

Risk Stratification Using Cardiac Imaging: A Comprehensive Review

Editor's Pick

My Editor's Pick for this year's edition of *EMJ Radiology* is an insightful review article, in which the authors explore the different imaging modalities for coronary artery disease. King et al. emphasise the importance of understanding the options in light of patients' clinical presentations, and choosing the correct modality based on this analysis. The authors highlight the value of combining clinical experience with existing guidelines.



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Abstract

There are numerous cardiac imaging modalities which aid in the diagnosis and management of coronary artery disease (CAD). Each modality has variable efficacy in detecting stenosis and stratifying risk among those with CAD. Clinicians must evaluate these methods in light of their patients' clinical presentations, to choose the most appropriate imaging technique. Understanding the unique benefits and indications of each modality aids in the selection of high-value imaging. Following is a review of the available cardiac imaging methods for the identification and risk stratification of CAD.

Key Points

1. When screening for obstructive coronary disease, and risk stratifying those with known stenosis, there are multiple imaging modalities available to the clinician; however, the indications and benefits of each are not always readily apparent.
2. This review article describes and compares the techniques used for the evaluation of stable coronary disease, taking into account their unique risks, benefits, and the current guidelines.
3. While guidelines and expert recommendations are necessary to consider when choosing the most appropriate screening technique, they must be utilised alongside clinical acumen, informed by an accurate understanding of the available imaging modalities.

INTRODUCTION

There are numerous cardiac imaging modalities which aid in the diagnosis and management of coronary artery disease (CAD). Each modality has variable efficacy in detecting stenosis and stratifying risk among those with CAD. Clinicians must evaluate these methods in light of their patients' clinical presentations, to choose the most appropriate imaging technique. However, deciding between tests can be challenging. Guidelines determined by expert panels can suggest if one test modality is clinically superior, or whether imaging is indicated at all.¹ As with most areas of clinical medicine, discrepancies exist between the guidelines of professional societies.² Some experts have advocated that imaging modalities can adequately fulfil multiple roles, including diagnosis and risk stratification, serving as a 'one-stop shop'.³ Others assert that a combination of several techniques can provide highly effective screening.⁴ In light of these disparate views, the American College of Cardiology (ACC) and American Heart Association (AHA) published updated guidelines on the appropriate use of imaging for patients with stable chest pain, based primarily on clinical risk stratification, which guides recommended testing.⁵ Understanding the unique benefits and indications of each modality in accordance with these guidelines elucidates the selection of high-value imaging. Following is a review of the available cardiac imaging methods for the identification and risk stratification of CAD.

CORONARY ARTERY CALCIUM SCORE

The coronary artery calcium score (CACS), also called the Agatston score, is an application of CT imaging which quantifies calcified plaque in the coronary arteries, allowing for measurement of atherosclerotic burden. A positive CACS has a sensitivity of 98%, specificity of 40%, negative predictive value (NPV) of 93%, and positive predictive value of 68% for detecting the presence of >50% stenosis.⁶ Given these statistics, some clinicians have argued that a CACS of zero does not warrant further cardiac evaluation; however, a subgroup analysis of the CORE64 study showed an NPV of 68%, concluding that a CACS score of zero could not exclude coronary disease. Further, a subgroup of the CONFIRM registry demonstrated coronary stenosis in 3.5% of patients with CACS of 0.⁷ In combination with the Framingham risk score (FRS), which predicts a patient's 10-year cardiovascular event risk, coronary calcium scoring can assist with this clinical decision. For individuals who fall within the intermediate-risk category (FRS >10%), assessing their CACS can predict for elevated risk. In fact, CACS was predictive of risk among patients with an FRS higher than 10% ($P < 0.001$). For patients with FRS of 5.0–7.5%, an elevated CACS can reclassify their risk up or down, clarifying the necessity for statin therapy.⁸

CORONARY CT ANGIOGRAPHY

Coronary CT angiography (CCTA) is another non-invasive technique that visualises the coronary arteries. The 2021 ACC/AHA guidelines for the evaluation and diagnosis of chest pain gives a Class 1A recommendation for intermediate-risk patients with acute chest pain and no known CAD.⁵ Diagnosing CAD via CCTA has a sensitivity ranging from 90–98%, and specificity of 70–95%, with values increasing as slice resolution increases.^{9–13} These sensitivities and specificities are comparable to invasive coronary angiography (ICA). CCTA thereby decreases procedural risk by excluding patients without significant lesions, and allows for the rapid, early detection of CAD.¹⁴ However, limitations exist, including radiation exposure, administration of contrast, and difficulty visualising heavily calcified vessels.

