Cardiovascular imaging techniques for the assessment of coronary artery disease

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Abstract

Coronary artery disease continues to be the leading cause of morbidity and mortality worldwide. Recent clinical trials have not demonstrated any mortality benefit of percutaneous coronary intervention compared to medical management alone in the treatment of stable angina. While invasive coronary angiography remains the gold standard for diagnosing coronary artery disease, it comes with significant risks, including myocardial infarction, stroke and death. There have been significant advances in imaging techniques to diagnose coronary artery disease in haemodynamically stable patients. The latest National Institute for Health and Care Excellence and European College of Cardiology guidelines emphasise the importance of using these imaging techniques first to inform diagnosis. This review discusses these guidelines and imaging techniques, alongside their benefits and drawbacks.

Key words: Cardiac magnetic resonance imaging; Computed tomography coronary angiogram; Coronary artery disease; Dobutamine stress echocardiography; Myocardial perfusion scan; Percutaneous coronary intervention

Submitted: 2 April 2022; accepted following double-blind peer review: 4 May 2022

Introduction

It is currently estimated that 7.4 million people are living with ischaemic heart disease in the UK (British Heart Foundation, 2020). Despite a significant reduction over the last 50 years, the mortality rate for coronary artery disease remains high in some areas of the UK and particularly the central belt of Scotland. Consequently, coronary artery disease confers a significant health burden and is estimated to cost the UK £9 billion a year (British Heart Foundation, 2020). Admissions to hospital with chest pain account for a significant proportion of the acute medical take and while it is important to remain vigilant for acute coronary syndromes, a reasonable proportion of these admissions will involve patients with stable coronary disease or angina (Goodacre et al, 2005). Cardiovascular imaging involves an array of potential modalities that are appropriate for the investigation of coronary artery disease, but all have their potential benefits and limitations.

Invasive coronary X-ray angiography is commonly recognised as the reference standard for the investigation of coronary artery disease (Knuuti et al, 2020). X-ray angiography gives anatomical information and identifies coronary stenoses in patients presenting with chest pain, as well as allowing invasive pressure measurements. However, it does not give information on the burden of ischaemia unless invasive pressure wire assessment (fractional flow reserve or instantaneous wave-free ratio) is used (Tonino et al, 2009). As an invasive investigation, it confers both morbidity in terms of radiation burden and potential vascular complications, and has a very low but potential (1/1000) risk of mortality. Furthermore, there is a low yield of obstructive coronary artery disease seen in those referred for angiography (Patel et al, 2010). Indeed, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHAEMIA) trial demonstrated that percutaneous coronary intervention showed no mortality benefit compared to medical management alone in the treatment of patients with stable angina (https://clinicaltrials.gov/ct2/show/NCT01471522). Notably, the ISCHAEMIA trial excluded patients with left main stem disease and refractory angina despite optimal medical therapy. This forms a large cohort of patients who would benefit from revascularisation, limiting the external validity of the results in patients with stable coronary disease.

How to cite this article:
Ahmed R, Carver C, Foley JRJ, Fent GJ, Garg P, Ripley DP. Cardiovascular imaging techniques for the assessment of coronary artery disease. Br J Hosp Med. 2022. https://doi.org/10.12968/hmed.2022.0176

Table 1. Characteristics, advantages and disadvantages of different imaging modalities				
	Transthoracic or stress echocardiography	**Computed tomography coronary angiography**	**Single-photon emission computed tomography**	**Cardiovascular magnetic resonance imaging**
Time to perform test	30–45 minutes	<5 minutes	10 minutes on two sequential days	40–50 minutes
Bedside availability	Bedside, wide availability		Wide availability	Predominantly tertiary centre
Radiation	No	Yes	Yes	No
Contrast	No	Iodinated contrast	Radioactive isotope	Gadolinium-based
Assesses	Wall motion	Coronary anatomy	Ischaemia	Perfusion defects and wall motion
Advantages	Low cost High spatial and temporal resolution Feasible in renal disease Feasible with pacemakers	High spatial and temporal resolution High sensitivity Feasible with pacemakers	Feasible in renal disease Feasible with pacemakers	High spatial and temporal resolution Images in any plane High sensitivity and specificity Assessment of viability Gold standard functional and structural assessment
Disadvantages	Poor acoustic windows may limit image quality Requires high operator experience	Lower specificity Radiation burden Contraindicated in advanced renal disease	Low spatial resolution Lower sensitivity (especially in women) Radiation burden	Contraindicated in advanced renal disease Pacemakers need to be magnetic resonance imaging conditional

