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Comparative cost-effectiveness of non-invasive imaging tests in patients presenting with chronic stable chest pain with suspected coronary artery disease: a systematic review

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Abstract

Background:

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality globally. The most cost-effective imaging strategy to diagnose CAD in patients with stable chest pain is however uncertain.

Objective: To review the evidence on comparative cost-effectiveness of different imaging strategies for patients presenting with stable chest pain symptoms suggestive for CAD.

Design: Systematic review.

Study selection: Studies performing a formal economic evaluation or decision analysis in the English language published between January 1995 and December 2015 were identified using PubMed, Medline (OvidSP), Embase, Web of Science, Cochrane economic evaluations library and EconLit. Reviews and meta-analyses were excluded. Two independent reviewers assessed titles and abstracts. Of the 4498 titles identified 70 met our selection criteria.

Quality assessment: One reviewer used a modified version of the CHEERS checklist to assess study quality.

Data extraction: One reviewer extracted data on study details, which were checked by a second reviewer.

Results: There is a major heterogeneity between the available cost-effectiveness studies included in this study. The included studies compared very different testing strategies in very different ways and provided mostly short-term results. Strategies of no-testing and xECG were underrepresented. Nonetheless, the findings from this systematic review suggest that for patients with a low to intermediate prior probability of having obstructive CAD, CT coronary angiography (CTCA) may be cost-effective as an initial diagnostic imaging test in comparison with CAG or other non-invasive diagnostic tests. If functional testing is required, SE or SPECT are suggested to be cost-effective initial strategies in patients with intermediate prior probability of CAD. Yet, other functional testing strategies as xECG and PET scanning have not been studied as intensely. Immediate CAG is suggested

to be a cost-effective strategy for patients at a high prior probability of having obstructive CAD whom may benefit from revascularisation.

Conclusion.This study emphasises the inextricable link between clinical effectiveness and economic efficiency. Evidence suggests that the optimal diagnostic imaging strategy for individuals suspected of having CAD is CTCA for low and intermediate disease probability, followed by SE or SPECT as necessary, and invasive CAG for high disease probability. Further studies are needed to evaluate the cost-effectiveness of alternative non-invasive tests, including a no-testing strategy.

Keywords: Coronary artery disease; stable chest pain; comparative cost-effectiveness; willingness-to-pay threshold; non-invasive diagnostic imaging

Abbreviations:

CACS	Coronary artery calcium scoring
CAD	Coronary artery disease
CAG	Catheter-based (invasive) coronary angiography
CMRI	Cardiac magnetic resonance imaging
CTCA	CT coronary angiography
ETT	Exercise treadmill testing
FFR	Fractional flow reserve
MRI	Magnetic resonance imaging
MPI	Myocardial perfusion imaging
MPS	Myocardial perfusion spectroscopy
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality adjusted life year
SE	Stress echocardiography

SPECT Single photon emission computed tomography

xECG Stress electrocardiography

Introduction

Scope of the clinical problem

Coronary artery disease (CAD) remains one of the leading causes of death globally among adult males and females alike (1). Stable chest pain symptoms (also referred to as stable angina) is an important manifestation of CAD. The lifetime risk of developing CAD depends on age, gender, ethnicity, geographic region and the presence of cardiovascular risk factors and is estimated to be 38-51% in men and 12-33% in women (2). For patients who newly present with stable chest pain symptoms the evaluation of suspected CAD commonly includes a diagnostic workup to investigate for the presence of CAD. The evaluation should always begin with an appropriate history and physical examination. Catheter-based coronary angiography (CAG), at times combined with catheter-based fractional flow reserve (FFR) measurements, is the reference standard to diagnose functionally significant CAD. Since it is costly, invasive, and associated with a substantial risk of major adverse events, CAG is recommended as initial test for patients with a high prior probability of CAD (3). However, research has shown that only 41% of patients undergoing elective procedures of catheter based coronary angiographies are diagnosed with obstructive CAD (4). This stresses the need for better risk stratification, which is underlined by decision analyses showing that the optimal choice of further diagnostic investigation in patients with stable chest pain depends primarily on the prior probability of CAD (5-7). Deciding on subsequent diagnostic testing in patients with suspected CAD is however difficult, partly because of the many testing options currently available.