CCTA findings of $\geq 50\%$ and $\geq 70\%$ stenosis, as well as stenosis in the left main and proximal left anterior descending arteries, are predictors of all-cause mortality in patients with chest pain ($P < 0.0001$).¹⁵ In addition, vulnerable plaque characteristics, such as low-attenuation plaque, positive remodelling, napkin-ring sign, and spotty calcium pattern of calcification are also predictors of major adverse cardiac events (MACE).¹⁶ Of note, in the PROMISE trial, a strategy of initial CCTA as compared with functional testing did not improve clinical outcomes.¹⁷ This implies more than anatomical data from CCTA is needed, which is where CCTA-fractional flow reserve (FFR) plays a role.

CT FRACTIONAL FLOW RESERVE

FFR, the index measuring functional severity of coronary artery stenosis, is calculated as the ratio of the maximum achievable blood flow through a stenotic artery, to the maximum achievable blood flow in the absence of that stenosis. Traditionally, FFR is assessed during ICA to identify haemodynamically significant lesions, in addition to visual assessment. Studies have shown reductions of the composite endpoint of death, myocardial infarction (MI), and need for revascularisation with FFR-guided percutaneous coronary intervention (PCI).^{18,19} CT-FFR is a newer technology that utilises CCTA images and advanced computational modelling techniques to create an anatomic model with

FFR values of the entire coronary tree. It should be noted that, as CT-FFR is a function of CCTA imaging, it has similar efficacy in identifying CAD. Compared to the diagnostic value of CCTA alone, CT-FFR is noted to have increased accuracy per vessel and specificity in identifying significant stenosis.^{20,21} When comparing CT-FFR to invasive FFR, the accuracy of detecting an abnormal invasive FFR was only 50% for CT-FFR in the range of 0.76–0.80, whereas it was 75% in the range of 0.71–0.75, and 100% for CT-FFR < 0.7 .²² Data from CT-FFR registries demonstrate this tool's prognostic ability, with patients of CT-FFR values of > 0.80 having an excellent prognosis with no adverse events at 30 days, or 1 year.²³

STRESS ECHOCARDIOGRAPHY

Stress echocardiography utilises variability of endocardial wall motion to assess global and regional cardiac function, thereby assisting in the diagnosis and management of clinically significant CAD. Induction of stress may be physiologic, through exercise (e.g., treadmill or bicycle ergometer), or pharmacologic, through dobutamine or dipyridamole, with both agents carrying a strong evidence base for prognostic evaluation. The implications of normal stress echocardiography results have been well evaluated, and carry a low risk of subsequent cardiac events, with a cardiac event rate of $< 1\%$ per year.²⁴ In comparison to stress myocardial perfusion imaging, the negative predictive value of normal test results was similar in meta-analyses,^{24–26} highlighting the role of stress echocardiography as a cost-effective gatekeeper for more invasive strategies.

In patients with known or suspected CAD, peak wall motion stress index (WMSI) was able to effectively stratify patients into low (WMSI: 1.0; 0.9% per year), intermediate (WMSI: 1.1–1.7; 3.1% per year), and high (WMSI: > 1.7 ; 5.2% per year) risk of cardiac death, in both univariate ($P = 0.0001$), and multivariate analysis ($P = 0.04$). Furthermore, left ventricular ejection fraction (LVEF) during testing could also independently stratify patients into low-to-intermediate-risk (LVEF $> 45\%$), or high-risk (LVEF $\leq 45\%$) for cardiac events.²⁷

In the context of post-acute MI, regional systolic function assessed by WMSI yields significant

prognostic utility. In a large retrospective study on 767 patients post-MI, both WMSI ($P<0.0001$), and LVEF ($P<0.0001$), were strongly predictive of all-cause mortality.²⁸ By univariate analysis, WMSI proved to be an independent predictor of both death ($P<0.0001$) and hospitalisation for congestive heart failure ($P=0.002$) in this population.²⁸ LVEF did not provide additional prognostic information in this study when combined with WMSI, suggesting WMSI may be more valuable in risk stratification.²⁸ Notably, the impact of stress echocardiography in risk stratification can be applied to all subsets of patient populations, irrespective of age, sex, and comorbidities such as diabetes.²⁹ However, abnormal stress echocardiography test results should be analysed in the context of factors including patient comorbidities; the extent of dysmotility; presence of prior scar; ischaemic threshold; and in combination with additional testing, such as the Duke Treadmill Score.

