

CHRONIC ISCHAEMIC HEART DISEASE, NON-INVASIVE IMAGING

Optimal non-invasive imaging test selection for the diagnosis of ischaemic heart disease

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INTRODUCTION

The prevalence of angina is high in the general population, and increases with age in both sexes.¹ New onset, stable chest pain among patients without known coronary artery disease (CAD) is a common clinical problem that results in approximately four million stress tests annually in the USA.² Significant variations in features at presentation and diagnostic strategies are well-documented between both European countries and the USA, and may be related to differences in healthcare systems, access to testing technologies and risk tolerance.²⁻⁴ Furthermore, variation may be explained by the fact that limited information on health-related outcomes exists in this stable, undiagnosed population and there is little consensus about which test is preferable or even when one is required.⁵⁻⁷ In fact, major US and European guidelines differ fairly substantially in their basic approaches. The discrepancy between guidelines also differs significantly from other areas in cardiology (ie, therapy for acute coronary syndromes or chronic heart failure), where general consensus exists largely based on the availability of randomised clinical trial data. To this point, current guidelines for imaging stable chest pain of suspected cardiac aetiology do not yet incorporate recent randomised trials comparing functional versus anatomical testing strategies.^{8,9}

Non-invasive test selection remains a common but challenging decision for many clinicians, and a controversial topic for practice guidelines. The aims of the current paper are to provide a concise approach to non-invasive test selection based on recent guidelines and emerging evidence to:

1. Understand important patient characteristics that impact non-invasive test selection for the diagnosis of CAD.
2. Compare current guideline recommendations from the American College of Cardiology (ACC)/American Heart Association (AHA), European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE).
3. Incorporate recent data to enhance test selection through use of a unified approach for both functional and anatomical strategies.

PATIENT SELECTION FOR NON-INVASIVE TESTING**Clinical classification of chest pain**

The current discussion applies specifically to stable, symptomatic patients with suspected ischaemic heart disease on the basis of a thorough history,

Learning objectives

- Describe important patient characteristics that impact non-invasive test selection for the diagnosis of coronary artery disease.
- Compare and contrast current guideline recommendations from the American College of Cardiology/American Heart Association, the European Society of Cardiology and the UK National Institute for Health and Care Excellence.
- Incorporate recent clinical trial evidence to inform a contemporary approach to test selection that integrates both functional and anatomical strategies.

physical examination and laboratory data. The history should be used to classify symptoms as typical, atypical or non-cardiac chest, which in combination with age can be used to quantify the pretest probability (PTP) of underlying coronary disease (table 1).¹⁰ In the USA, this has been historically evaluated using a risk score such as the combined Diamond and Forrester and Coronary Artery Surgery Study risk score (table 2).⁶ The UK NICE guidelines advocate deriving this risk using another modified Diamond and Forrester clinical prediction rule by Pryor *et al.*^{5,11} More recently, a clinical prediction rule by Genders *et al.*¹² which aimed to validate, update and extend the Diamond-Forrester model reclassified 16% of men and 64% of females and has been adopted by the ESC guidelines (table 2). While these scores are easily implemented at the bedside, mounting evidence demonstrates that they largely overestimate the degree of obstructive CAD.^{8,9,13} Therefore, while we continue to rely on risk scores to predict the PTP of CAD based mainly on age and symptoms alone, improved strategies for risk stratification and subsequently test selection are warranted and have been proposed or are in development.

Quantifying 'intermediate' pretest probability of ischaemic heart disease (IHD)

Diagnostic testing is most valuable when the PTP of IHD is intermediate, since the application of a test result using Bayesian analysis drives the post-test probability sufficiently lower (negative test) or higher (positive test) to enhance future decision-making—usually whether the patient should proceed to cardiac catheterisation.¹⁴ While there is no strict definition of intermediate PTP, a definition of 10%–90%, first advocated in 1980,¹⁵ has been

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Table 1 Traditional clinical classification of chest pain. Adapted from Diamond¹⁵

Typical angina (definite)	Meets all three of the following characteristics:
	1. Substernal chest discomfort of characteristic quality and duration
	2. Provoked by exertion or emotional stress
	3. Relieved by rest and/or nitrates within minutes
Atypical angina (probable)	Meets two of these characteristics
Non-anginal chest pain	Lacks or meets only one or none of the characteristics

applied in several studies and is the current definition used in the ACC/AHA guidelines for stable IHD (table 3).^{16 17} This risk stratification scheme is also used by the most recent ACC/AHA Appropriate Use Criteria Task Force.¹⁸ In contrast, the current ESC guidelines using the Genders *et al* modified Diamond and Forrester clinical prediction rule stratifies patients into four groups: <15%, 15%–65%, 66%–85% and >85%. In comparison with the US guidelines, the intermediate group is defined by a PTP of 15%–85% by combining the two mid-risk groups. Based on these four groups, the ESC guidelines recommend specific test strategies (below). Finally, the UK NICE guideline differs markedly compared with the ACC/AHA and ESC guidelines, identifying an intermediate PTP as 30%–60%.⁵

GENERAL APPROACH: FUNCTIONAL TESTING STRATEGIES

If a functional strategy is considered, then the choice of stress must first be considered (exercise vs pharmacological) and, if exercise is employed,

whether additional imaging should be performed. Several stress imaging modalities currently exist, each with their advantages and disadvantages (table 4), and include radionuclide stress myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT) or positron emission tomography (PET), stress echocardiography and stress cardiac MRI (cardio-vascular MR, CMR).