Non-invasive imaging modalities such as single-photon emission computed tomography, dobutamine stress echocardiography, cardiovascular magnetic resonance imaging, computed tomography coronary angiography and positron emission tomography aim to diagnose coronary artery disease, quantify ventricular function and ischaemic burden, assess the viability and confer prognostic information. They are therefore identified for these roles in current clinical practice guidelines (National Institute for Health and Care Excellence, 2016; Knuuti et al, 2020). This review explains the role of each of these modalities in current guidelines and highlights the strengths and weaknesses of each. These characteristics, advantages, and disadvantages are summarised in Table 1.

Risk stratification

Historically, rapid access chest pain clinics used clinical history and examination followed by an exercise tolerance test to risk stratify patients presenting with chest pain caused by stable angina. This was generally followed by single-photon emission computed tomography or invasive coronary angiography if warranted. Exercise tolerance testing has since been removed from guidelines because of its limited diagnostic sensitivity (National Institute for Health and Care Excellence, 2016; Knuuti et al, 2020). The National Institute for Health and Care Excellence (2016) guidelines now highlight a 64-slice computed tomography coronary angiography as first-line investigation in patients with a high suspicion of ischaemic chest pain secondary to coronary artery disease, where a diagnosis cannot be reached solely on clinical assessment. This includes all patients with typical or atypical chest pain (Table 2) and those with non-anginal pain but with electrocardiogram changes. Functional imaging is recommended for those with previously documented coronary disease and unclear ischaemic morphology of chest pain, or an indeterminate computed tomography coronary angiography (National Institute for Health and Care Excellence, 2016).

Table 2. Typicality of chest pain for angina	
Typical angina (definite)	Meets all three of the following characteristics: 1. Constricting discomfort in the front of the chest, or in the neck, shoulders, jaw or arms 2. Precipitated by physical exertion 3. Relieved by rest or glyceryl trinitrate within about 5 minutes
Atypical angina (probable)	Meets two of the above characteristics
Non-cardiac chest pain	Meets one or none of the above characteristics

From Hassanabad et al (2019)

Non-invasive functional testing includes single-photon emission computed tomography, stress echocardiography, first-pass contrast-enhanced magnetic resonance perfusion or magnetic resonance imaging for stress-induced wall motion abnormalities. Invasive coronary angiography is commonly reserved as a third-line investigation in cases that remain inconclusive or if patients have contraindications to former techniques (National Institute for Health and Care Excellence, 2016). Therefore, understanding non-invasive imaging modalities is of paramount importance. The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial displayed no significant difference in overall outcome with computed tomography coronary angiography and non-functional imaging, and both accounted for a similar number of adverse events (Bavry et al, 2019). The chronic coronary syndrome guidelines of the European Society of Cardiology give no preference over non-invasive functional imaging or computed tomography coronary angiography as the first diagnostic test for coronary artery disease (Knuuti et al, 2020). The choice should be centred on the clinical likelihood of coronary artery disease and other patient and demographic parameters affecting the availability and performance of tests. Diagnostic testing is primarily recommended in the intermediate likelihood group of patients. A predictive model to estimate the pre-test probability of obstructive coronary artery disease based on age, gender and extent of symptoms was established on the dataset by de Jong et al (2012). Overall, studies have shown that patients classified with the new pre-test probability of less than 15% have good outcomes, making it safer to defer routine testing (Tables 2 and 3) (Wolk et al, 2014).