STRAIN AND STRAIN RATE ECHOCARDIOGRAPHY

Myocardial strain and strain rate (SR) echocardiography are newer imaging modalities that offer additive value over traditional echocardiography, which neglects the longitudinal and circumferential components of myocardial deformation. Strain and strain rate represent the magnitude and rate of myocardial deformation, respectively. Abnormalities of myocardial deformation are observed early in various cardiovascular disease states, and may be useful for identifying preclinical disease, or those at risk for developing a cardiac condition.³⁰ For patients with clinical suspicion for CAD, strain echocardiography provides a sensitivity of 86%, and specificity of 73%, for detecting significant coronary stenosis.^{31,32} Segmental left ventricular longitudinal strain specifically has been demonstrated to provide accurate localisation of stenotic vessels.³¹

Strain and SR echocardiography can provide important insights into various cardiovascular diseases, including CAD, detection of viable myocardium, sequelae of MI, and response to reperfusion. Although strain imaging has multiple applications, perhaps its most significant role is in the detection of ischaemic heart disease. For example, in patients with a normal LVEF

at increased risk of atherosclerotic disease, a progressive impairment of 2D global strain and SR correlated with increasing severity of CAD.³³ In another study of 2D strain imaging, peak systolic longitudinal SR and early diastolic SR predicted significant ($>70\%$) arterial stenosis.³⁴ Furthermore, 2D peak systolic longitudinal strain of the left ventricle has been shown to discriminate severe triple vessel or left main disease from lesser CAD,³⁵ demonstrating the utility of SR echocardiography in cardiac risk-stratification.

SINGLE-PHOTON EMISSION CT MYOCARDIAL PERFUSION IMAGING

Single-photon emission CT (SPECT) myocardial perfusion imaging (MPI) utilises gamma rays to evaluate the flow-dependent selective uptake of a radioactive tracer, typically thallium-201 or technetium (sestamibi or tetrofosmin). SPECT MPI is typically done both at rest and with stress, to assess for inducible ischaemia, giving qualitative or semi-quantitative assessment of myocardial perfusion. Physiologically, myocardial arterioles distal to a significant epicardial coronary stenosis are autoregulated and dilated at rest to maintain myocardial blood flow. Under stress, normal vascular beds dilate more than abnormal vascular beds, leading to relative differences in tracer uptake, referred to as 'perfusion defects'. Stress and rest images are compared in transverse, vertical, and horizontal axes, and perfusion defects are described in a standardised model of the left ventricle, allowing semi-quantitative scoring of defects.³⁶ It is the most commonly used imaging modality in nuclear cardiology, as it is able to evaluate for the physiologic presence, extent, and degree of myocardial ischaemia or infarction, and assists with prognostication in patients with suspected or known CAD. The sensitivity and specificity of SPECT has been measured at 88% and 76%, respectively, when compared with ICA.³⁷ SPECT MPI also assesses viability of myocardial tissue when evaluating for further interventions.³⁶

With regard to prognostication, SPECT adds independent and incremental value to predict cardiac death or non-fatal MI, even when accounting for exercise tolerance testing, clinical, and angiographic variables.³⁸ SPECT has a high negative prognostic value, with

a meta-analysis indicating that a normal or low-risk stress MPI is associated with a 0.6% annual MACE rate, approaching that of a normal age-matched population, and a population of patients with normal coronary angiography.³⁹ This persists even in patients with strongly positive exercise electrocardiogram testing, or angiographically significant coronary disease.⁴⁰ The prognosis seems to be sustained for up to 3 years in one meta-analysis, indicating a negative predictive value for MI and cardiac death at 98.8% over 36 months.²⁵ On the other hand, if SPECT MPI is abnormal, the extent and severity of the abnormal findings are able to predict progressively higher annual cardiac death rates.⁴⁰ Even when a study is mildly abnormal, high-risk features can help with risk stratification, including transient or persistent left ventricular cavity dilation, LVEF <45%, and defects in more than one coronary vascular territory, with any of these indicating a higher annual mortality rate.³⁹ Because of this feature, SPECT MPI is commonly used for patients pre-operatively at intermediate risk, to help with risk stratification. Additionally, SPECT can help guide treatment decision-making and prognosis following treatment. Studies have suggested that revascularisation may be favoured when >10% of the myocardium is ischaemic.³⁹ Some limitations of the modality include the inability to distinguish global blood flow reduction due to balanced perfusion defects during stress; the exposure of the patient to radiation; limited off-hours availability; inability to measure absolute myocardial blood flow; and attenuation artifacts from surrounding soft tissues, the diaphragm, or extracardiac radioisotope uptake. The use of ECG-gating and attenuation correction software is able to improve the accuracy of the study, and help with alleviating some of these limitations.

