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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 [1–3]. Incremental prognostic value over standard clinical assessments including the Framingham Risk Score and other scores of global risk has also been consistently reported [3–4]. Consequently, the application of CAC scanning for assessing asymptomatic patients with intermediate clinical risk has now become part of clinical guidelines[5–6].

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 [7]. 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. While 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 [8].

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 CAD. Several of these potential uses of CAC scanning arise from its combination with the application of stress myocardial perfusion imaging (MPI) (Table).

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Disclosures
None.

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 the present issue of *Circulation: Cardiovascular Imaging*, Engbers et al report findings relating to two 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 [9].

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 last two decades [10], a need for better selection of patients for cardiac imaging procedures has become imperative within our increasingly value-based environment. Since the MPI study is designed to evaluate ischemia—whether for diagnostic or prognostic reasons—the pre-test likelihood of ischemia is of paramount importance in determining the need for ischemia testing. The Diamond-Forrester classification of pre-test likelihood of obstructive CAD (11), while having proven of immense clinical importance over three decades, is currently inaccurate and overestimates CAD likelihood [12–13]. 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 (14–15). Of interest, Diamond and Forrester initially suggested the incorporation of coronary fluoroscopy in their landmark publication regarding the Bayesian assessment of CAD likelihood [11]. Data confirming this relationship with CT based CAC scanning was later reported by Budoff et al (16). Given the need to better predict the likelihood of ischemia, one might have expected that there would have by now been 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 over a 15 year period (2000 to 2015) [17]. During this time, there were 20 publications that examined the relationship between CAC results and myocardial ischemia. However, most of these were very small studies, and only five of these studies involved patient populations with >500 patients. This paucity reflects the relative lack of interest in exploring and developing this potential clinical application. Most notably, the meta-analysis revealed a literature that is quite 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 present study, Engbers et al examined the relationship between CAC score and inducible myocardial ischemia in a large cohort of 4,897 patients, dwarfing the size of all prior publications in this regard [9]. 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 frequency of ischemia in each CAC subgroup [17]. For instance, among CAC scores of 0, the frequency of ischemia varied from 6.4% to 28.6%, and among those with CAC scores >400, the frequency of ischemia ranged from 11.7% to 65.7%. Many factors could account for these differences, including differences in the acuity of the patients, the frequency of co-morbid 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. The present study by Engbers et al serves to emphasize this important limitation in the literature. In the present study, the presence of ischemia was 12% among the patients with a normal CAC scan. Such a frequency would preclude the use of a zero CAC scan for excluding the likelihood of inducible myocardial ischemia in symptomatic patients. At the same time, 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 employed too lenient a criterion for interpreting studies as abnormal. In the present study, a summed difference score ≥ 2 was employed to define ischemia. By contrast, in many institutions, a score ≥ 4 is employed 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 in this study compared to prior reports. Thus, how many studies that were characterized as mild ischemia in the present study might be characterized as normal at other institutions? One approach to addressing this clinical question is to report results according to standardized and unbiased quantitative analysis.

Alternatively, clinical factors may be important drivers of the higher rate of ischemia observed in the present study. Here, various clinical factors could be particularly relevant, such as gender, CAD risk factors, chest pain and exercise capacity. For instance, studies involving the comparison of diabetes to non-diabetics 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 ischemia was substantially lower among patients with typical angina than in patients with atypical chest pain [19]. In a third study, exercise capacity modified the frequency of ischemia associated with intermediate CAC scores (20). Further, combining the results of chest pain and exercise ECG testing resulted in a markedly lower threshold of ischemia among patients with a high likelihood of CAD compared to patients with an intermediate likelihood of CAD (Figure) [19]. As in most prior studies, these potential modifiers of the relationship between CAC score and myocardial ischemia were not assessed in the present study. For instance, the study did not report chest pain symptoms and because pharmacologic testing was performed on a routine basis, no exercise data were available. Because the reported frequencies of