Notably, for patients with a very high-risk pre-test likelihood of coronary artery disease, the 2010 National Institute for Health and Care Excellence guidelines suggested performing no investigation and to treat it as angina. However, this may potentially be denying this group an assessment of their ‘ischaemia burden’, a discriminator that is known to confer prognostic information (Nagel and Shaw, 2014). The CE-MARC 2 trial identified that the 2010 National Institute for Health and Care Excellence guidelines led to higher rates of unnecessary angiography compared to functional imaging-guided care; a strategy that potentially increases patient morbidity and healthcare costs (Walker et al, 2021). The mechanism is likely a result of an overestimation of the risk of coronary artery disease by the pre-test likelihood model used in the 2010 National Institute for Health and Care Excellence) guideline. Notably, the more recent European guidelines used an updated pre-test likelihood model to risk stratify patients (National Institute for Health and Care Excellence, 2016; Knuuti et al, 2020). In the latest National Institute for Health and Care Excellence (2016) guidelines, pre-test likelihood estimation is no longer recommended. The 2016 guidelines now recommend referral for computed tomography coronary angiography in all patients with typical or atypical chest pain (Table 1) and in those with non-anginal pain but with electrocardiogram changes, with functional imaging being reserved for those who have previously documented coronary disease or revascularisation (National Institute for Health and Care Excellence, 2016).

Computed tomography coronary angiography

Computed tomography can be used in the assessment of coronary artery calcium score which uses an estimate of calcium burden within the heart to predict the presence or absence of coronary artery disease, as well as computed tomography coronary angiography

Table 3. Pre-test probabilities of obstructive coronary artery disease in 15815 symptomatic patients according to age, sex, and the nature of symptoms in a pooled analysis of contemporary data

	Typical		Atypical		Non-anginal chest pain	
Age (years)	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
30–39	3%	5%	4%	3%	1%	1%
40–49	22%	10%	10%	6%	3%	2%
50–59	32%	13%	17%	6%	11%	3%
60–69	44%	16%	16%	11%	22%	6%
70+	52%	27%	34%	19%	24%	10%

In addition to the classic Diamond and Forrester classes, 59 patients with dyspnoea only or dyspnoea as the primary symptom are included. The regions shaded dark blue denote the groups in which non-invasive testing is most beneficial (pre-test probability >15%), and those shaded pale blue denote the groups with pre-test probabilities of coronary artery disease between 5–15%, in which testing for diagnosis may be considered after assessing the overall clinical likelihood. From Knuuti et al (2020)

which allows visualisation of the coronary arteries. Coronary artery calcium score is a quick and simple test acquired in a single breath-hold, without the need for any contrast agent. It is used to estimate the degree of calcification within the coronary arteries, with an excellent correlation to total coronary calcium burden in histological samples (Rumberger et al, 1995). Coronary calcium scoring predicts future risk of coronary events (myocardial infarction, death from coronary heart disease or resuscitated cardiac arrest) in asymptomatic patients more accurately than clinical risk scoring alone (Polonsky et al, 2010); scores in symptomatic patients correlate positively with the degree of luminal coronary artery obstruction (Knez et al, 2004). However, a large international, multi-centre trial demonstrated that a coronary artery calcium score of 0 is insufficient to rule out significant coronary artery disease (Villines et al, 2011). For this reason, coronary artery calcium score is now nearly always combined with computed tomography coronary angiography in the assessment of patients with chest pain at low to intermediate risk. More recently, computed tomography-fractional flow reserve can also be calculated to elicit the functional ischaemic nature of a coronary lesion (Figure 1), but this is expensive and is currently only available in certain UK centres.

Computed tomography coronary angiography allows visualisation of the lumen and wall of the coronary arteries and takes 20–30 minutes, with few contraindications. The heart rate is optimised to obtain better quality imaging, usually with a beta-blocker or ivabradine, before starting computed tomography coronary angiography. Intravenous iodinated contrast agent is then required to produce images. Contraindications include allergy to contrast agent and a relative contraindication is significant cardiac arrhythmia, such as atrial fibrillation. The key strength of computed tomography coronary angiography lies in its high negative predictive value, meaning it correctly classifies a high proportion of patients not to have significant coronary artery disease. The level of spatial resolution (the ability to discriminate between two adjacent high contrast objects) of modern scanners allows detection of atherosclerotic plaques within coronary arteries, leading to a diagnosis of coronary artery disease (Budoff et al, 2016).

Meta-analyses comparing the diagnostic accuracy of 64-slice (or more) computed tomography coronary angiography in detecting significant coronary artery stenosis have estimated the sensitivity as between 98% and 99% and specificity between 64% and 89% (Mowatt et al, 2008).

Limitations of computed tomography include the potential nephrotoxic effects of intravenous contrast, exposure of the patient to ionising radiation, and its very limited ability to assess heart structure and function beyond the coronary arteries. The radiation exposure from computed tomography coronary angiography is in the region of 3–4 millisievert (mSv) or below (Menke et al, 2013), although with newer technology sub-mSv scans are possible. The typical radiation dose associated with coronary artery calcium scoring is less than 1 mSv (Baron et al, 2016).