PET MYOCARDIAL PERFUSION IMAGING

PET MPI utilises positron emitting radiotracers (rubidium-82 or nitrogen-13 ammonia) administered under rest and stressed conditions. Detection and distribution of these radiotracers allows for 3D mapping of cardiac perfusion.⁴¹ PET MPI image quality is superior to most SPECT MPI set-ups, although widespread adoption of PET MPI is limited by equipment cost, expertise, reimbursement, and a number

of other factors.⁴² A particular strength of this method over other modalities is the ability to measure coronary flow reserve (CFR).⁴³⁻⁴⁶ For detecting CAD with at least one coronary artery with >50% stenosis, PET MPI has an average sensitivity of 90%, and an average specificity of 80%, yielding a positive predictive value of 94%, and NPV of 73%.⁴⁷ It is notable that, for the purpose of predicting cardiac death, all cause death, and MACE in patients with known or suspected CAD, other studies have found an NPV of 98%.⁴⁸ Multiple studies have shown that a normal PET MPI confers a <1% annual cardiac event rate, while there is incrementally increasing risk of MI and death based on the extent of cardiac involvement.^{43,44} Similar to SPECT, risk of MACE after PET MPI is often classified by the percentage defect size, low risk with <5% involvement of the myocardium, intermediate risk involving 5–10%, and high risk involving >10%.⁴⁹ Patients with high risk findings are suitable to be referred for left heart catheterisation.⁵⁰ One advantage of PET MPI is the use of PET-derived CFR, which can further risk stratify patients; there is evidence of elevated risk of MACE with poor CFR, independent of the size of the perfusion defect.^{44,45} One study found a 5.6-fold higher risk of cardiac mortality in the lowest tertile as compared to the highest.⁴⁶ When comparing PET to SPECT MPI, multiple studies have shown similar patient outcomes and rates of diagnostic failure.^{51,52} One additional advantage of PET MPI over SPECT is the lower radiation exposure of 3.7 mSv, much lower than the equivalent test using SPECT with a mean exposure of 12.8 mSv, due to the short half-lives of the radiotracers administered.^{53,54}

CARDIAC MRI

Cardiac magnetic resonance imaging (CMR) is a reliable clinical technique for the evaluation of myocardial structure, function, perfusion, and viability, serving as an important predictor of MACE.^{55,56} Meta-analysis has demonstrated that CMR can detect CAD of $\geq 50\%$ with a sensitivity of 89%, and specificity of 72%, increasing to 95% and 80%, respectively, with utilisation of contrast material and 3T magnets. Additionally, elevated plaque-to-myocardium signal intensity ratios of ≥ 1.4 obtained via CMR have been shown as significant predictors of coronary

events at 2-year follow-up.^{57,58} Compared to another anatomic imaging technique, CCTA has excellent spatial resolution that permits robust coronary plaque composition analysis,⁵⁹ while CMR resolution is often limited to the presence or absence of clinically significant CAD.⁶⁰

CMR also provides valuable prognostic information for individuals with ischaemic and non-ischaemic cardiomyopathy, through measurement of late gadolinium enhancement (LGE).⁶¹ Elevated LGE has been found by meta-analysis to be associated with appropriate implantable cardioverter-defibrillator discharges, aborted sudden cardiac death, and sudden cardiac death events.⁶² Arrhythmic MACE occurs in 23.9% of patients with positive LGE for an annualised event rate of 8.6%, while only 4.9% of individuals with negative LGE results experienced arrhythmic MACE at an annualised event rate of 1.7%.⁶³ However, as LGE detects fibrotic scars, it may be limited in the evaluation of progressive non-ischaemic cardiomyopathies.⁶¹ The use of other CMR-derived values, including extracellular volume quantification, bridges this gap, as elevated extracellular volume quantification values indicate strong association with MACE in NICM.