Decision-making should proceed with a series of basic questions:

- ▶ **Would the patient benefit from revascularisation?** If the patient has significant comorbidities or their quality-of-life is not expected to benefit from revascularisation, then optimising medical therapy is likely a more reasonable approach.
- ▶ **Can the patient exercise?** Symptom-limited exercise with an exercise treadmill test (ETT) is the preferred functional stress testing modality (over pharmacological) since it provides information concerning reproducibility of symptoms, cardiovascular function, exercise capacity and the haemodynamic response during usual forms of activity. Furthermore, a score such as the Duke Treadmill Score when applied to data generated by the ETT can improve diagnostic certainty over and above its prognostic implications.¹⁹ However, a patient may be unable to exercise due to one or more non-cardiac reasons. These include obesity, orthopaedic limitations, balance issues or limb dysfunction as a result of paraplegia from a prior cerebrovascular event. A detailed discussion on the various forms of exercise modalities (treadmill, upright or supine bicycle) and protocols (Bruce, Modified Bruce, Naughton) is presented elsewhere.²⁰
- ▶ **Does the patient have any contraindications to exercise stress testing?** If absolute contraindications exist, then pharmacological stress should be used; if relative contraindications exist, pharmacological stress should be considered.^{20 21}
 - Absolute contraindications include: acute myocardial infarction (within 2 days), unstable angina, uncontrolled cardiac arrhythmias causing symptoms or haemodynamic compromise, symptomatic severe aortic stenosis, uncontrolled symptomatic heart failure, acute pulmonary embolus or pulmonary infarction, acute myocarditis or pericarditis, active endocarditis, acute aortic dissection, acute non-cardiac disorder that may affect exercise performance or be aggravated by exercise (eg, infection, renal failure, thyrotoxicosis) or inability to obtain consent.
 - Relative contraindications, which may be superseded if the clinical benefits are felt to outweigh the risks, include: Left main coronary stenosis or its equivalent, moderate stenotic valvular heart disease, electrolyte abnormalities, severe hypertension (systolic ≥ 200 mmHg and/or diastolic ≥ 110 mmHg), tachyarrhythmias or bradyarrhythmias including atrial fibrillation with uncontrolled

Table 2 Calculation of patient PTPs of CAD used to determine eligibility for non-invasive test selection in the 2012 ACC/AHA (A), 2013 ESC (E) and 2010 NICE guidelines (N) in males and females

Guideline	Non-anginal chest pain			Atypical angina			Typical angina		
	A	E	N	A	E	N	A	E	N
Males									
30–39	4	18	3–35	34	29	8–59	76	59	30–88
40–49	13	25	9–47	51	38	21–70	87	69	51–92
50–59	20	34	23–59	65	49	45–79	93	77	80–95
60–69	27	44	49–69	72	59	71–86	94	84	93–97
70–79		54			69			89	
>80		65			78			93	
Females									
30–39	2	5	1–19	12	10	2–39	26	28	10–78
40–49	3	8	2–22	22	14	5–43	55	37	20–79
50–59	7	12	4–25	31	20	10–47	73	47	38–92
60–69	14	17	9–29	51	28	20–51	86	58	56–84
70–79		24			37			68	
>80		32			47			76	

(A) Combined Diamond and Forrester and Coronary Artery Surgery Study risk score. Each value represents the per cent with obstructive CAD on catheterisation. Adapted from Fihn *et al.*⁶ (E) Updated Diamond and Forrester prediction score. Adapted from Genders *et al.*¹² (N) Modified Diamond and Forrester prediction score adapted from Pryor *et al.*¹¹ A range is provided for each estimate from 'Low' to 'High' risk depending on the presence of the additional factors of diabetes, smoking, and hyperlipidaemia (total cholesterol >6.4 mmol/L).

ACC, American College of Cardiology; AHA, American Heart Association; CAD, coronary artery disease; ESC, European Society of Cardiology; NICE, National Institute for Health and Care Excellence; PTP, pretest probability.