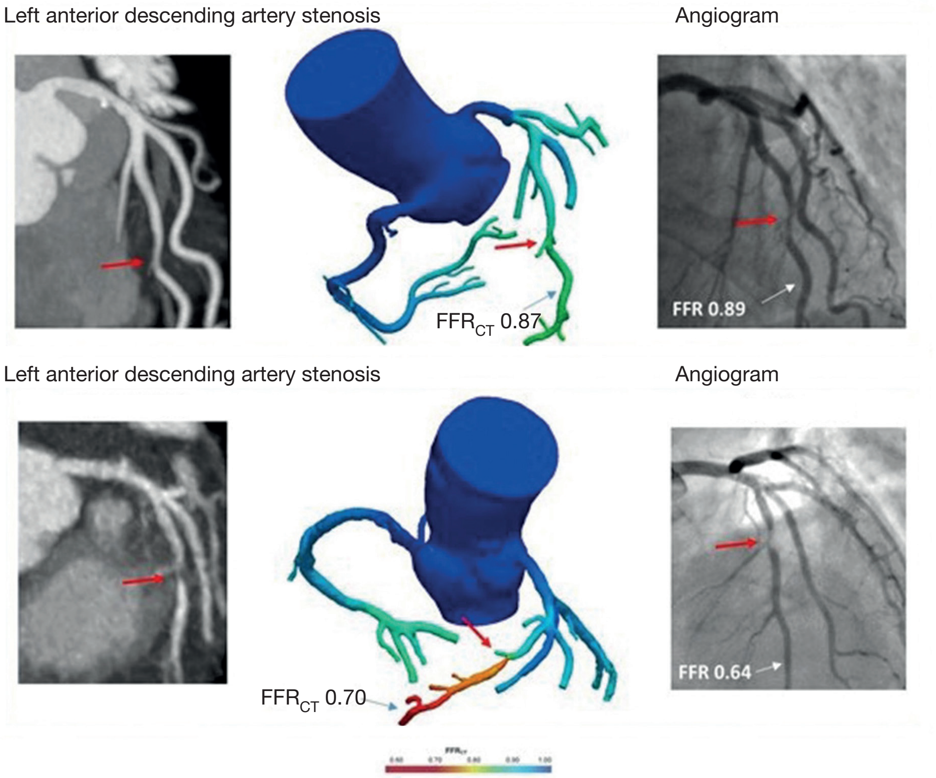

Figure 1. Computed tomography fractional flow reserve. a. A mid-left anterior descending artery stenosis with fractional flow reserve demonstrating it is not haemodynamically significant (FFR_{CT} 0.87) correlating with the invasive fractional flow reserve measurement of 0.89. b. A mid-left anterior descending stenosis with a haemodynamically significant FFR_{CT} of 0.70, correlating with the invasive fractional flow reserve measurement of 0.64. FFR_{CT} = fractional flow reserve derived from computed tomography.

Single-photon emission computed tomography

Single-photon emission computed tomography is a non-invasive nuclear imaging test that uses radioactive tracers to evaluate myocardial perfusion and systolic function in patients with suspected coronary artery disease. It requires administration of an intravenous radioactive perfusion tracer and uses a gamma camera system for the detection of gamma photons. Single-photon emission computed tomography is based upon the flow-dependent and metabolism-dependent selective uptake of the radioactive tracer by functional myocardial tissue. Images are commonly taken at rest and then following stress, with 2-day rest-first single-photon emission computed tomography protocols mainly being used. Stress testing is performed using either exercise (treadmill or bicycle), pharmacological agents (mainly vasodilators, but if contraindicated, dobutamine), or a combination of both vasodilator stress and low-level exercise. The vasodilator stressors most used are adenosine, regadenoson and dipyridamole. The benefit of the rest–stress myocardial perfusion scanning protocol is that it also provides information on the presence or absence of myocardial infarction and viability. For example, a fixed perfusion defect seen at rest and stress implies the presence of a scar with no perfusion. Conversely, if there is a perfusion defect at stress vs no defect at rest, this implies myocardial ischaemia in the given territory. The radiation dose from single-photon emission computed tomography is around 8–14 mSv, depending on the sequence and hardware used (Perrin et al, 2015).