Currently available non-invasive imaging tests

Imaging tests play an important role in the diagnostic workup, and imaging results often determine prognosis and treatment. Stress electrocardiography (xECG) is a non-invasive diagnostic procedure

that has been in widespread clinical use for decades to determine the presence of significant CAD. In clinical practice, cardiac imaging strategies are used when ECG abnormalities during xECG are nondiagnostic and when it is important to determine the extent and distribution of ischaemic myocardium. In addition, cardiac imaging strategies are used to exclude or confirm a positive or negative xECG as well as to decide whether a patient requires CAG (8).

Owing to the rapid technological advancement in cardiovascular diagnostic imaging, many non-invasive diagnostic tests are currently available which either evaluate coronary anatomy or the presence of inducible myocardial ischaemia (functional ischaemia testing), or both. CT coronary angiography (CTCA) evaluates coronary anatomy. Tests evaluating the presence of inducible myocardial ischaemia include stress echocardiography (SE), stress perfusion cardiac magnetic resonance imaging (CMRI), and myocardial perfusion imaging (MPI), i.e. myocardial perfusion scintigraphy (MPS) (either single-photon emission computed tomography [SPECT] or positron-emission tomography [PET]). Furthermore, FFR can now be estimated from acquired computed tomography data (FFRct) based on computational fluid dynamics (9). Yet, although these tests are relatively non-invasive compared to catheter-based CAG, it should be noted that they still pose a burden to the individual patient, the health care system, and society at large, because they are associated with significant patient time, costs, radiation exposure and the risk of adverse events. Compounding the problem, physicians often request multiple tests in order to increase their confidence in the diagnosis and treatment plan of patients presenting with stable chest pain.

Diagnostic imaging algorithms

In order to minimise risks and burden to patients, radiation exposure and health care costs, diagnostic algorithms have been developed to optimise the diagnostic workup. These algorithms define a combination and sequence of tests, where the choice of each imaging test is determined by patient characteristics and the results of previously performed diagnostic tests. Imaging algorithms recommended by guidelines vary widely, demonstrating variability in clinical practice and attesting to

the uncertainty about which algorithm is optimal (3, 10, 11). For example, the American College of Cardiology/American Heart Association and European Society of Cardiology recommend exercise electrocardiography to select patients for further diagnostic investigation, while the UK guidelines recommend using the computed tomography (CT) based coronary calcium score (CACS) in patients with a low to intermediate prior probability (10-29%) (11, 12). It has yet to be elucidated which imaging algorithm is optimal in terms of both costs and outcomes, i.e. is cost-effective.

Purpose of this study

In this paper we present a systematic review of available evidence on cost-effectiveness of currently available non-invasive imaging tests and imaging algorithms for the diagnostic workup of patients with stable chest pain symptoms who are suspected of having obstructive CAD.

Materials and methods

In a systematic literature search, we identified original articles that economically evaluated non-invasive cardiac imaging strategies. We searched the electronic databases PubMed as publisher, Medline (OvidSP), Embase, Web of Science, Cochrane economic evaluations library and EconLit. The search included keywords corresponding to the index tests (CTCA, SE, MPS, PET, SPECT, CMRI, CACS, xECG, FFR), the reference test (CAG), the target condition CAD and cost-effectiveness. We used various synonyms including both text words and Medical Subject Headings (MeSH) terms to maximise the sensitivity of our search.

We restricted our search to papers in English language published during the last 20 years (between January 1995 and December 2015) to identify economic evaluations studies and decision models with respect to non-invasive cardiac imaging tests. We only included papers dealing with adult patients presenting with chest pain symptoms suggesting the presence of stable CAD. Studies were excluded if the target condition was suspected acute coronary syndrome. We also excluded guidelines and studies focusing on detecting high risk (left main and triple vessel) CAD only, however, the references were checked for additional papers.

