Editorial

Extending the Use of Coronary Calcium Scanning to Clinical Rather Than Just Screening Populations
Ready for Prime Time?

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Twenty-five years after its initial development, coronary artery calcium (CAC) scanning has become a relatively inexpensive test that has been extensively validated as a potent noninvasive means for assessing the burden of coronary atherosclerosis in asymptomatic individuals. A proportional relationship between the magnitude of CAC abnormality and the frequency of subsequent cardiac events over long-term follow-up has been consistently demonstrated, including observations from large patient and population-based cohorts. Incremental prognostic value over standard clinical assessments including the Framingham Risk Score and other scores of global risk has also been consistently reported. Consequently, the application of CAC scanning for assessing asymptomatic patients with intermediate clinical risk has now become part of clinical guidelines.

Beyond its use for risk-stratifying asymptomatic individuals, there is now strong reason to consider applications of CAC scanning in symptomatic or asymptomatic patients being evaluated for obstructive coronary artery disease (CAD). Several of these potential uses of CAC scanning arise from its combination with the application of stress myocardial perfusion imaging (MPI; Table). CAC scanning can be used to improve the selection of patients for stress MPI procedures, aid in the overall risk stratification and guidance of management in patients undergoing MPI, and improve the actual interpretation of MPI results. In this issue of Circulation: Cardiovascular Imaging, Engbers et al. report findings relating to 2 of the potential applications as they relate to MPI: the use of CAC scanning to select patients for stress MPI and the combined use of CAC scanning and MPI for predicting overall patient risk.

Selection of Patients for MPI

The potential exists to incorporate the results of CAC scanning into the Bayesian analysis of the likelihood in hemodynamically significant CAD. Given the dramatic reduction in the frequency of abnormal stress MPI procedures over the past 2 decades, a need for better selection of patients for cardiac imaging procedures has become imperative within our increasingly value-based environment. Because the MPI study is designed to evaluate ischemia—whether for diagnostic or prognostic reasons—the pretest likelihood of ischemia is of paramount importance in determining the need for ischemia testing. The Diamond–Forrester classification of pretest likelihood of obstructive CAD, while having proven of immense clinical importance for >3 decades, is currently inaccurate and overestimates CAD likelihood. The potential use of CAC scanning for better selection of patients for stress imaging is based on an underappreciated proportional relationship between the magnitude of CAC abnormality and the likelihood of obstructive CAD. Of interest, Diamond and Forrester initially suggested the incorporation of coronary fluoroscopy in their landmark publication on the Bayesian assessment of CAD likelihood. Data confirming this relationship with computed tomography (CT)–based CAC scanning was later reported by Budoff et al. Given the need to better predict the likelihood of ischemia, one might have expected that there would have been by now extensive investigation into the clinical use of CAC scanning for guiding patient selection for MPI testing. In this regard, a recent meta-analysis assessed all studies that have reported the relationship between CAC scan results and the frequency of myocardial ischemia on MPI during a 15-year period (2000–2015). During this time, there

See Article by Engbers et al

Information from CAC scanning may be used to favorably alter patient management in clinical practice. As an example, in the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) trial, subjects were randomized to routine risk management with and without a concomitant CAC scan. In the scan group, incurred costs and intensity of treatment increased with high CAC scores, but decreased in the zero CAC subgroup. This counterbalance resulted in no net increase in downstream medical costs, which had been an initial concern with CAC scanning. Although there have been no subsequent large randomized clinical trials involving the effect of CAC scanning on patients management, its ability to aid in clinical management of selected asymptomatic patients is now endorsed in recent preventive guidelines.

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were 20 publications that examined the relationship between CAC results and myocardial ischemia. However, most of these were small studies and only 5 of these studies involved patient populations with >500 patients. This paucity reflects a relative lack of interest in exploring and developing this potential clinical application. Most notably, the meta-analysis revealed a literature that is deficient in reporting and analyzing clinical parameters that might influence the relationship between CAC abnormality and inducible myocardial ischemia, such as the presence and quality of patients’ chest pain.

