Coronary artery calcium score as a gatekeeper: are we there yet?

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In recent decades, the clinical manifestation of patients presenting with coronary artery disease (CAD) has changed with a decline in prevalence of typical angina among patients being referred for myocardial perfusion imaging (MPI) as well as the declining frequency of inducible myocardial ischemia being visualized.[1] Thus, appropriate patient selection is underscored by the importance of risk stratification in order to identify patients most likely to benefit from further non-invasive testing and therapeutic interventions.[2] Several risk stratification scores have been proposed by established guidelines, including the American Heart Association and the American College of Cardiology (AHA/ACC 2021) and European Society of Cardiology (ESC 2019) pre-test probability scores for obstructive coronary artery disease.[3,4]

The objective of assessing MPI using positron emission tomography (PET) imaging is to identify clinically significant narrowing of the coronary arteries, aiding in the management of patients with established or suspected coronary artery disease (CAD), providing valuable guidance in diagnosis and management, and thus has been recommended in international guidelines as a non-invasive method of risk stratification.[5–7] Although studies suggest the cost-effectiveness of PET in patients with high pre-test probability for CAD and the potential for reducing the demand for subsequent invasive intervention, the cost may be higher compared to the more widely available conventional single-photon emission computed tomography (SPECT) MPI.[8–10]

The coronary artery calcium score (CACS) is a quantitative measure of the extent of atherosclerosis in the coronary arteries. It acts as a surrogate marker and has been found to be a reliable predictor of various cardiovascular outcomes including events such as myocardial infarction and all-cause mortality.[11] The advantage of CACS is that it is simple, relatively inexpensive, and confers a strong negative risk indicator for CACS of 0. This indicates a favorable prognosis for mortality and major cardiovascular events,[11] with several studies and a recent meta-analysis advocating for its use as a ''gatekeeper'' to rule out obstructive CAD before proceeding to more expensive imaging tests.[12] The test can be done in combination with MPI (SPECT or PET), together with CT coronary angiography or as a stand-alone test, often in asymptomatic patients. Conversely, CACS will not detect soft plaque and hence obstructive coronary disease can still be evident in a small group of patients with CACS of 0, particularly the young.

In the current issue of Journal of Nuclear Cardiology, Clerc et al. aimed to evaluate and compare the effectiveness of CACS, pre-test probabilities, and combinations of both (post-test probabilities) in predicting myocardial PET perfusion defects in patients suspected

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of having CAD, excluding patients with known CAD. Additionally, the study aimed to assess the gatekeeping performance a CACS of 0, pre-test probabilities $\leq$ 5%, and post-test probabilities (a composite risk score based on pre-test probability and CACS) $\leq$ 5%, based on recently updated established guidelines from AHA/ACC 2021 and ESC 2019. The guidelines do differ, particularly in their assessment of the type of pain, but both fared well, particularly with post-test probability assessment. The ultimate goal is to identify and discharge patients at low probability of perfusion defects from CAD without further testing in order to ultimately reduce healthcare costs, radiation burden, and waiting times for cardiac imaging.[13]

The significant findings from this study demonstrated that a CACS of 0 has a high sensitivity and negative predictive value for abnormal perfusion on PET images and severe ischemia, comparable to that of pre-test AHA/ACC $\leq$ 5% and pre-test ESC $\leq$ 5% probabilities. However, only 2% of participants had such pre-test AHA/ACC $\leq$ 5% and 7% had pre-test-ESC $\leq$ 5% probabilities, while 26% had CACS of 0. Hence, by using CACS of 0, a greater proportion of patient with low probability of perfusion defects can be excluded from further imaging. The authors propose that in order to further refine the classification of the low-risk patient group based on AHA/ACC and ESC guidelines, the addition of CACS would allow for the generation of post-test probabilities. As a result, more patients—23% based on post-test AHA/ACC and 32% based on post-test ESC—were recategorized as having a low probability of perfusion defects. Furthermore, 30% based on post-test AHA/ACC and 37% based on post-test ESC were reclassified as having a low probability of experiencing severe ischemia on MPI PET. Importantly, this was achieved while maintaining a similar sensitivity and negative predictive value (NPV), thus allowing a much greater percentage of patients to be triaged to a ''no further imaging'' strategy.

The authors proposed that individuals with suspected CAD should be initially evaluated by their pre-test probability. If the pre-test probability is $\leq$ 5%, no further imaging would be required. However, if the pre-test probability is $\geq$ 5%, they recommend measuring CACS to recategorize the prediction and further imaging avoided if the CACS is 0 or if the post-test probability is $\leq$ 5%.[13] This study builds upon a recently published study performed by the same authors which highlighted the strong NPV of a CACS of 0 across sex and age groups but goes further to show the value of CACS relative to two widely used pre-test risk scores, AHA/ACA and ESC.[14]

Previous studies assessing the prognostic and diagnostic value of adding CACS to MPI are well recognized in the literature for SPECT imaging. A recent study demonstrated that the routine reporting of CACS in addition to MPI SPECT impacted on clinical management, changing patient management in 47% of patients, especially if the MPI was normal and CACS abnormal.[15] However, the value of CACS in myocardial perfusion PET is less well defined (see Table 1). This may be attributable to differing study end-points and the additional value of PET over SPECT in being able to assess both relative and absolute myocardial perfusion including myocardial flow reserve (MFR), which has been implicated in major cardiac events (MACE) as a result of microvascular disease and non-obstructive coronary artery disease.[16–18]