We included studies if they met all of the following criteria: the study (1) performed a formal economic evaluation or decision analysis, (2) provided a thorough accounting of costs or evaluated both costs and effectiveness, (3) demonstrated total cost differences or reported either cost savings and increased effectiveness (= defined as dominance) or cost increases and gains in (quality adjusted) life year ([QA]LY) or healthy-year equivalents. Full-texts of articles containing the search terms in the title and/or abstract were selected by two reviewers independently (C.N.v.W. and M.Y.K.). Articles were excluded if both reviewers agreed they were ineligible. Discrepancies were resolved by consensus. Data of the included full texts on authors, reference, journal, year of publication, time horizon, perspective, country, imaging modalities compared, type of model, data sources, currency (type and year), threshold willingness-to-pay, reference case analysis, reference case result, suggested imaging strategy for low- intermediate prior probability of CAD, sensitivity analysis, influential input parameters, and generalisability were extracted by one reviewer (C.N.v.W.). Extracted data were checked for accuracy by a second reviewer (T.G.). Discrepancies were resolved by consensus. The quality of included studies was assessed by one reviewer (C.N.v.W.) using a modified version of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (13) (see appendix table 4), as recommended by published guidelines (14, 15).

Data synthesis

Given the heterogeneity of the data, no formal quantitative pooling of results was performed. Synthesis of the data was performed qualitatively, and clinical implications are drawn. To enhance comparability, results were adjusted from the original papers by rounding the numbers and using a reporting format as recommended by reporting standards for cost-effectiveness analyses. Therefore, the data presented here may be different from the data reported in the original papers. Reported incremental cost-effectiveness ratios (ICERs) were recalculated from the reported data to ensure a correct comparison across the diagnostic imaging strategies.

Results

Comparative cost-effectiveness of non-invasive diagnostic imaging strategies

Quality of included studies

Our search resulted in 4498 titles of which 231 were identified as potentially eligible for inclusion based on title and/or abstract (see figure 1). Finally, 231 studies met our inclusion criteria. After161 studies were excluded on the basis of our exclusion criteria, 70 were left for analysis. We present the results of our analysis in tables 1, 2, 3 and online appendix tables and figures. Quality of the studies was assessed according to a modified version of the CHEERS checklist and is presented in figure 2. The quality of the included cost-effectiveness studies was generally moderate to good. Most studies, however, did not provide details on price adjustments for inflation or currency conversion (item 11) and generalisability issues were poorly addressed. In addition, most studies provided details on currency type (item 10) used in the analyses, but some studies did not report the currency exchange year.

Main findings

There are some important differences between the included cost-effectiveness studies. A major issue is the heterogeneity of the studies included in this analysis. Many studies originate from different countries (see appendix figure 3), often take the perspective of the health care payer or health care provider (hospital), use a short term time horizon, or did not report the willingness-to-pay threshold (see appendix table 5 and 6). Therefore, the purpose was often to inform reimbursement or hospital services decisions, rather than decision making from a societal perspective as generally recommended in cost-effectiveness analyses (see appendix table 6 and appendix figures 4 & 5).

There is also variation in the type of model used to perform an economic evaluation or decision analysis as well as the type of data sources used to inform these models. As can be seen from appendix table 7 and appendix figures 6 & 7, about one third of the studies (n=27/ 39%) used a decision tree combined with a long-term outcome modelling approach including Markov cohort

simulation and state-transition microsimulation. In addition, some studies (n=13/ 19%) used a simple decision tree without modelling of long-term outcomes.