In the current study, Engbers et al9 examined the relationship between CAC score and inducible myocardial ischemia in a large cohort of 4897 patients, dwarfing the size of all prior publications in this regard. All patients were referred for testing because of a clinical suspicion of CAD, and the vast majority of patients had an intermediate likelihood of CAD. As in prior studies, a proportional relationship was observed between the magnitude of CAC abnormality and the frequency of inducible myocardial ischemia. Yet while useful, this larger analysis still does not sufficiently establish how to best use CAC scanning for selecting patients for cardiac stress testing. This is because in the aforementioned meta-analysis, there was a marked variation in the 6 studies reporting frequency of ischemia by CAC subgroup.17 For instance, among CAC scores of 0, the frequency of ischemia varied from 0%-24%, and among those with CAC scores >400, the frequency of ischemia ranged from 12%-57%. Many factors could account for these differences, including differences in the acuity of the patients, the frequency of comorbid medical conditions, the concentration of CAD risk factors, the intensity of medical therapies, and a variety of technical factors, including a propensity for readers at some centers to read myocardial perfusion studies with a greater or lesser threshold for interpreting studies as abnormal. To date, there has only been limited study as to how these individual factors might govern the relationship between the magnitude of CAC abnormality and the likelihood of ischemia. This study by Engbers et al9 serves to emphasize this important limitation in the literature. In this study, the presence of ischemia was 12% among the patients with a normal CAC scan. Such a frequency would limit the use of a zero CAC scan for reducing the likelihood of inducible myocardial ischemia in asymptomatic patients.

Of note, the presence of ischemia among the patients with zero CAC scores did not serve to increase patients’ clinical risk. This observation begs for further analysis. One of the possible explanations may be that the investigators used too lenient a criterion for interpreting studies as abnormal. In this study, a summed difference score ≥2 was used to define ischemia. By contrast, in many institutions, a score ≥4 is used to define abnormality. This difference is magnified by the finding that most ischemic defects among those without CAC were small defects. This finding may be the dominant reason for the increased frequency of abnormal MPI that was reported in all CAC subgroups in this study compared with prior reports. Thus, how many studies that were characterized as mild ischemia in this study might be characterized as normal at other institutions? One approach to addressing this clinical question is to increase the utilization of standardized and unbiased quantitative analysis in image interpretation and reporting.

Alternatively, clinical factors may be important drivers of the higher rate of ischemia observed in this study. Here, various clinical factors could be particularly relevant, such as sex, CAD risk factors, chest pain, and exercise capacity. For instance, studies involving the comparison of diabetes mellitus with nondiabetics suggest the former have a higher frequency of inducible myocardial ischemia among subjects with an intermediate CAC score (100–400 range).18 In another study, the threshold CAC score for a moderate frequency of ischemia was substantially lower among patients with typical angina than in patients with atypical chest pain.19 In a third study, high exercise capacity lowered the frequency of ischemia associated with intermediate CAC scores.20 Furthermore, combining the results of chest pain and exercise ECG testing resulted in a markedly lower threshold for predicting ischemia among patients with a high pre-scan likelihood of CAD compared with patients with an intermediate likelihood of CAD (Figure).19 As in most prior studies, these potential modifiers of the relationship between

### Table. Clinical Applications of Combining Coronary Artery Calcium Scanning and Myocardial Perfusion Imaging

<table>
<thead>
<tr>
<th>Aiding the triage of patients for cardiac stress testing</th>
<th>Improving risk prediction and clinical management in conjunction with cardiac stress testing</th>
<th>Improving the interpretation of stress myocardial perfusion imaging studies</th>
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**Table. Clinical Applications of Combining Coronary Artery Calcium Scanning and Myocardial Perfusion Imaging**

![Figure. The frequency of ischemic stress/rest myocardial perfusion imaging studies according to baseline coronary calcium scores among patients divided according to post-test likelihood (LKHD) of obstructive coronary artery disease (CAD), incorporating the results of age, sex, CAD risk factors, chest pain, and exercise ECG results. Both among patients with low and intermediate CAD likelihood, the frequency of ischemia was low for patients with coronary artery calcium (CAC) scores ≤400. By contrast, the CAC threshold for ischemia was substantially lower among patients with a high likelihood of CAD. Reprinted from Rozanski et al15 with permission of the publisher. Copyright ©2007, Springer.](http://circimaging.ahajournals.org/content/early/2017/08/18/CIRIMAT.117.027766)
CAC score and myocardial ischemia were not assessed in the present study. For instance, the study did not report chest pain symptoms and because pharmacological testing was performed on a routine basis, no exercise data were available. Because the reported frequencies of ischemia according to CAC score vary so widely, there is an important need to evaluate how clinical and technical factors modify this relationship.