ischemia according to CAC score range 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 [21]. For instance, Chang et al followed 1,126 generally asymptomatic patients for a median of 6.9 years for the cardiac death, nonfatal myocardial infarction and the need for coronary revascularization [22]. 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 high CAC scores and inducible myocardial ischemia. The present study of Engbers et al extends these findings to a more symptomatic population undergoing MPI with a hybrid SPECT/CT system. The added prognostic value of the CAC score to MPI in a symptomatic population was also previously assessed with hybrid 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 the present study, CAC abnormality and the presence of myocardial ischemia were found to provide synergistic information in predicting major adverse cardiac events (MACE), defined as death, non-fatal myocardial infarction and late revascularization. When the CAC score was zero, the frequency of MACE was very low, regardless of the presence of ischemia. For each subsequent CAC score grouping, MACE 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 borderline 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 is found 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, who found that this led to greater accuracy in predicting obstructive CAD [24]. This was accomplished by 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 MPI maps that could eliminate soft-tissue artifacts by 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 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 [26]. Further, 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 two 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 little impact of normal MPI test results, found in the vast majority of patients, upon subsequent patient medical management. Since 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 non-obstructive as well as 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 at the same time 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 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 two tests ready for prime time? It may not be proven, but it merits further study and even at this time should be strongly considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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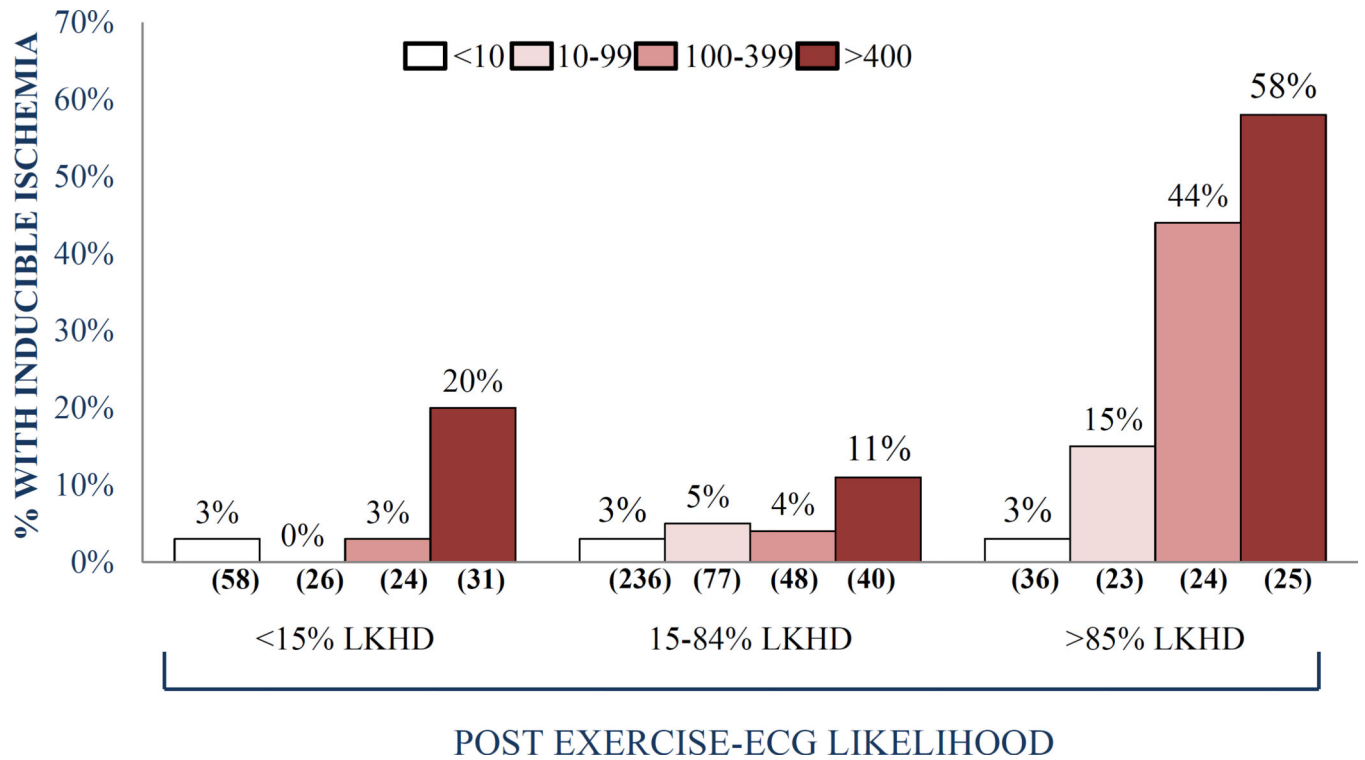


Figure.
 The frequency of ischemic stress/rest myocardial perfusion imaging (MPI) studies according to baseline coronary calcium scores among patients divided according to post-test likelihood (LKHD) of obstructive coronary artery disease (CAD), incorporating the results of age, gender, CAD risk factors, chest pain, and exercise ECG results. Both among patients with low and intermediate CAD likelihood, the frequency of ischemia was low for patients with CAC scores <400. By contrast, the CAC “threshold” for ischemia was substantially lower among patients with a high likelihood of CAD. Reproduced from Rozanski et al¹⁹, with permission of the publisher. ©Springer 2007.

Table

Clinical applications of combining coronary artery calcium scanning and myocardial perfusion imaging

1	Aiding the triage of patients for cardiac stress testing
2	Improving risk prediction and clinical management in conjunction with cardiac stress testing
3	Improving the interpretation of stress myocardial perfusion imaging studies

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