Furthermore, a few studies (n=8/ 11%) used a Bayesian mathematical simulation model. The earlier mathematical simulation models, such as the one by Patterson et al 1995 (16), focused on diagnostic accuracy statistics as drivers for evaluating economic efficiency. In fact, these models were built on the principles of minimising costs through higher sensitivity and lower false-positive rates. Although these models rely on unrealistic assumptions, such as 100% of the patients with abnormal tests proceeding to CAG, they provide some insight into potentially cost-effective strategies and formed groundwork for several recent mathematical simulation models. The majority (n=35 / 50%) of studies however, used methods to look at costs only (n=17) or used miscellaneous methods to look both at costs and effectiveness (n=18). Some of these studies used costs per correct diagnosis as outcome (n=5) making them incomparable to cost/QALY cost-effectiveness studies.

Looking at the willingness-to-pay (WTP) threshold, i.e. what society should be paying for a gain in effectiveness, many studies do not report a WTP threshold since they look only at costs or use short term outcomes. Few studies do report a WTP threshold (n=12/ 17%), however there is no international consensus on which WTP threshold to use and this threshold thus varies across countries, ranging from £10.000-€80.000/QALY. Additionally, we found considerable variability in the reporting of cost data (see appendix table 9) as well as in the quoted costs of different tests depending on assumptions about patient volumes and whether bottom-up costs or prices have been used.

Furthermore, we found that about two-third of the included studies performed sensitivity analysis (see table 1). Of these, sensitivity analyses showed that the optimal diagnostic imaging strategy depends mostly on the prior probability of CAD, test characteristics and costs of a test. Only a few studies (n=10 / 14%) modelled all parameter uncertainty simultaneously (probabilities, utilities and costs) with probabilistic sensitivity analysis.

There are also important differences in the reference case analyses performed and algorithms compared. In most studies the reference case analysis was not stratified by gender, although men and women may be quite different given their age and prior probability for CAD (see appendix table 8). Arguably, only the study by Genders et al. 2015 (17), considered most but not all possible imaging tests. In fact, a wide range of imaging strategies was compared across the studies included in this systematic review. CTCA-based strategies are commonly compared, while only few studies comparing PET-based strategies (see table 2). In addition, only few studies considered a 'no testing' strategy (n=9/ 13%). Further, only few studies compared functional and anatomical tests (n=20/ 29%). Most studies compared only functional tests (n=34/ 49%) and suppose SE to be superior over SPECT or CMRI. Furthermore, although potential cost savings are reported when SPECT-guided diagnostic strategies are compared with xECG-guided strategies, for example in a report by Marwick et al 2003 (18), it is not the case that SPECT is cost-effective when compared with other diagnostic imaging modalities (17).

As can be seen from appendix table 5 and table 3, for most patients who present with typical or atypical angina, performing a non-invasive diagnostic test is a reasonable use of health care resources. Yet, as also can be seen from table 3, the cost-effectiveness of diagnostic strategies is strongly influenced by the prior probability of CAD. In 26 out of 32 studies considering CTCA, CTCA was cost-effective and suggested as a 'gatekeeper' (initial) test for adult patients with low-intermediate prior probability of CAD (10%-≤50%) and prior to cardiac stress imaging. Yet, the prior probability thresholds for CAD below which CTCA is suggested and above which SE or SPECT varied across studies. CMRI and SE were preferred over xECG as initial stress test, and SE was cost-effective compared to SPECT in patients with a low-intermediate prior probability. Coronary angiography was cost-effective in patients with a high prior probability of CAD (≥70%).

Discussion

We present a systematic review of the published evidence on the comparative cost-effectiveness of currently available non-invasive imaging tests for the diagnostic workup of patients with stable chest pain symptoms who are suspected of having CAD. Our findings indicate that, in a setting of low to intermediate prior probability, there is no simple answer to what the optimal diagnostic imaging strategy is for individuals who are suspected of having CAD, as this depends on several variables: costs of the tests, test characteristics, prior probability, society's willingness-to-pay threshold, optimisation criterion, availability of imaging tests, patient preference and local expertise.