Table 3 Selected sensitivities and specificities of non-invasive tests for the detection of coronary artery disease as reported in the ACC/AHA 2012 and ESC 2013 guidelines

	Sensitivity		Specificity	
	ACC/AHA 2012	ESC 2013	ACC/AHA 2012	ESC 2013
Exercise ECG	0.68	0.45–0.50	0.77	0.85–0.90
ECHO				
Exercise or pharm	0.76		0.88	
Exercise		0.80–0.85		0.80–0.88
Pharm		0.79–0.83		0.82–0.86
SPECT				
Exercise or pharm	0.88		0.77	
Exercise		0.73–0.92		0.63–0.87
Pharm		0.90–0.91		0.75–0.84
PET				
Exercise or pharm	0.91		0.82	
Pharm PET		0.81–0.97		0.74–0.91
CMR				
Dobutamine		0.79–0.88		0.82–0.86
Vasodilator		0.67–0.94		0.61–0.85
CCTA		0.95–0.99		0.64–0.93

ACC/AHA 2012 estimates adapted from Garber and Solomon.²⁸ ESC 2013 estimates were collated from multiple studies and adapted from Montalescot *et al.*⁷

ACC, American College of Cardiology; AHA, American Heart Association; CMR, cardiovascular MR; ESC, European Society of Cardiology; PET, positron emission tomography; SPECT, single photon emission CT.

ventricular rate, hypertrophic cardiomyopathy and other forms of outflow tract obstruction, or mental or physical impairment leading to inability to cooperate or high-degree atrioventricular block.

- *Is the resting ECG interpretable?* Certain conditions interfere with the diagnosis of ischaemia and when present should lead to use of imaging,²¹ including: Ventricular pre-excitation

Table 4 Advantages and disadvantages of stress imaging techniques and coronary CTA

Technique	Advantages	Disadvantages
Echocardiography	<ul style="list-style-type: none"> ► Wide access ► Portability ► No radiation ► Low cost 	<ul style="list-style-type: none"> ► Echo contrast needed in patients with poor ultrasound windows ► Dependent on operator skills
SPECT	<ul style="list-style-type: none"> ► Wide access ► Extensive data 	Radiation
PET	Flow quantitation	<ul style="list-style-type: none"> ► Radiation ► Limited access ► High cost
CMR	<ul style="list-style-type: none"> ► High soft tissue contrast ► Precise imaging of myocardial scar ► No ionising radiation 	<ul style="list-style-type: none"> ► Limited access in cardiology ► Contraindications ► Functional analysis limited in arrhythmias ► Limited 3D quantification of ischaemia ► High cost
CCTA	High negative predictive value (NPV) in patients with lower PTP	<ul style="list-style-type: none"> ► Limited availability ► Radiation ► Assessment limited with extensive coronary calcium ► Image quality limited with arrhythmias or higher heart rates that cannot be lowered ► Low NPV in higher PTP

Adapted from Montalescot *et al.*⁷

CMR, cardiovascular MR; NPV, negative predictive value; PET, positron emission tomography; PTP, pretest probability; SPECT, single photon emission CT.

(Wolff–Parkinson–White pattern), ventricular paced rhythm, left bundle branch block ≥ 1 mm ST depression at rest, digoxin use with associated ST-T abnormalities, left ventricular hypertrophy with ST-T abnormalities or hypokalaemia with ST-T abnormalities.

If the patient is unable to exercise to sufficient workload, then pharmacological stress is considered. The decision regarding which agent to use will depend on patient factors including suitability of the stress agent and the imaging modality; ischaemic end points may vary accordingly.²² If MPI is used, then vasodilators are the preferred pharmacological stress agents, and perfusion is assessed. If echocardiography is used, then inotropic agents are most commonly used, although this can vary by country, and wall motion is assessed. For CMR, either inotropes or vasodilators can be used.

► *Does the patient have any contraindications to pharmacological stress testing?*

- The vasodilator stress agents (adenosine; dipyridamole and the selective A2A receptor agonists including regadenoson, binodenoson and apadenoson) increase coronary blood flow on the order of three to five times that of resting myocardial blood flow through their effects on adenosine A2A receptors.^{23–26}

Contraindications include: Pronounced bronchospastic airway disease, significant hypotension, sick sinus syndrome and high degree atrioventricular block or unstable or complicated acute coronary syndrome.

- Dobutamine, a synthetic catecholamine which stimulates β 1-adrenergic receptors with the effect of increasing the heart rate (chronotropic effect) and myocardial contractility (inotropic effect), is typically used in stress echocardiography.²⁷ Contraindications include: Sustained ventricular arrhythmias, atrial fibrillation with rapid ventricular response, recent myocardial infarction (within 1–3 days) or unstable angina haemodynamically significant left ventricular outflow tract obstruction, aortic dissection or moderate to severe systemic hypertension (resting systolic blood pressure >180 –200 mm Hg).

If the patient is not a candidate for exercise or pharmacological stress testing, an anatomical strategy with coronary computed tomography angiography (CCTA) should be considered. However, based on recently published trial data, an anatomical-first strategy may be a reasonable alternative in selected patients (discussed below).

