UNCERTAINTIES

Assessment of chest pain in a low risk patient: is the exercise tolerance test obsolete?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic for this series, please email us at uncertainties@bmj.com

A 55 year old man presents with chest pain that he has had for a few months. He is a keen cyclist and a non-smoker with normal blood pressure. He has a serum total cholesterol concentration of 6.1 mmol/L (with an high density lipoprotein cholesterol concentration of 1.5 mmol/L). The chest pain is anterior, poorly localised, mild, and intermittent, though sometimes associated with exercise. It generally resolves after a few minutes whether or not the patient continues to exercise. Examination and his resting 12 lead electrocardiograph are normal.

Assessment guidelines

Three international guidelines for the assessment of new onset of chest pain provide different advice about how an individual at low or medium likelihood of coronary artery disease should be investigated (table 1). The American Heart Association[1] (AHA) and European Society of Cardiology[2] (ESC) advocate the exercise tolerance test or functional cardiac imaging. However, in 2010, the UK National Institute for Health and Care Excellence (NICE) took a new approach and recommended that, for patients who had a low likelihood of coronary artery disease, coronary artery calcium scoring should be the first line investigation, replacing the exercise tolerance test.[3] For patients of medium likelihood of coronary artery disease, NICE recommend functional cardiac imaging.[3]

Chest pain accounts for about 1% of all primary care consultations.[4] The assessment of chest pain in individuals at low risk of coronary artery disease is not always straightforward. There are three main types of cardiac tests available:

Exercise tolerance test—This has been the main test in chest pain clinics for decades. It potentially measures maximum exercise capability, but has historically been assessed as positive, negative, or equivocal for ischaemia based on symptoms and electrocardiographic and blood pressure changes.
Functional cardiac imaging uses a pharmacological stress (vasodilator or dobutamine) or exercise to identify flow limiting coronary disease by inducing myocardial ischaemia that is then detected by imaging (usually by radionuclide perfusion scintigraphy or echocardiography, and occasionally magnetic resonance imaging).
Coronary artery calcium score—Coronary stenoses may be suspected with a calcium score, measured by means of cardiac computed tomography (CT), and then imaged and their severity assessed by invasive or non-invasive angiography.

One concern is whether particular cardiac tests lead to increased diagnostic labelling of coronary artery disease and unnecessary treatment of lower risk patients, which may result in physical and psychological harm.

The diagnostic value of the exercise tolerance test for the detection of coronary artery disease is hampered by equivocal results, false positives, and false negatives. However, the exercise tolerance test does provide valuable prognostic information about five year risk of death from any cause. A low risk patient who performs well on an exercise tolerance test may have a risk of death that is the same as that of the background population (yet may still have a coronary stenosis). On the other hand, the coronary artery calcium score has a high sensitivity for detecting coronary disease, but a low specificity, and it gives limited prognostic data unless it is negative.[5] As both non-cardiac chest pain and asymptomatic and often minor coronary artery disease are common, initial use of the calcium score may identify common but prognostically insignificant coronary artery disease, giving the patient a potentially misleading and worrying label and triggering a cascade of investigations. In some countries the rate of cardiac imaging has increased significantly without evidence of improvements in survival or reduction in cardiac events.[6-8]

The uncertainty is whether the aim of investigation should be to identify coronary stenoses (which may be prognostically significant or insignificant) or to clarify whether

Table 1 | Guidance from NICE 2010, AHA 2012, and ESC 2013 on the assessment of new onset chest pain in patients with low or intermediate pre-test risk of coronary artery disease (CAD)

NICE	AHA	ESC
If estimated likelihood of CAD is 10–29% ("low likelihood" of CAD), offer cardiac CT calcium scoring as first line diagnostic investigation If estimated likelihood of CAD is 30–60%, offer functional imaging as first line diagnostic investigation	Standard exercise ECG recommended for patients with low or intermediate pre-test probability of ischaemic heart disease who have an interpretable ECG result and at least moderate physical functioning or no disabling comorbidity The guidance states: "The precise definition of intermediate probability (ie, between 10% and 90%, 20% and 80%, or 30% and 70%) is somewhat arbitrary"	Exercise ECG recommended as initial test for establishing a diagnosis of stable CAD in patients with symptoms of angina and intermediate pre-test probability of CAD (15–65%), free of anti-ischaemic drugs, unless they cannot exercise or display ECG changes that make the ECG non-evaluable Stress imaging is recommended as initial test option if local expertise and availability permit