Differences across studies

There are a number of differences across the included studies in our systematic review that should be recognised. Whereas the societal perspective is generally recommended in most countries, most studies took the perspective of the health care payer or health care provider (hospital). In addition, most studies used a short term time horizon for their analyses. Depending on the assumptions made, however, it is possible that long-term analyses produce results that are significantly different from those obtained with short-term analyses (19). For this reason, it is hard to draw any definitive conclusions from the data presented in this systematic review. In addition, in most of the included studies the diagnostic performance of non-invasive imaging tests is used in terms of ability to identify or exclude luminal stenosis, often compared with invasive CAG as reference standard. Yet, in clinical practice the primary aim of is rather to assess the origin of symptoms and the risk of acute (major) cardiac events, so that both hopefully can be minimised (20). Treatment strategies differed across studies with regards to revascularisation and optimal medical therapy. Yet, as has been shown in recent clinical trials, cardiac event rates with optimal medical therapy are quite low, even in patients with established CAD. The recent FAME 2 trial demonstrated no reduction in death or myocardial infarctions (MI) in patients with single or multi-vessel stable chest pain symptoms who underwent FFR-guided PCI of significant lesions, when added to OMT vs. OMT alone (21). Also in the COURAGE

trial, a lack of clinical benefit for death or MI when PCI of angiographically significant lesions was added to OMT in stable CAD patients was shown (22). This supports the concept that the incremental use of preventive therapies will have a long-term beneficial effect. In addition, in the DIAD study patients with type 2 diabetes and no symptoms of CAD were randomly assigned to be screened with adenosine-stress radionuclide MPI or not to be screened. In this contemporary study population of patients with diabetes, the cardiac event rates were low and were not significantly reduced by MPI screening for myocardial ischaemia over 4.8 years (23). Furthermore, the FACTOR-64 study in patients with type 1 or type 2 diabetes of at least 3 to 5 years' duration and without symptoms of CAD were included and randomly assigned to CAD screening with CTCA or to standard national guidelines-based optimal diabetes care. For this population it was shown that the use of CTCA to screen for CAD did not reduce the composite rate of all-cause mortality, nonfatal MI, or unstable angina requiring hospitalisation at 4 years (24). Therefore, in patients with a low prior probability of CAD, it seems very unlikely that any testing will reduce cardiac events compared to no testing and appropriate risk factor modification. Moreover, for patients with stable CAD (excluding left main trunk disease and multi-vessel disease in diabetics), there are no randomised trials that support revascularisation to reduce hard cardiovascular end-points (cardiovascular death or MI). Therefore, unless these patients have limiting angina despite medical therapy, these revascularisations may be unnecessary (this is the so-called oculostenotic reflex).

Furthermore, in an analysis of the National Cardiovascular Data Registry (NCDR) in patients undergoing elective CAG, it was found that in 70% of the patients undergoing invasive CAG after CTCA had obstructive disease, which represents more than 50% improvement in identifying patients with obstructive disease compared to any functional test (i.e. xECG, SE, and CMRI) (P <.001) (25). Based on these results the PROMISE trial (26) was undertaken, in order to provide a snapshot of real-world care for patients with suspicion of CAD. The most remarkable finding in the PROMISE trial was the diagnostic performance of CTCA over functional testing to identify obstructive CAD, i.e. 71.2% of