Single-photon emission computed tomography is a well-validated diagnostic tool for the detection of myocardial ischaemia. American and European guidelines recommend the use of single-photon emission computed tomography for investigating patients with stable chest pain, where the pre-test likelihood is intermediate to high (Wolk et al, 2014; Knuuti et al, 2020). Large datasets derived from several large population studies demonstrate the prognostic power of single-photon emission computed tomography. In a pooled analysis of 20 963 patients from 16 published studies with a follow up of slightly more than 2 years, the event rate of cardiac death and non-fatal myocardial infarction was only 0.7% per year (Klocke et al, 2003).

Stress echocardiography

Stress echocardiography enables the detection of significant coronary artery disease using transthoracic echocardiography to detect the characteristic changes in the contraction of the left ventricular myocardium that occur with increased myocardial oxygen demand. The test is simple, cost-effective and does not involve ionising radiation. In addition to ischaemia testing, it can provide useful information regarding valvular and left ventricular function. Contraindications include severe aortic stenosis and severe uncontrolled hypertension. The diagnostic accuracy of stress echocardiography depends on the patient having good acoustic windows to allow visualisation of the left ventricular endocardial borders. Where acoustic windows are poor, microbubble echocardiographic contrast agents may be used to improve endocardial definition and test accuracy (Supariwala et al, 2014). Incremental increases in myocardial oxygen demand are brought about by either increasing levels of physical exercise (eg exercise bike or treadmill), pharmacologically (typically with increasing doses of intravenous dobutamine) or electrically (by increasing the heart rate via the pacemaker). In turn, these stimuli bring about changes in the contraction of the left ventricular myocardium as they are increased. Myocardial ischaemia is suggested when a region of the left ventricular myocardium contracts less well (becomes hypokinetic) with stress compared with rest.

Stress echocardiography has a good safety record, with a recorded incidence of life-threatening complications of 1 in 6574 with exercise, and 1 in 557 with dobutamine in a large international registry (Varga et al, 2006). Meta-analysis has demonstrated the overall accuracy of stress echocardiography to be in the region of 81% sensitivity and 82% specificity (Schinkel et al, 2004). A negative stress echocardiogram in a patient with chest pain and suspected coronary artery disease is associated with a low risk of cardiac death, with one study demonstrating a risk of 0.6% per annum over a mean 7-year follow-up period (Schinkel et al, 2004).

Cardiovascular magnetic resonance

Cardiovascular magnetic resonance is an established and advanced imaging modality for a wide range of cardiovascular diseases. It is a unique multi-parametric test that gives a high degree of anatomical and functional parameters in a single study, while not being limited by acoustic windows such as dobutamine stress echocardiography or the risks of ionising radiation. The MR Perfusion Imaging to Guide Management of Patients With Stable CAD trial demonstrated that myocardial-perfusion cardiovascular magnetic resonance imaging was associated with a lower incidence of coronary revascularisation than fractional flow reserve, and was non-inferior to fractional flow reserve with respect to major adverse cardiac events (https://clinicaltrials.gov/ct2/show/NCT01236807).

A cardiovascular magnetic resonance imaging study protocol for the investigation of stable coronary artery disease typically takes 30–60 minutes and involves the acquisition of cine images in multiple planes for the assessment of left ventricular function and volumes, first-pass stress and rest myocardial perfusion, and late gadolinium enhancement for the assessment of viability and scar quantification (**Figure 2**). The combination of these methods enables the diagnosis of coronary artery disease and quantification of ischaemia burden, as well as identifying viable myocardium with the potential to regain function following myocardial revascularisation.