NICE=National Institute for Health and Care Excellence clinical guideline 95, 2010.[3] AHA=American Heart Association guideline 2012.[1] ESC=European Society of Cardiologists guidelines 2013.[2] CT=computed tomography. ECG=electrocardiography.

THE BOTTOM LINE

- The coronary artery calcium score has high sensitivity for detecting coronary stenosis—so a negative result makes significant coronary stenosis unlikely—but low specificity, and 60% of those without coronary artery disease will also have a positive result
- Thus many low risk patients may be diagnosed with coronary artery disease using the calcium score, although they may have clinically insignificant or "bystander" disease. These patients may benefit little from investigation and treatment and may be harmed
- The exercise tolerance test is a quick, functional investigation that measures maximum exercise tolerance. In low risk patients who are likely to achieve a high workload the test can identify patients with high relative survival without the need for further imaging

Table 2 | Percentage of people estimated to have coronary artery disease according to type of chest pain*, age, sex, and presence of risk factors†

	Non-anginal chest pain				Atypical angina				Typical angina			
	Men		Women		Men		Women		Men		Women	
Age (years)	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	86	20	51	93	97	56	84

*Chest pain is characterised as typical angina if it has these three features: (*a*) cardiac-type pain, which (*b*) comes on exertion and (*c*) is relieved by rest or glyceryl trinitrate within 5 minutes. Atypical angina has two of these features. Non-anginal pain has only one or none of these features.
†"High risk" patients have one or more of the following risk factors: diabetes, smoking, and hyperlipidaemia (total cholesterol >6.47 mmol/L). "Low risk" patients have none of these risk factors.
This pre-test risk for coronary artery disease was derived from a study of the prevalence of coronary disease by Diamond and Forrester in US autopsy data from 23 996 patients (deaths from all causes) published in 1979.[10] The pre-test risk of (at least single vessel) coronary artery disease was then calculated by multiplying the baseline prevalence for each category of patient by the likelihood ratio derived for the type of chest pain (typical, atypical, or non anginal),[11] and the presence or absence of important risk factors (diabetes, smoking, hyperlipidaemia).

patients are at low, medium, or high risk of adverse outcome. This is a key distinction because, typically, patients die of atherothrombosis rather than coronary stenoses.[9]

What is the evidence of uncertainty?

All three guidelines provide comprehensive reviews of the evidence in this subject up to 2012-3. We also searched PubMed and the Cochrane Library for relevant studies published in 2013-4 ("chest pain" AND ("assessment" OR "investigation") in title/abstract). The diagnostic strategies suggested for the investigation of patients at lower and medium likelihood of coronary artery disease in the three guidance documents are summarised in table 1.

Determining the pre-test risk of coronary artery disease

The investigative strategy in all three guidelines is determined by an initial clinical assessment of baseline risk that the patient will have significant (≥50% of diameter) luminal stenosis of at least one coronary artery. This pre-test risk was derived in 1979 from autopsy data[10] and calculated for each patient based on the type of chest pain (typical, atypical, or non-anginal pain), as well as the presence of risk factors (diabetes, smoking and hyperlipidaemia) (table 2).[11]

However, all three guidelines may overestimate the likelihood of coronary artery disease, particularly in those at low risk. This is because the US autopsy data are over three decades old, and the likelihood ratios were derived from a university hospital population referred for the assessment of possible coronary artery disease. Thus, contemporary pre-test probabilities are likely to be lower in a symptomatic but unselected primary care population.[12]

Furthermore, the categorisation of the type of chest pain (see table 2) may also be subjective and not reproducible between clinicians. Moving from one category to another substantially changes the pre-test probabilities. In our case scenario, it is not entirely clear from the history whether the patient has "atypical" pain (with 45% risk of coronary artery disease) or "non-anginal" pain (with 23% risk of coronary artery disease).