Miller et al. found that patients with CACS of 0 were at low risk for MACE regardless of the presence of regional myocardial ischemia on PET perfusion studies.[19] In addition, the risk associated with increasing ischemic burden was not modified by CACS risk category and vice versa. This therefore suggests some interchangeability of CACS risk stratification with PET perfusion. Similarly, Aljizeeri et al. found independent predictive value of CAC and MFR on PET to the composite endpoint of cardiac death and nonfatal myocardial infarction.[16] In addition, the predictive model with both MFR and CACS did not significantly predict outcomes better than models with MFR and CACS alone. However, Patel et al. found that although CACS had additional prognostic value for cardiac and all-cause mortality and correlated well with relative perfusion defects, 4 in 10 patients with CACS of 0 had reduced MFR.[18] This suggested that using CACS of 0 as a screening tool among symptomatic patients may fail to identify a significant portion of patients with coronary microvascular dysfunction with a higher mortality risk, of which the referring clinician should be aware.

The main endpoints of this current study assess PET perfusion abnormalities including abnormal perfusion and severe ischemia. Low MFR was calculated for each PET perfusion study and defined as < 2.0; however, the discrimination capacity of CACS for low MFR was limited. The prevalence of low MFR increased across all categories of CACS, pre-test-AHA/ACC and pre-test ESC categories, but a substantial proportion of low MFR (5–11%) was identified in the lowest risk categories including those with CACS of 0, who had a low MFR in 11% of cases. In order to confidently utilize CACS as a gatekeeper for perfusion PET imaging, this relationship of CACS and clinical end-points of myocardial infarction or death with non-obstructive coronary artery disease (MINOCA/INOCA) and microvascular disease will need to be carefully examined.

Clerc et al. strengthens the evidence for the advantages of utilizing CACS as a predictor of PET

Table 1. Previous studies investigating the value of CACS as gatekeeper for MPI with PET

Author Date	Type	Outcome measures	Key outcomes
Frey 2023	Consecutive patients referred for MPI PET N = 2640	CACS. Abnormal PET findings (ischemia, MFR) ROC analysis of CACS to exclude abnormal PET	CACS was higher in abnormal PET Abnormal PET was significantly less frequent in patient with CACS of 0
Miller 2022	Consecutive patients who underwent MPI PET with CAC scoring N = 2507	Follow-up for MACE, myocardial infarction (MI), admission for unstable angina, and late revascularization Associations between CAC and MACE	Presence of severe ischemia and CAC were independently associated with MACE Combining CAC and functional measures improves the prediction of MACE risk, with CAC of 0 identifying low-risk patients
Patel 2022	Consecutive patients who underwent MPI PET with CAC scoring N = 5983	All-cause death over median of 3 years Assessment of prognostic value and incremental risk discrimination	Addition of CACS to a model which included myocardial perfusion and MFR did not provide incremental prognostic value MFR <2 was present in 37.8% of patients with CACS of 0, associated with higher risk of all-cause death
Aljizeeri 2021	4,008 consecutive patients	Composite of cardiac death and nonfatal myocardial infarction Assessment of prognostic value of CACS and MFR	CACS and MFR independently added incremental prognostic value over clinical and MPI variables. A model with both MFR and CAC did not significantly predict outcomes better than models with MFR and CAC alone

MACE major adverse cardiovascular events, *ROC* receiver operator curve, *MFR* myocardial flow reserve, *MPI* myocardial perfusion imaging, *PET* positron emission tomography, *CAC* coronary artery calcium, *CACS* coronary artery calcium score[14,16,18,19]

perfusion abnormalities either as an independent measure or in combination with widely used pre-test criteria. This is especially the case for low-risk patients with a CACS of 0. However, the significant advantage of PET perfusion and the ability to quantify myocardial flow reserve, which can be independent of atherosclerotic disease and coronary artery calcification, will need to be taken into consideration.[20] In the context of increasing prevalence of diabetes and atypical presentations of chest pain, the prevalence of microvascular dysfunction will likely increase and the jury remains out as to whether CACS will be an adequate discriminator in this group. Future research should be aimed at further risk stratification for these patients undergoing CACS and consider proceeding to PET perfusion testing for those patients who would benefit most from the accurate assessment of MFR.

We congratulate Clerc and his team for their innovative work. While we are in an era of cost awareness in the setting of high-cost technology and increased utilization world wide of cardiac PET, the authors are giving us a strong message to use the relatively cheap CACS together with pre and now post-test probabilities to obviate the need for PET imaging in a certain low-risk group of patients. However, we must be cognisant of missing certain patients with this algorithm, particularly the young and those with a high risk of microvascular disease. A compromise for these patients, after a CACS of zero or low post-test probability, could be to utilize low-cost alternatives such as a simple exercise electrocardiogram, without further imaging. So, coronary calcium as a gatekeeper for most patients – are we there yet? Probably yes. For all patients? Probably no. As we continue to use this expensive technology, clinical input remains critical.

Disclosures

Bonnia Liu and Nathan Better have no conflicts of interest to disclose.

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