Stress cardiovascular magnetic resonance imaging can be performed in a similar manner to stress echocardiography, by giving incremental doses of dobutamine and acquiring cine sequences to observe for a regional wall motion abnormality. This has similar diagnostic accuracy to dobutamine stress echocardiography but has the advantage of not having image degradation by limited acoustic windows (Goodacre et al, 2005; Nandalur et al, 2007). However, stress cardiovascular magnetic resonance imaging is predominantly performed by first-pass perfusion imaging. Perfusion cardiovascular magnetic resonance imaging

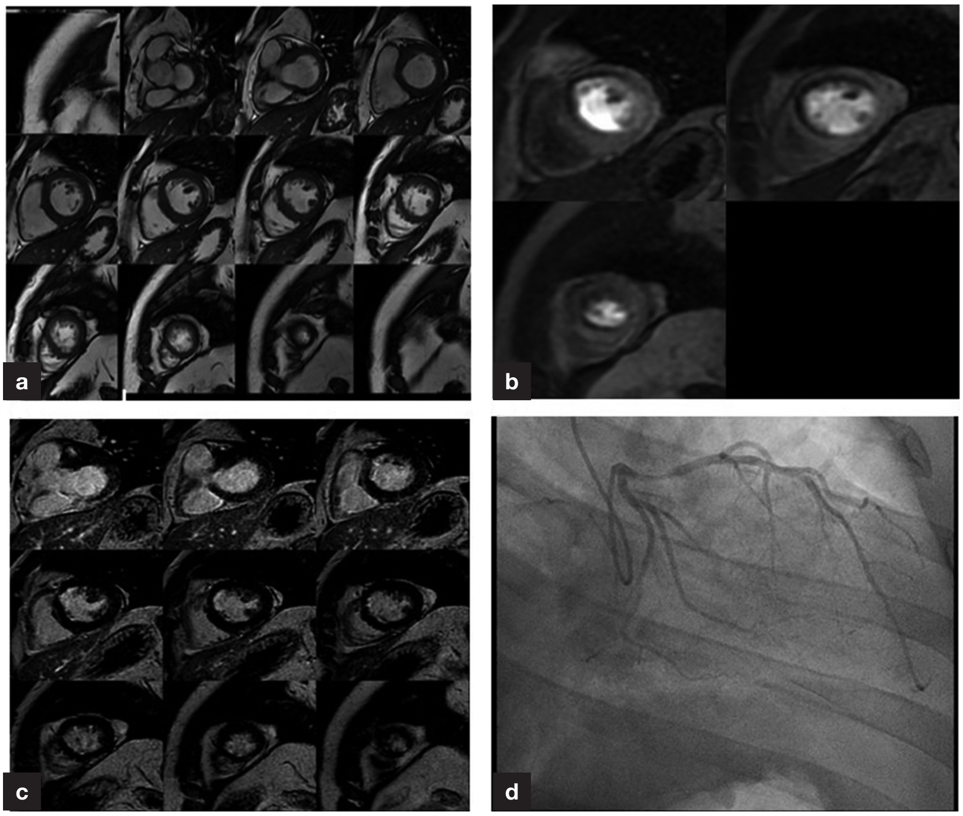

Figure 2. Cardiovascular magnetic resonance demonstrating subendocardial left anterior descending artery territory infarct with extensive ischaemia (eight segments) and preserved myocardial viability. a. Cine imaging in multiple short axis planes for the assessment of left ventricular function and volumes. b. Regadenoson stress first pass myocardial perfusion demonstrating extensive ischaemia (eight segments) in a proximal left anterior descending artery territory. c. Late gadolinium enhancement imaging with subendocardial late gadolinium enhancement (fibrosis) in the basal to mid septum. d. Invasive coronary angiogram with proximal severe stenosis in the left anterior descending artery.

entails the induction of maximal coronary hyperaemia with adenosine/regadenoson or dipyridamole, and visually following the passage of a gadolinium-based contrast agent through the myocardium; normally perfused myocardium becomes bright as a result of transit of gadolinium, while areas of hypoperfusion caused by coronary stenosis are identified by remaining dark (**Figure 2c**).

Perfusion cardiovascular magnetic resonance imaging as the first-line test for patients presenting with chest pain has been the subject of several large clinical trials that have validated its high diagnostic accuracy for the detection of coronary artery disease (Greenwood et al, 2009, 2012; Schwitter et al, 2013). The CE-MARC trial demonstrated the superiority of perfusion cardiovascular magnetic resonance imaging over single-photon emission computed tomography, with a higher sensitivity (87% vs 67%, $P<0.0001$) but similar specificity (83% vs 83% $P=0.916$) (Greenwood et al, 2012). The diagnostic accuracy of cardiovascular magnetic resonance imaging was maintained for both men and women in a pre-specified gender sub-analysis compared to single-photon emission computed tomography, which had significantly worse sensitivity for women than men (Greenwood et al, 2014).

