment of CVD risk, there is also a well-established body of evidence on the utility of noninvasive imaging. Accordingly, imaging has been frequently applied to detect subclinical atherosclerosis and differentiate among at-risk individuals those who would benefit from more intensive therapies in the primary prevention of CVD. Specifically, advanced imaging modalities have been used to target well-defined subcomponents of atheromatous disease, such as coronary artery calcification (CAC), as a means to further improve detection of high risk individuals.

CAC scoring, in particular, has been shown to provide significant value in estimating CVD events with higher strata of Agatston scores corresponding with increasing elevations of risk. Importantly, the development of atherosclerotic disease is not exclusive to the coronary arteries but rather is a systemic process that develops in heart valves, throughout the aorta, and peripheral arteries. Differential rates and patterns of plaque development exist within each vascular bed mediated by clinical, genetic, and comorbid factors associated with atherosclerosis. Thus, given the heterogeneous distribution and variable degrees of atherosclerotic progression, the utility of imaging the coronaries alone is expectedly suboptimal for estimating the total burden of CVD risk.

Current evidence for the prognostic significance of extra-coronary calcification, in particular as it relates to added prognostic value above CAC scoring, is limited, but interest in this area is growing. Several recent studies have assessed carotid intima–media thickness, as well as aortic calcification, in relationship to CVD risk, revealing different degrees of incremental contribution in predicting CVD risk beyond CAC imaging. The current study by Bos et al, in this issue of Circulation: Cardiovascular Imaging, adds to existing literature by assessing the relationship between atherosclerotic burden in multiple vessel beds as estimators of mortality risk. Interestingly, calcified plaque in the aortic arch (AAC) seems to correlate most strongly with all-cause and CVD-specific mortality.

However, the extent to which calcification at each individual vascular site can be used to accurately reflect the systemic and pervasive nature of atherosclerosis is unclear. Accordingly, concerted efforts have been made in clinical studies to characterize the pathophysiologic relationship between coronary and noncoronary arterial atherosclerosis. Registry data from the Multi-Ethnic Study of Atherosclerosis have previously demonstrated that CAC was broadly predictive of total CVD outcomes, including extracoronary events, such as stroke. Additional investigations have found that thoracic aortic calcification correlated with higher CAC scores and carotid atherosclerosis. Similarly, abdominal aortic calcium has also been described to coexist with higher risk CAC, carotid intima–media thickness, and ankle-brachial index measures. From this latter study, a significant number of individuals with abdominal aortic calcification did not have any evidence of CAC (40% of women and 20% of men), and in contrast, a large number of those without detectable abdominal aortic calcium had visualized atherosclerosis in other vessels (21% of women and 47% of men). Thus, dependence on any one imaging measurement alone, such as CAC, may be insufficient to accurately represent an individual’s global atherosclerotic risk.

Currently, minimal data are available to fully describe whether a CVD risk-based hierarchy exists among different vascular sites. The report by Bos suggests that AAC may serve as a more robust marker for CVD mortality than CAC. To illustrate the difference in risk, we calculated the proportion of excess mortality risk explained by clinical covariates, revealing that 69% of the mortality risk for CAC may be explained by age and noncoronary calcification. For AAC, the proportion of excess mortality risk explained by coronary and carotid calcification was 55%. Although it is difficult to directly compare these 2 statistics, these data lend credence to the concept that calcification is a subcomponent of atherosclerosis that may affect other arterial beds with an ensuing impact on patient mortality. Furthermore, detection of CAC may have resulted in the early initiation of statin therapy along with potential benefits of behavioral or lifestyle changes, resulting in a mortality reduction. Clearly, our understanding of the natural progression of atherosclerosis and its longitudinal correlation with clinically significant events in different vascular sites remains incomplete.

Thus, based on the Rotterdam findings, an important question is how extensively should patients be screened for subclinical atherosclerosis? All-cause mortality has
historically been used as a primary outcome measure in studies on risk assessment because this end point was considered more reflective of global health. Does the Rotterdam\textsuperscript{7} approach then advocate for individuals to undergo expansive, full-body examinations to detect systemic atherosclerosis to estimate overall risk? Or conversely, is the presence of CAC still sufficiently predictive for selected middle-aged individuals with an intermediate CVD risk score? Innovative strategies to bridge these gaps in knowledge have previously been proposed by Blaha and colleagues,\textsuperscript{13–15} and it is interesting and it is interesting to consider the use of multisite imaging or the creation of a composite score for coronary and extracoronary calcification to improve risk discrimination for disease-specific outcomes. Pinpointing which combination of imaging targets yield the greatest predictive and clinical utility, while balancing financial costs and potential safety concerns (e.g., harms of radiation exposure), presents a significant challenge for population screening.

A second question from the Bos\textsuperscript{1} investigation to consider is which population is the most appropriate to target for risk stratification with noninvasive imaging? The median age of the Rotterdam cohort was nearly 70 years\textsuperscript{2} and included 1 in 10 individuals with a previously established CVD diagnosis, as well as an unspecified number with angina or other ischemic symptoms. Importantly, implementation of screening in a largely elderly cohort with a higher prevalence of traditional risk factors should be contrasted to the predominantly middle-aged and asymptomatic populations that traditionally undergo risk assessment. At our own institution, the average age of screened individuals is approximately 55 years, which is similar to other longitudinal cohorts undergoing CAC scanning.\textsuperscript{16,17} Furthermore, it was primarily among individuals within the fourth quartile of AAC scores for whom adverse mortality risk was greatest as compared with calcified plaque in other vascular beds.\textsuperscript{7} Notably, part of the definition for CVD mortality used in the Rotterdam study included ruptured abdominal aortic aneurysms.\textsuperscript{7} It has been well described based in large part on literature using cardiovascular magnetic resonance that the extent of atherosclerosis along the aorta increases significantly with age.\textsuperscript{18,19} Thus, the extent to which this fourth quartile of AAC scores represented extensive aortic atherosclerosis with calcified and noncalcified plaque that ultimately led to death is unknown but potentially highly influential in the prognostic models presented in the Bos\textsuperscript{1} report.

We think that the report from the Rotterdam\textsuperscript{7} group is intriguing and underscores the complexity of the atherosclerotic disease as a process that diversely impacts risk. There is ever-increasing and well-deserved enthusiasm for using noninvasive imaging to better characterize subclinical atherosclerosis in an attempt to improve personalized CVD risk prediction. However, what remain ill-defined are the clinically significant thresholds of CAC scores because it relates to the gradation of risk associated with systemic atherosclerotic progression and the optimal population to target for screening. Clearly, additional research in this area is warranted. Nonetheless, the role of noninvasive imaging of coronary and extracoronary atherosclerosis holds great promise in providing a novel strategy to improve the quality and delivery of individualized preventive care.

None.

Disclosures

References


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