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is an imaging modality that is often used during ICA with planned intervention, including stent placement, suction thrombectomy, and balloon angioplasty. It allows the operator to visualise high resolution intracoronary images and assess coronary plaques, thereby optimising coronary interventions.⁶⁴ Data on the routine use of OCT outside of PCI is limited.⁶⁵ In the acute setting, there is clear description that OCT helps to prevent complications related to stent placement and other procedural-based complications, as it provides a superior assessment of fibrous cap, intracoronary thrombus, and plaque morphology.⁶⁵ Operators' decision-making can be altered by OCT findings.

Despite no current application in the preventative risk assessment setting, OCT offers improved visualisation of the coronary lumen, including visualisation of the vessel, the plaque, and the coronary thrombus, if present. Prior work has

shown that OCT can be used to detect plaque areas with thin fibrous caps and lipid cores with high sensitivity.⁶⁶ These are the areas thought to be primarily responsible for acute rupture and coronary vessel occlusion.⁶⁶ Further work needs to be conducted in order to determine if there is a role for OCT in other settings, including if use impacts long-term clinical outcomes for patients.⁶⁷

INTRAVASCULAR ULTRASOUND

Although ICA allows for prompt evaluation of CAD and vessel patency, diagnostic information is limited to 2D fluoroscopy acquired from multiple sequential angles with contrast dye administration. Similar to OCT, intravascular ultrasound (IVUS) is an adjunct tool that is used during ICA for the real-time assessment of coronary artery vessel architecture. IVUS can elucidate multiple lesion characteristics, including numeric dimensions and the composition of surrounding coronary plaque/thrombosis, offering up to two- to three-times the axial resolution of angiography alone.⁶⁸ IVUS is useful during PCI, as it can help guide stent placement, and enable precise deployment without the use of radiation via fluoroscopy. Additionally, its ability to provide useful information to operators about the presence of dissection, thrombus, and calcium burden enables them to use situation-specific therapies, including distal embolic protective devices and atherectomy, as needed.⁶⁹

Direct intravascular visualisation has been shown to improve outcomes in patients undergoing IVUS-guided stent placement versus angiographically-guided stent placement.⁷⁰ Although the use of IVUS has been increasing in recent years, only a minority (<20%) of ICAs are performed with IVUS.⁷¹ The 2021 AHA Guideline for Coronary Artery Revascularization gives IVUS a Class 2a indication for assessing the severity of left main coronary artery stenosis, but there are sparse data from large trials demonstrating its impact on long-term clinical outcomes.⁶⁸

Near-infrared spectroscopy technology can be used in conjunction with IVUS to detect the presence of lipid-rich coronary plaques, which are associated with higher incidence of MACE and cardiac-related deaths.⁷² With continued research and newer clinical adaptations of IVUS, its use may likely increase over the coming years.

CONCLUSION

In summary, each modality discussed offers unique benefits in the correct clinical circumstance. CACS is an effective anatomic evaluation for screening out young patients with low risk for obstructive CAD. CCTA provides similar benefit for intermediate- to high-risk individuals without known CAD, as well as to evaluate stent patency in those with known obstructive disease. Based on local availability, patient characteristics, and individual contraindications, the stress imaging modalities, including stress echocardiography, SPECT/PET MPI, and CMR, effectively assess for significant obstructive lesions. When management remains unclear, CT-FFR in combination with stress imaging or positive CCTA results can determine the presence of functionally high-grade stenosis. Lastly, IVUS and OCT provide

valuable information during PCI to direct stent placement, and delineate further high-risk characteristics of culprit lesions.

The clinician's role is to choose the most appropriate imaging modality for each scenario, with the assistance of expert guidelines and decision-making tools, including appropriate use criteria. Granted, this task is more complicated than simply selecting the recommended test; as evidenced by Bayes' theorem, false positive and false negative testing, especially in low-risk populations, can significantly impact the value of these tests and the clinical courses for many patients. Factors including local availability, radiation exposure, contrast administration, procedural risk, and cost must be weighed as well. An understanding of each modality, its indications, and its shortcomings allows the clinician to offer patients the highest value cardiovascular imaging.

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