patients undergoing invasive CAG after CTCA had obstructive disease compared to only 47.5% of functional test group patients (27). These numbers are remarkably similar to the NCDR data. This is crucial information as we attempt to properly stratify chest pain patients based on symptoms, with revascularisation and proper diagnosis of angina hanging in the balance (25). Couched in those terms, the sensitivity and specificity of non-invasive tests, particularly the functional ones which do not demonstrate stenosis directly, in relation to an angiographic standard may not be the best outcome parameter to use in economic modelling. Furthermore, although the results of PROMISE demonstrated better diagnostic accuracy of CTCA, it also demonstrated an obvious advantage of an anatomic approach, allowing more preventive therapies to be applied. Yet, in stable chest pain, there is no improvement in outcomes in the first year of statin or aspirin use, but as time progresses, the event curves in multiple studies diverge. This was impressively demonstrated in a second large scale study published simultaneously to PROMISE called SCOT-HEART assessing CTCA in patients with suspected angina due to CAD (28). In SCOT-HEART patients with suspected CAD were randomised to receive either only standard workup (in most cases, functional testing) or standard workup plus CTCA. In this trial, CTCA reclassified the diagnosis of CAD in 27% of the patients, and the diagnosis of angina due to CAD in 23% of patients (standard of care respectively 1% and 1%; P<.0001). This changed planned investigations (15% vs. 1%, P<.0001) and treatments (23% vs. 5%, P<.0001). Three year follow-up in SCOT-HEART demonstrated that the cardiovascular event rate was reduced by 50% in the CTCA group (28).

Furthermore, analyses were performed for several different countries including USA, UK, Australia and countries in Europe and Asia. Health care costs vary considerably across countries. In addition, and the threshold willingness-to-pay ranged from £10.000-€80.000/QALY. In this respect we recognise that diagnostic strategies and treatment decisions may also vary across countries. Significant variations in diagnostic strategies between European and the United States are well documented and may be related to differences in health care systems, access to testing technologies, and risk tolerance (29-31). Furthermore, a wide range of different combinations of imaging strategies

were compared, and only one study compared arguably all possible imaging modalities. Direct clinical comparisons of the outcomes of different strategies are commonly limited to 2 or 3 alternatives, whereas decision modelling studies have been able to assess larger number of choices. Only a few studies considered a 'no testing' strategy, which reflects the natural history of the included patient population and associated costs. In addition, the quoted costs of the different tests vary widely between the studies included in this systematic review, depending on the assumptions on patient volume (for modalities where fixed hardware costs are high) and whether bottom-up costs or prices have been used. This has a big impact on the relative cost-effectiveness of tests whose diagnostic performances are relatively similar. For example, the differences between the findings of the study of Stacul et al. (32) and Dewey et al. (33) considering CTCA can be explained by such factors. Also the supposed superiority of SE over SPECT or CMRI can be explained by such factors, as for example shown in the study by Marwick et al. (18) and Tan et al. (34). In addition, Hunink et al.(35) used a decision model to determine parameters that would indicate a new non-invasive test could be cost-effective compared with SE or SPECT, and suggested the costs would have to be lower than $1,000 with sensitivity and specificity of 95% or more. Further, the recently published SPARC registry study in JACC by the group of DiCarli et al. (36) showed that at 2-years the mean costs for patients undergoing SPECT as the first-line investigation compared with CTCA or PET as the first-line investigation were significantly lower, and patients who underwent CTCA and PET experienced significantly higher 90-day rates of downstream CAG (16% and 15%, respectively) as compared with patients who underwent SPECT (7%) and new prescriptions for aspirins and statins.

The higher rate of downstream CAG after CTCA has been documented in some of the included studies (37), but not in others (38), (39), (40), (41). The use of invasive procedures varied with: a) the degree of abnormality seen on the CTCA, with very few cardiac catheterisations done in patients with normal or near-normal CTCA findings, but with a higher rate of catheterisation among patients with an abnormal CTCA (42). This observation suggests that the differences in the composition of the patient population and in the prevalence of underlying CAD may explain differences between prior