DIAGNOSTIC ACCURACY OF FUNCTIONAL TESTING STRATEGIES

There are distinct strengths and weaknesses of each imaging modality (table 4), and test selection ultimately depends on many factors, including local availability, local expertise, existence and relevance of prior imaging data, cost, the patient's body habitus (eg, morbid obesity), radiation exposure and the need for concomitant assessment of

haemodynamics or valvular disease. Diagnostic performance should be considered when multiple options exist, ideally based on local lab performance rather than the literature. Since such detailed data are often not available, a cost-effectiveness meta-analysis by Garber and Solomon²⁸ that includes information on diagnostic accuracy of individual tests is cited by the ACC/AHA guidelines as evidence for differing diagnostic accuracy between modalities (table 3). PET is the most sensitive non-invasive test and exercise testing the least sensitive. SPECT is nearly as sensitive as and somewhat less specific than PET (specificity, 0.77 for SPECT and 0.82 for PET). Echocardiography is more specific than PET (0.88 compared with 0.82) but less sensitive (0.76 compared with 0.91). While not mentioned in the ACC/AHA guidelines, the CMR and single-photon emission CT for diagnosis of coronary heart disease (CE-MARC) study directly and prospectively compared CMR with SPECT.²⁹ Compared with SPECT, CMR had greater sensitivity (0.87 compared with 0.67) and similar specificity (0.83). Alternatively, the ESC guidelines use multiple primary studies to determine accuracy.⁷ A major difference between the reference data used by each guideline is the lower reported sensitivity of the exercise ECG in the ESC guidelines—only 50% (despite an excellent specificity of 90%, values obtained from studies avoiding verification bias).³⁰ Because this lower sensitivity means that the number of false test results will become higher than the number of correct test results in populations with a PTP of >65%,³¹ the ESC does not recommend employing the exercise stress test (without imaging) in such higher-risk populations for diagnostic purposes. In general, it may be more appropriate to employ more specific testing for patients with a low-intermediate PTP of CAD and reserve more sensitive testing for those with high-intermediate PTPs.

CHOOSING A FUNCTIONAL TEST: WHAT DO THE GUIDELINES SAY? ACC/AHA 2012 guidelines

There are strong recommendations for ETT for patients with an intermediate PTP of IHD, and exercise stress with nuclear MPI or echocardiography for those with an intermediate to high PTP of IHD who have an uninterpretable ECG (Class I).⁶ The remaining Class I recommendation is for pharmacological stress with nuclear MPI or echocardiography for patients who are unable to exercise. The guidelines recommend against the use of pharmacological stress with nuclear MPI, echocardiography or CMR for patients who can exercise with interpretable ECGs or among patients who can exercise with an interpretable ECG who have only a low PTP of IHD (<10%; Class III). The other testing strategies fall within the IIa or IIb classes of recommendations. While no specific recommendations are provided for patients with a PTP of >90%, it is reasonable to consider cardiac catheterisation as the initial test, which is supported

by the ACC/AHA 2012 diagnostic angiography appropriate use criteria.³²

ESC 2013 guidelines

Exercise ECG is recommended as the initial test for establishing a diagnosis of CAD in patients with symptoms of angina and intermediate PTP of CAD of 15%–65% (Class I).⁷ Furthermore, stress imaging (echocardiography, CMR, SPECT or PET) is strongly recommended as the initial option if local expertise and availability permit (Class I). Exercise ECG in patients with ≥0.1 mV ST depression on resting ECG or taking digitalis is not recommended for diagnostic purposes (Class III). An imaging stress test is recommended as the initial test for diagnosing CAD with a high-intermediate PTP between 66% and 85% or if left ventricular ejection fraction is <50% in patients without typical angina (Class I). While there are no specific recommendations for pharmacological stress, ETT is recommended over pharmacological testing whenever possible (Class I). A PTP > 85% establishes the presumptive diagnosis of CAD, at which point risk stratification should be performed. In patients with severe symptoms or a clinical constellation suggesting high-risk coronary anatomy, clinicians are advised to initiate guideline-directed medical therapy and consider invasive catheterisation. In patients who have mild symptoms, non-invasive testing for risk stratification should be considered only if there is agreement to proceed to revascularisation in the event of high-risk test findings.

UK 2010 NICE guidelines

For patients with chest pain and who have an estimated PTP of 30%–60% the clinician is advised to offer non-invasive functional imaging for myocardial ischaemia as the first-line test.⁵ If the PTP is 10%–29%, a ‘rule out’ CAD strategy was felt to be best achieved with initial coronary artery calcium (coronary artery calcium (CAC)) scoring (and then CCTA if the CAC score is 1–400) and is justified based on cost-effectiveness and low radiation doses.^{33–36} Alternatively, patients with a high CAC may be investigated by functional assessment, depending on the score and patient factors (see below) or invasive angiography. If the estimated PTP is 61%–90%, the clinician should offer invasive coronary angiography as the first-line diagnostic investigation. Notably, exercise testing without imaging is not recommended in the investigative pathway for patients with no prior history of established CAD, representing a significant change to current practice and in contrast to other major guidelines.³⁶ This is based on the evidence of poorer diagnostic accuracy of exercise testing compared with the other tests and supported by a cost-effectiveness model derived specifically for these guidelines.³³