If we assume our patient has non-anginal pain (23% likelihood of coronary artery disease) then under the AHA guidance it is likely that our patient would have an exercise tolerance test.[1] Under the ESC guidance our patient would have either an exercise tolerance test or functional cardiac imaging to detect ischaemia.[2] In contrast, the NICE CG67 guidance recommends cardiac CT for a coronary artery calcium score.[3]

How do the exercise tolerance test and coronary artery calcium score compare as diagnostic and prognostic tests?

Coronary artery calcium score as a diagnostic test

The calcium score is a test with a low radiation dose that is carried out without contrast medium and detects and quantifies coronary artery calcification. It has a sensitivity of 98% for detecting coronary stenoses but a specificity of only 40%.[5] The high sensitivity means a negative result makes the presence of significant coronary stenoses unlikely, but 60% of those without coronary artery disease will also have a positive result.

Coronary artery calcium score as a prognostic test

One meta-analysis assessed the prognostic value of a coronary artery calcium score in 3924 symptomatic patients. Of these, 23% had a calcium score of zero,[5] and only 1.8% of these patients with a negative test had cardiovascular events in the next 17 to 84 months.[5] However, 77% of the patients had a positive test, and would therefore have had further investigations such as coronary CT angiography. This is usually undertaken immediately afterwards, and involves administration of intravenous contrast and (usually) a β blocker (given either orally or intravenously). It has a sensitivity of 93–97% and a specificity of 80–90% for coronary stenosis.[1]

Exercise electrocardiography as a diagnostic test

The exercise tolerance test is a functional investigation that measures maximum exercise tolerance and may diagnose myocardial ischaemia. Historically, the results of the investigation were labelled "positive" if more than 1 mm of ST segment depression (at a point 80 mm after the QRS complex) was elicited or ischaemic chest pain occurred during exercise. It was "negative" if the target heart rate was achieved without the above criteria. It was "equivocal" if the target heart rate was not achieved or the electrocardiographic results were indeterminate. It has a low sensitivity and only moderate diagnostic specificity (particularly in women) compared with the gold standard of coronary angiography for at least single coronary artery stenosis. The quoted sensitivity of the exercise tolerance test to detect significant coronary artery disease ranges from 23% to 100% and specificity from 17% to 100%.[13 14]

Notably, its performance characteristics do not justify its use as a binary diagnostic test (positive or negative). In a study of 4873 patients attending a rapid access chest pain clinic between 1996 and 2002 with a mean follow up of 2.5 years, 1% died from coronary artery disease and

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8% developed an acute coronary syndrome. The exercise tolerance test tests were classified as positive, negative, or equivocal. Of those who died from coronary artery disease or developed an acute coronary syndrome, 47% had originally had an exercise tolerance test that was reported as negative.[15]

Exercise electrocardiography as a prognostic test

There are ample data, however, showing that the maximum exercise capacity on an exercise test is a good predictor of prognosis in symptomatic individuals.[16 17] Two scores that facilitate prognostication, but which are little used, are the Duke University treadmill score and the Lauer score.[16 17] Using data such as age, sex, symptoms during the test, maximal exercise level achieved, and electrocardiographic changes, the scores give an estimate of the five year risk of death from all causes. Patients who achieve high workloads without chest pain or electrocardiographic changes have five year survival rates that approach those of the background population matched for age and sex.[16 17]

What would happen to our patient under these different protocols?

If our patient was assessed as having a low likelihood of coronary artery disease then NICE recommends he would initially undergo coronary artery calcium scoring. He would have a 77% chance of having a positive test result and would then proceed (often immediately) to coronary CT angiography. As a man in his 50s (if the 1979 Diamond and Forrester autopsy data remain correct), he would have about a 1 in 10 chance of having a coronary stenosis detected.[9] If one was detected, he would probably go on to receive additional investigations (such as invasive coronary angiography) and be prescribed antianginal medications as well as aspirin and a statin and may have a revascularisation procedure.