The CE-MARC 2 trial used perfusion cardiovascular magnetic resonance imaging compared to single-photon emission computed tomography and the National Institute for Health and Care Excellence guidelines (CG95) directed care to identify rates of unnecessary angiography (Ripley et al, 2015; Walker et al, 2021). CE-MARC 2 showed that the cardiovascular magnetic resonance imaging-guided strategy resulted in significantly lower rates of coronary angiography, with no difference in cardiovascular outcomes (Walker et al, 2021).

Gadolinium contrast does not cross intact cell membranes; following myocardial infarction residual scar tissue is made up of a matrix collagen fibre that leads to an accumulation of gadolinium contrast, so late gadolinium enhancement imaging allows the delineation of myocardial infarction with greater accuracy than histology (Knuuti et al, 2020). Furthermore, the extent of scarring enables the identification of 'viable' myocardium that has the potential to regain functional recovery following revascularisation (Kim et al, 2000) (**Figure 2c**). Most patients can be given gadolinium contrast agents, although caution is exercised in those with a glomerular filtration rate below 30 ml/min/1.73m^2 or those on dialysis because of the risk of nephrogenic sclerosing fibrosis. This is an ultimately fatal fibrosis of skin and internal organs following exposure to gadolinium, but is exceptionally rare with newer cyclical agents. Those unable to have gadolinium contrast can still undergo dobutamine stress testing (Bruder et al, 2015).

A meta-analysis of 11 636 patients showed an annualised event rate of 0.8% for negative stress cardiovascular magnetic resonance imaging over a mean follow up of 32 months (Greenwood et al, 2016). Moreover, the 5-year follow-up data from CE-MARC identified that cardiovascular magnetic resonance imaging was the only predictor of major adverse cardiovascular events in a multi-variable analysis (Nordbeck et al, 2015).

Long scanning times, limited availability and narrow bores gave preconceptions of the restricted utility of cardiovascular magnetic resonance imaging, but larger 80 cm bores allow larger patients to be scanned, and improved technology has reduced scanning times. Implantable cardiac devices are another relative contraindication because of imaging artefacts and local energy deposition down pacing wires, but the increasing use of magnetic resonance compatible leads and devices are overcoming this issue and magnetic resonance imaging can be performed with high diagnostic accuracy (Nordbeck et al, 2015). Previously, trials have excluded patients with arrhythmia amid concerns over electrocardiogram gating, but patients with atrial fibrillation or frequent ectopy can now be scanned with high diagnostic accuracy (Greulich et al, 2015). Furthermore, concerns over the high cost of cardiovascular magnetic resonance imaging have not been borne out with cost analyses identifying that, despite a higher initial cost of cardiovascular magnetic resonance imaging compared to single-photon emission computed tomography, greater overall cost-effectiveness can be seen in models of both UK and international healthcare systems (Boldt et al, 2013).

Conclusions

This review has covered the range of non-invasive anatomical and functional diagnostic tests available for the investigation of stable coronary artery disease. Each diagnostic modality has strengths and weaknesses and thus an integrated care pathway should be applied to direct patients to the appropriate investigation and thus streamline care, while minimising healthcare costs. Computed tomography coronary angiography is an excellent 'rule out' test for low-risk groups; single-photon emission computed tomography is widely available and has established prognostic data; stress echocardiography benefits from the use of physiological stress as well as giving incremental information in patients with valvular disease; cardiovascular magnetic resonance imaging diagnoses ischaemia with high accuracy while giving gold standard volumetric data, identifying regional wall motion abnormalities, scar burden and viable myocardium.

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Key points

- Each modality of cardiovascular imaging has its own strengths and weaknesses, and an integrated pathway should be used to ensure patients receive appropriate imaging.
- Echocardiography represents a safe way to view changes to the myocardium under stress and identify ischaemic change without the need for ionising radiation, but this requires highly skilled operators.
- Computed tomography coronary angiography is a quick imaging tool for visualising the coronary anatomy and is a useful tool for risk stratification of coronary artery disease.
- Single-photon emission computed tomography is a well-established technique for assessing myocardial ischaemia, with a comparable specificity to magnetic resonance imaging, and is feasible with pacemaker.
- Cardiac magnetic resonance imaging offers the highest sensitivity of all modalities.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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