GENERAL APPROACH TO AN ANATOMICAL IMAGING WITH CCTA

CCTA: recent clinical trial evidence

The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) randomly assigned 10 003 symptomatic stable outpatients requiring evaluation for suspected CAD to either CCTA or functional stress testing (ETT, nuclear stress testing or stress echocardiography) with a median follow-up of 25 months.⁹ The composite primary end point (death, myocardial infarction, hospitalisation for unstable angina or major cardiovascular (coronary artery calcium (CV)) procedural complication) occurred at similar rates in the CCTA and functional testing groups (3.3% and 3.0%), which was lower than previously established historical rates. More patients in the CCTA group underwent cardiac catheterisation within 90 days after randomisation (12.2% vs 8.1%), but the frequency of catheterisation showing no obstructive CAD was significantly lower in the CCTA group (6.2% vs 3.2%). The Scottish Computed Tomography of the HEART (SCOT-HEART) trial enrolled 4146 patients with stable chest pain to CCTA in addition to usual care (which generally included stress testing) or to usual care alone.⁸ The trial's primary end point, certainty of the attribution of symptoms to CAD, showed an increase in the CCTA group (relative risk 1.79, 95% CI 1.62 to 1.96), as did the secondary end point of certainty of diagnosis of CAD (2.56, 95% CI 2.33 to 2.79). There was also a non-significant reduction in the rate of death or myocardial infarction in the CCTA group at 1.7 years, although event rates were low in both arms. Taken together, while the trials were of different design, the consistent finding was that while event rates were comparable, obstructive coronary disease was more frequently detected using an anatomical strategy of CCTA. Moreover, these top line results from two trials provide support for consideration of an anatomical strategy as viable option for initial non-invasive test selection. This notion is further supported by other smaller, but contemporary studies favouring a role for CCTA over functional imaging to improve both diagnostic accuracy³⁷ and patient outcomes.^{38 39} This may be particularly important in the future, as patient selection for CCTA may become less restricted (ie, due to arrhythmias, or high CAC) as a result of newer technologies and software algorithms.⁴⁰

Approach to patient selection for CCTA

Similar to functional testing, decision-making when considering anatomical testing should proceed with a series of basic questions:

- *Would the patient benefit from revascularisation?*
If the patient has significant comorbidities or if their survival or quality-of-life is not expected to benefit from revascularisation, then optimising medical therapy is likely a more reasonable approach.
- *Is this patient a good candidate for CCTA?*
According to a report from 2014 Society of

Cardiovascular Computed Tomography Guidelines Committee,⁴¹ only patients with adequate breath holding capabilities, without severe obesity ($>39 \text{ kg/m}^2$), with a favourable calcium score (Agatston score <400) and distribution, in sinus rhythm and with a heart rate of $\leq 60 \text{ bpm}$ and with normal or near normal renal function should be considered for CCTA. If necessary, the patient should be able to tolerate use of short-acting β blockers or other heart rate-lowering medication to achieve target heart rates.

- *Does the patient have any absolute contraindications to CCTA?* These include definite acute coronary syndromes, glomerular filtration rate (glomerular filtration rate (GFR)) <30 unless on chronic dialysis, previous anaphylaxis after iodinated contrast administration, previous episode of contrast allergy after adequate steroid/antihistamine preparation, inability to cooperate, including inability to raise arms, or pregnancy or uncertain pregnancy status in premenopausal women.⁴¹

DIAGNOSTIC ACCURACY OF CCTA

Multicentre studies evaluating the diagnostic accuracy of 64-slice multidetector CCTA for detection of significant (at least 50% stenosis) CAD on quantitative invasive coronary angiography have found sensitivities of between 85% and 99% and specificities between 64% and 90%.⁴²⁻⁴⁴ Although newer equipment and scan protocols may improve the diagnostic accuracy.⁴⁵ The variability in specificity, in particular, is strongly influenced by the baseline prevalence of CAD in the population studied. The Assessment by Coronary Computed Tomography Angiography of Individuals Undergoing Invasive Coronary Angiography trial found that specificity was reduced significantly in the presence of coronary artery calcium.⁴² In contrast, negative predictive values for CCTA have generally been high (95%–100%).^{42 43 46} This has garnered significant interest in using CCTA in scenarios to 'rule out' coronary artery stenosis. This strategy was found to provide superior efficiency in the emergency department for low-to-intermediate risk chest pain to 'rule out' acute coronary syndromes while providing excellent event-free survival similar to usual care, with no increase in cost or radiation exposure.⁴⁷⁻⁴⁹

CHOOSING AN ANATOMICAL TEST: WHAT DO THE GUIDELINES SAY?