If our patient had an exercise tolerance test (recommended by the AHA and ESC) and managed 9 minutes on a Bruce protocol without electrocardiographic changes or pain then the Duke treadmill score[17] and the Lauer score[16] would estimate his five year survival to be approximately 97%. This would be the same as that for the average 55 year old man living in England and Wales,[18] so his relative survival (compared with his peers) would be 100%, and he would be unlikely to receive further investigations or medications.

Does the coronary artery calcium score have a clinical advantage over the less accurate diagnostic characteristics of the exercise tolerance test?

Currently separate NICE guidelines dissociate diagnosis of coronary stenosis[3] from risk stratification and management.[19] Coronary artery calcium scores (and coronary CT angiography) have a high sensitivity for detecting coronary stenosis but, unlike the exercise tolerance test and functional cardiac imaging, do not distinguish functionally significant from insignificant coronary disease.

The difficulty of assessing the clinical usefulness of the exercise tolerance test against a "gold standard" of detecting at least single vessel coronary artery stenosis is that in many populations (such as middle aged men and older patients generally) there will be a large reservoir of asymptomatic disease for which the prognosis is uncertain. It could be argued that there are likely to be health benefits from the detection of "bystander" coronary artery disease because it will encourage lifestyle changes and a focus on primary prevention treatments. However, this is unproven. The diagnosis may have significant negative effects if patients are labelled unnecessarily with a diagnosis of a disease that they perceive, albeit erroneously, to be dangerous.

We know from large studies carried out in the 1980s (in which patients who had undergone angiography for symptoms were randomised to surgical or medical therapy) that there is a correlation between the severity of coronary disease detected by angiography and survival. In the medically treated symptomatic patients with angina, annual mortality with medical therapy ranged from 1.4% for single vessel disease to 8.2% for triple vessel disease.[20]

However, there is little published data that estimates the prognosis of asymptomatic, limited disease, of which there is a large reservoir. It is biologically plausible that such individuals will have increased risk, but it is uncertain what the level of that risk is.

What little evidence there is suggests that increased rates of cardiac imaging do not reduce rates of cardiovascular events such as myocardial infarction.[8] The assessment of half a million US patients with chest pain in 244 hospitals showed a fourfold variation in rates of cardiac imaging in different hospitals and no correlation between rates of imaging and survival at two months.[7]

In a meta-analysis of over 3000 patients in the United States presenting to emergency departments with chest pain but not an acute coronary syndrome, those randomised to having coronary CT angiography were 1.8 times more likely to have receive coronary artery revascularisation than those randomised to "usual care."[21] There was no difference in rates of subsequent hospitalisations. However, in none of the trials was allocation to coronary CT angiography or usual care concealed, and this may have biased the rate of use of other investigations and treatments.

The recently published CAPP (Cardiac CT for the Assessment of Pain and Plaque) study randomised 488 UK patients referred to a rapid access chest pain clinic in low, medium, or high risk categories (for coronary artery disease) to have either a standard exercise tolerance test (graded as positive, negative, or inconclusive) or both coronary artery calcium score and coronary CT angiography.[22] They were followed up for a year. In the CT arm 15.2% underwent revascularisation procedures and 99 had medical treatment. In the exercise tolerance arm 7.7% underwent revascularisation procedures and 35 had medical treatment. There was no difference in the rate of major adverse cardiovascular events.[22]

The PROMISE trial (Prospective Multicentre Imaging Study for Evaluation of Chest Pain) was published in April 2015.[23] This randomised 10 003 symptomatic patients in the US to either anatomical testing with coronary CT angiography or functional testing with an exercise tolerance test, nuclear stress testing, or stress echocardiography. The patients were of intermediate rather than low risk (25.3%

had diabetes or known vascular disease, 65% had hypertension, the mean pre-test likelihood of coronary artery disease was 53.3%, and the mean body mass index was 30.5). In the coronary CT angiography arm 6.2% had a revascularisation procedure, compared with 3.2% in the functional testing arm. There was no difference in primary outcomes (death, myocardial fraction, unstable angina, or major procedural complication) in the two groups over a mean follow up of 25 months (3.3% *v* 3.0%).