**Combined Use of MPI and CAC Scanning for Risk Assessment**

CAC scanning can serve as an adjunct to predicting clinical outcomes based on the results of stress imaging. For instance, Chang et al.22 followed up 1126 generally asymptomatic patients for a median of 6.9 years for the cardiac death, nonfatal myocardial infarction, and the need for coronary revascularization. In patients both with and without inducible myocardial ischemia, the event rate increased with increasing CAC score. The highest event rates occurred among both patients with both high CAC scores and inducible myocardial ischemia. This study of Engbers et al.9 extends these findings to a more symptomatic population undergoing MPI with a hybrid single-photon emission CT (SPECT)/CT system. The added prognostic value of the CAC score to MPI in a symptomatic population was also previously assessed with hybrid positron emission tomography (PET)/CT as reported by Schenker et al.23 Such hybrid systems—whether SPECT/CT or PET/CT—provide the opportunity to routinely add CAC scanning in patients undergoing MPI.

In this study, CAC abnormality and the presence of myocardial ischemia were found to provide synergistic information in predicting major adverse cardiac events, defined as death, nonfatal myocardial infarction, and late revascularization. When the CAC score was zero, the frequency of major adverse cardiac events was low, regardless of the presence of perfusion defects. For each subsequent CAC score grouping, major adverse cardiac event was more frequent if myocardial ischemia was also present. This study thus provides strong confirmatory evidence for the complementary use of CAC score and stress test results for predicting subsequent cardiac events.

**Aid in Interpretation of Nuclear MPI Studies**

The use of CAC scanning might also aid the interpretation of MPI studies, particularly in the setting of borderland MPI abnormalities or when there is discordance between the MPI results and clinical or ECG responses to stress. In the presence of a borderline perfusion defect, the finding of a zero or low CAC score can lead to a test being interpreted as normal. In contrast, the finding of a borderline MPI study in a patient with extensive CAC or a high CAC score can lead to a study being interpreted as abnormal. The added value of combined CAC scanning with MPI with quantitative MPI analysis was recently demonstrated by Brodov et al.,24 who found that this led to greater accuracy in predicting obstructive CAD. This was accomplished by the development of a novel combined CAC-MPI score, by logistic regression methods, which allowed assignment of the quantitative post-test probability of the obstructive disease on a per-vessel or per-patient basis in an objective quantitative manner. Such combined score does not need exact registration, but rather the per-vessel CAC score. It could be readily obtained in patients who have a prior CAC scan from a separate CT scanner or from a single session on a hybrid SPECT/CT or PET/CT scanner.

For future applications, modified protocols for attenuation correction have been proposed in which a separately acquired CAC scan could also be used with image registration to provide attenuation correction of the stand-alone SPECT or PET systems.25 The possibility that CAC scanning might improve assessments of MPI even with stand-alone SPECT systems has also been suggested. Schepis et al.26 described that a separately acquired CAC scan could provide attenuation maps that could be used for attenuation correction of SPECT-MPI, thus potentially providing an aid to reducing image artifacts. Furthermore, software methods have been proposed for MPI to CT registration, which can register a single CAC or CT attenuation correction scan to both stress and rest MPI, replacing the 2 separate low-dose CT acquisitions currently required for attenuation correction.27 A simulation study also suggests that the combined use of CAC scanning with a stress-only SPECT MPI study might potentially reduce the number of patients who require a subsequent rest MPI study.28

**Other Future Directions**

In the coming era of value-based imaging, tests must improve outcomes or reduce costs. In order for an imaging test to improve outcomes, it must lead to a change in therapy. A drawback of stress imaging without anatomic assessment in patients with suspected CAD is that the methods detect only patients with hemodynamically significant lesions and fail to identify patients with subclinical atherosclerosis in whom aggressive medical and lifestyle modification might prevent subsequent cardiac events. Thus, there is often little impact of normal MPI test results, found in the vast majority of patients, on subsequent patient medical management. Because preventive therapies have been established to reduce cardiac events, identifying patients with normal MPI who have coronary atherosclerosis might lead to a change in preventive therapy which in turn may improve clinical outcomes. The ability of coronary CTA to assess the presence of both nonobstructive and obstructive CAD provides an advantage over stress imaging alone in guiding patient management;29 however, CTA, when assessed for anatomic disease alone, may have the potential to lead to an increased use of coronary angiography.13,30 The combination of stress MPI with CAC might result in a lower frequency of invasive coronary angiography than associated with coronary CTA, while resulting in effective initiation or cessation of preventive therapies. Thus, the combined functional and anatomic information of MPI with CAC scanning could increase the frequency of changes in the management based on SPECT MPI alone.

The evidence to date suggests that the use of CAC scanning will aid in better selection of patients for MPI, improved diagnostic interpretation, improved prognostic assessment, and greater change in therapy after MPI. It is likely that this combination will be a strong factor in improving the value of MPI procedures. Is the routine combination of these 2 tests ready for prime time? It may not be proven, but it merits further study and even at this time should be strongly considered.
Disclosures

References


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