ACC/AHA 2012 guidelines

There are currently no strong (Class I) recommendations for CCTA as the initial test.⁶ CCTA may be considered for patients who cannot exercise or for those patients who have a prior normal functional test but ongoing symptoms, an inconclusive functional test or are unable to undergo stress MPI or echocardiography (all Class IIa).

ESC 2013 guidelines

Similar to the ACC/AHA 2012 guidelines, there are no strong recommendations (Class I) for CCTA as the initial test.⁷ It is a Class IIa recommendation that CCTA be considered as an alternative to stress imaging techniques for ruling out CAD in patients who have a non-conclusive exercise ECG or stress imaging test or who have contraindications to stress testing in patients with a low-intermediate PTP (15%–65%). This recommendation is not restricted to patients who cannot exercise, and excludes the highest range of PTP as advocated by the ESC to improve accuracy by selecting patients less likely to have significant coronary calcium, which decreases diagnostic accuracy (discussed above). Class III recommendations include using CCTA for patients with prior coronary revascularisation (not applicable to this population) and not using as a 'screening' test in asymptomatic individuals.

UK 2010 NICE guidelines

In contrast to the above guidelines, NICE recommends CAC scoring as the first line test in patients with an estimated PTP of CAD of 10%–29%.⁵ Further management depends on the calcium score:

- ▶ 0, consider other causes of chest pain
- ▶ 1–400, offer 64-slice (or above) CCTA
- ▶ >400, offer invasive coronary angiography. If this is not clinically appropriate or acceptable to the person and/or revascularisation is not being considered, offer non-invasive functional imaging.

MAJOR DIFFERENCES BETWEEN GUIDELINE RECOMMENDATIONS

Guidelines for the diagnosis of IHD in patients with stable chest pain have several notable differences (table 5). These include use of different risk scores to calculate PTP of underlying CAD, defining cut points for intermediate risk, and even variations in the strength of recommendations for functional imaging modalities. The ESC recommendations for CCTA apply to patients who cannot exercise or those with inconclusive initial testing (as in the ACC/AHA guidelines) and to those with a low-intermediate PTP and for 'ruling out' CAD. This is reasonable, and incorporates the finding that greater coronary calcification is associated with reduced diagnostic accuracy.⁴² The NICE guidelines take a vastly different approach by not ever recommending exercise treadmill testing without functional imaging as an initial approach, and advocating for CAC scoring for patients with low-intermediate PTP (10%–29%) as the first line strategy.⁵

FUTURE OF NON-INVASIVE CARDIOVASCULAR IMAGING FOR THE DIAGNOSIS OF CAD**Improving patient selection**

Traditional risk scores overestimate the degree of CAD on subsequent cardiac catheterisation.^{8 9 13} Future secondary analyses from PROMISE and SCOT-HEART, as well as current proposed scores from contemporary registries such as CONFIRM, could help develop improved risk prediction models. Furthermore, given the historically high rates of normal functional tests,^{50 51} as well as non-obstructive CAD frequently identified during elective coronary angiography,⁵² future studies should focus on identifying a low-risk subset of patients with chest pain who may not require any form of non-invasive testing, and/or those with truly a high PTP who would be better served with direct referral to coronary angiography. Once defined, large-scale randomised trials would be needed to demonstrate the safety, effectiveness and efficiency of these approaches in the selected patient groups. A possible role for use of newer genomic approaches such as the Corus CAD gene expression score in selecting patients for testing is as yet unknown, but such a strategy may be more cost efficient.^{53 54}

Understanding downstream testing and therapy: radiation, medication use and cost

In the PROMISE trial, among those patients randomised in an intended nuclear test strata, the mean cumulative radiation exposure was lower in the CCTA group compared with functional testing group (12.0 ± 8.4 vs 14.1 ± 7.6 mSv).⁹ This included all downstream radiation within 90 days, including that associated with cardiac catheterisation, and is particularly intriguing given that a greater proportion of CCTA patients received cardiac catheterisation. Whether this persists, and what the impact of newer scanners and scan protocols will have on reducing both CCTA and nuclear radiation

Table 5 Selected guideline recommendations for the use of non-invasive testing for the diagnosis of IHD

	AHA/ACC (2012)	ESC (2013)	NICE (2010)
Patient selection			
Risk score to calculate PTP	Combined Diamond Forrester—CASS	Genders et al ¹²	Pryor et al ¹¹
Intermediate PTP	10%–90%	15%–85%	10%–60%
Functional test selection			
Exercise treadmill test alone if PTP 15%–65%*	Class I	Class I	Not recommended
Stress imaging if local expertise and availability	Class IIa	Class I	First line if PTP 30%–60%
Stress imaging if PTP 66%–85%†	Class IIa	Class I	Invasive angiography if PTP 60%–90%
Stress imaging if non-evaluable ECG	Class I	Class I	Not specified
Anatomical (CTA) test selection			
'Rule out' if PTP 15%–65%	Not specified	Class IIa	CAC scoring first line if PTP 10%–29%; proceed to other testing depending on score
Non-conclusive functional test or contraindications	Class IIa	Class IIa	Not specified

*Able to exercise with an evaluable ECG.