Is ongoing research likely to provide relevant evidence?

We searched the clinical trials database www.clinicaltrials.gov with the terms "exercise tolerance test" and "CT." There is one ongoing study that may help clarify the optimal strategy in the assessment of chest pain in individuals with a low likelihood of coronary artery disease, though this does not use exercise tolerance tests.

The RESCUE trial (Randomized Evaluation of Patients With Stable Angina Comparing Diagnostic Examinations; clinicaltrials.gov identifier NCT01262625) compares patients with chest pain receiving coronary CT angiography with single photon emission tomography or myocardial perfusion imaging. The outcome measure is the rate of cardiovascular events at up to two years in the groups evaluated in the two ways.

What should we do in the light of the uncertainty?

If our 55 year old patient managed 9 minutes of exercise on a Bruce protocol without chest pain or ST segment depression then his predicted five year survival would be about 97%—the same as that of his age and sex matched peers.

A coronary artery calcium score has a 77% chance of being positive, and what little data there are suggests the patient would be more likely to be diagnosed with coronary artery disease (either significant or insignificant) with this diagnostic path. The possibility of unnecessary diagnostic labelling could be discussed with the patient and he could choose.

However, it is imperative that the exercise tolerance test is used appropriately. If it is considered as a binary diagnostic tool (either "positive" or "negative") rather than as a prognostic tool, it could offer false reassurance about the risk of coronary artery disease in "low risk" individuals who subsequently die from cardiovascular disease.

The exercise tolerance test remains a useful tool if it is not assessed against the surrogate endpoint of angiographic evidence of mild coronary disease. It may be mistaken not to use a huge body of prognostic data, established over decades of practice, that accurately estimate that most useful of endpoints—survival.

RECOMMENDATION FOR FURTHER RESEARCH

Population—Patients referred with undiagnosed chest pain who are referred for non urgent assessment

Intervention—Patients with estimated prior likelihood of coronary artery disease of 10–29% who are considered suitable for exercise electrocardiography are randomised to have, initially, either an exercise tolerance test with Lauer score or a coronary artery calcium score

Comparison—Outcome in the two groups is assessed at three years

Outcome—The proportion of patients diagnosed with angina in the two groups, the proportion who undergo invasive coronary angiography as part of the diagnostic workup, and the proportion who have coronary events in those with angina diagnosed and not diagnosed after the initial investigation

ANSWERS TO ENDGAMES, p 37

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ANATOMY QUIZ

Coronal T2 weighted image of the right iliac fossa from a magnetic resonance enteroclysis study

A: Caecum

B: Ileocaecal valve

C: Terminal ileum

D: Jejunal loop

E: Urinary bladder

MRE combines the advantages of MRI with more traditional barium/contrast enteroclysis

STATISTICAL QUESTION

How to read a receiver operating characteristic curve

Statements *a*, *b*, and *c* are all true.

CASE REVIEW

A young woman with recurrent perianal sepsis

1 Magnetic resonance imaging (MRI) of the pelvis.

2 Perianal abscesses and fistulas are thought to be acute and chronic manifestations of the same disease process. Primary disease results from obstruction of the anal glands, which then become infected (cryptoglandular hypothesis); a minority are secondary to Crohn's disease (as in this case), cancer, previous radiotherapy, atypical infection (such as tuberculosis), or iatrogenic trauma.

3 The most widely used system is the Parks classification, with the St James's University Hospital classification also being commonly used.

4 Acute management involves surgery, with examination under anaesthesia to identify the fistula tract, incision and drainage of the abscess, and placement of a draining seton suture in the fistula. In patients with Crohn's disease medical treatment can be started when the sepsis has settled.