†ACC/AHA quantify risk as 'intermediate to high'.

ACC, American College of Cardiology; AHA, American Heart Association; CASS, Coronary Artery Surgery Study; ESC, European Society of Cardiology; NICE, National Institute for Health and Care Excellence; PTP, pretest probability.

exposure, is unknown. Increased rates of medical therapy were seen in the PROMISE CCTA arm relative to the functional arm (unpublished observations), consistent with previous results.^{55–57} Putatively, this could lead to improved outcomes but future analyses are required for confirmation. Finally, while the final PROMISE cost analyses manuscript is anticipated shortly,⁵⁸ a recent analysis using both US and European data found CCTA to be as cost-effective as MPI and CMR.⁵⁹

Integrating functional and anatomical strategies

The association between coronary anatomy and ischaemia is variable, as patients can have no ischaemia in the presence of significant stenosis and ischaemia with no severe stenosis.⁶⁰ Fractional flow reserve CT (FFR CT) is a non-invasive means of calculating coronary ischaemia through the three-dimensional mathematical modelling of coronary flow, pressure and resistance.⁶¹ Diagnostic performance of the addition of FFR CT to anatomic CCTA has been validated in three prospective multicentre trials using intention-to-treat approaches to assess

FFR CT performance against the reference standard of invasive FFR for the identification of lesion-specific ischaemia.^{62–64} In order to determine the 'real world' impact of integrating FFR CT into practice, the Prospective Longitudinal Trial of FFR CT: Outcome and Resource Impacts trial found that FFR CT resulted in the cancellation of planned invasive coronary angiography in 61% of patients without adverse consequences, and a dramatically higher rate of obstructive CAD among those receiving coronary angiography.⁶⁵ Although the evidence supporting its modality is limited to date, CT perfusion may also be a promising future strategy to combine anatomical and functional imaging in patients with stable chest pain.⁶⁶

While FFR CT appears to be the most promising modality combining functional and anatomical imaging, other strategies exist. Hybrid SPECT/CCTA imaging results in improved specificity and positive predictive value (PPV) to detect haemodynamically significant coronary lesions in patients with chest pain.⁶⁷ However, there is some concern that radiation doses may be prohibitive. Other

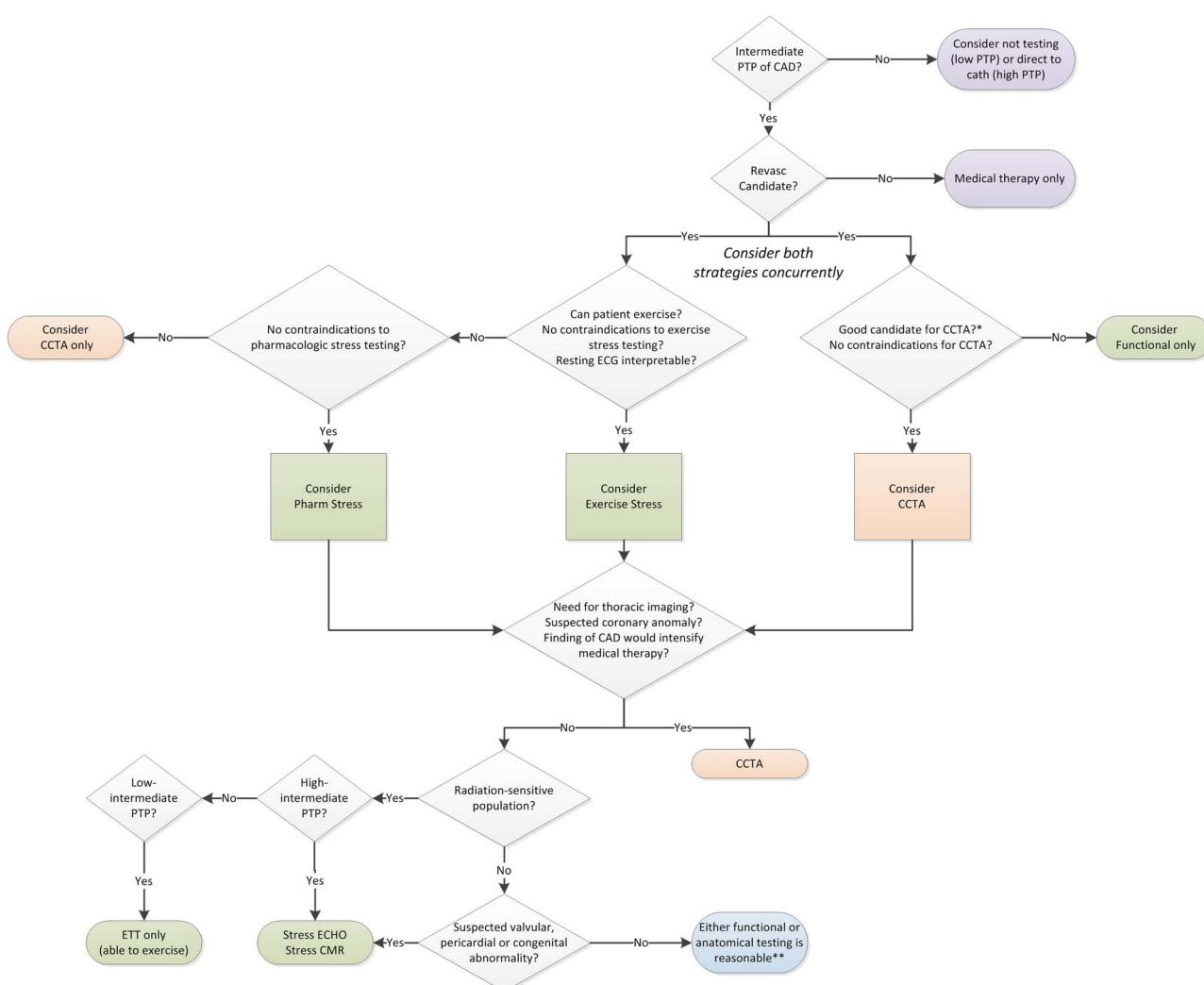


Figure 1 Proposed integrated approach to initial non-invasive test selection using both functional and anatomical approaches for the diagnosis of IHD in stable chest pain patients. *See text; **Consider exercise treadmill test (ETT) or CCTA for low-intermediate pretest probability (PTP); consider stress echo, myocardial perfusion imaging (MPI) or cardiovascular MR (CMR) for high-intermediate PTP. CAD, coronary artery disease.

Key messages

- Optimal test selection for the diagnosis of coronary artery disease (CAD) in stable patients with chest pain begins with the history and physical examination and an assessment of the patient's symptoms and pretest probability of CAD using validated tools.
- Patients with both an intermediate pretest probability of CAD, and who are revascularisation candidates, should be referred for non-invasive testing.
- Based on recent clinical trial evidence, CCTA may be considered as an initial test for the diagnosis of CAD.
- While either an anatomical or functional strategy is reasonable for many patients, test selection may be driven by the presence of important patient factors, such as the need for further CT imaging, radiation-sensitive populations or suspected structural or congenital abnormalities.

hybrid imaging modalities remain an area of increasing interest and research.⁶⁸ Finally, while data for CMR perfusion are excellent (above), data are not sufficient to support clinical CMR for the routine anatomical identification of CAD.⁶⁹ However, there is likely a role for CMR in the assessment of congenital coronary anomalies and coronary artery aneurysms.

SELECTING THE OPTIMAL NON-INVASIVE TEST FOR IHD DIAGNOSIS: A PROPOSED APPROACH

The approach to selection of non-invasive testing for the diagnosis of IHD in patients with stable chest pain must take into account both patient and test characteristics, cost, as well as local availability and expertise (see online supplementary figures S1–S5, and supplementary video 1 for representative examples). For example, access to CMR is greater in some parts of Europe⁷⁰ compared with the rest of the

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world, including the USA. However, as data from pragmatic clinical trials emerge, other salient features should also be considered. These include imaging of other possible abnormalities or causes for chest pain that could be captured with a given imaging modality, as well as radiation exposure. Furthermore, the PROMISE and SCOT-HEART trials demonstrate that an initial anatomical strategy with CCTA could be considered a reasonable alternative to functional testing. A proposed rational approach is outlined in figure 1, which includes other imaging-specific considerations:

- Consider CCTA
 - If needed for additional thoracic CT imaging, for example, a triple or double rule out in suspected pulmonary embolism (d-dimer positive) and aortic dissection or if an intrathoracic pathology is suspected, such as pericardial disease.⁴¹
 - If there is a suspected coronary anomaly.⁷¹
 - If diagnosis of non-obstructive or obstructive CAD alone would result in a change in medical therapy.^{55–57}
- Consider stress echocardiography or CMR
 - If evaluation of radiation-sensitive population is required; for example, gender and age or previous radiation exposure history.⁴¹
 - If valvular, pericardial or congenital abnormality is concomitantly suspected.
 - To potentially mitigate cost.
- Consider ETT
 - If evaluation of radiation-sensitive population is required; for example, gender and age or previous radiation exposure history.⁴¹
 - To mitigate cost.

SUMMARY

The prevalence of angina is high in the general population, and increases with age in both sexes. Little consensus exists about which test is preferable when one is required for diagnosis, including significant differences in the current US and European guidelines. However, the recent PROMISE and SCOT-HEART trials incorporating the use of CCTA have demonstrated that an anatomical strategy is a reasonable alternative initial approach to use in intermediate-risk patients with stable chest pain for the diagnosis of IHD. Contemporary approaches should therefore consider both functional and anatomical strategies in an integrated decision-making model.

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Optimal non-invasive imaging test selection for the diagnosis of ischaemic heart disease

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