studies in subsequent use of invasive CAG testing after CTCA. Studies that enrolled younger and lower-risk populations (40) should have more frequently normal CTCA findings, and, consequently, fewer invasive tests than studies with patient populations that are older, have a higher risk, or both (36). Furthermore, the findings of the SPARC registry in favour of SPECT, are in line with findings in some of the included studies. A decision model by Garber et al. (41) showed SPECT to be more cost-effective than PET for non-invasive diagnosis of CAD, and SPECT to be a better option than immediate CAG. It should, however, be noted that in their study CTCA was not evaluated, since this had not yet been developed. A similar included decision model by Kuntz et al. (43) found SE and SPECT to be reasonable initial choices for patients with intermediate probability of CAD, but invasive CAG to be optimal for patients with high prior probability of CAD. It should, however, be noted that their study did not evaluate PET or CTCA. The decision model of Hernández et al. (44) suggested that SPECT was cost-effective compared with xECG or invasive CAG without non-invasive testing. One needs to be mindful that this study did not consider CTCA or PET as alternatives. Min et al. (7) used a decision model to assess five different strategies using CTCA or SPECT, and projected that strategies based on CTCA might be more cost-effective than SPECT-based strategies. In terms of outcomes, Shaw et al. (45) (END study) found that patients who underwent initial SPECT with selective cardiac catheterisation had lower costs than patients who underwent routine coronary angiography. In the EMPIRE study by Underwood et al. (46) it was demonstrated that strategies using MPI were cheaper and equally effective when compared with strategies that did not use MPI, both for the cost of diagnosis and for overall 2-year management costs; the 2-year patient outcome was the same. Sharples et al. (47) randomised 898 patients to SPECT, SE, CMRI, or direct CAG, and found SPECT to be as useful as immediate CAG with similar costs. At last, it is not necessarily clear in the current iteration that NICE guidance recommends risk assessment to direct choice of investigation of patients with stable chest pain and advocates CTCA at any rate rather than functional testing. Yet, many people in the low to intermediate probability group of having obstructive CAG will not have a calcium

score of zero and will therefore go to CTCA directly, but when the prior probability is high enough they will go directly to CAG (12).

Furthermore, the prior probability of CAD differed widely across studies ranging from 1%-90%. Yet, research has shown that clinical estimates of prior probability are grossly overinflated in real world application. For example, in the CONFIRM CT registry, the actual prevalence of obstructive CAD in patients with typical or atypical angina across the range of prior probabilities was only 20-50% of that predicted by the traditional Pryor approach (48). Irrespective of age, sex, risk factors and the typicality of angina, no patient group had an observed prevalence of obstructive CAD >60%. Other studies have also shown that most patients who undergo invasive CAG after ischaemia testing have non-obstructive or normal arteries (49). Therefore, in real life, the group of patients for whom direct CAG is cost-effective compared with CTCA may actually not exist. Interestingly, as in the case of the main population of the EVINCI study, traditional criteria for calculating prior probability overestimated the prevalence of haemodynamically significant CAD by 37% (50).

Limitations of this study

Our study has several limitations. First, although we carefully developed a search strategy, the search strategy could have missed possible relevant articles. Second, the review is based solely on published papers, and is thus restricted to the level of detail reported in the original papers. Third, studies evaluating CTCA based strategies were overrepresented in this systematic review. Studies evaluating a strategy of no testing were underrepresented. In addition, even though xECG and PET were included in some studies, these testing strategies have also been underrepresented. This may have biased the results presented in this systematic review. Fourth, most diagnostic accuracy studies suffer from referral bias. This may have distorted the diagnostic test characteristics used in the published cost-effectiveness analyses, which in turn diminishes the comparability and generalisability of the included cost-effectiveness studies. Further, all studies except three used CAG alone as the reference standard, whereas over the past years, CAG is increasingly used in combination with

functional testing using catheter-based FFR for determining significance of stenosis. Finally, this systematic review is based on cost-effectiveness literature about stable chest pain patients, and the results should not be extrapolated to other settings, such as the diagnostic evaluation of patients presenting with acute chest pain.

Implications for clinical practice

The results of this systematic review suggest that for patients with a low to intermediate prior probability of having significant CAD, the optimal (sequence of) diagnostic imaging tests remains uncertain.

Although CTCA is gaining acceptance as a tool in the initial diagnostic approach of patients with low to intermediate prior probability of CAD, it is unlikely that the test will completely replace functional or invasive testing since this is still commonly used in patients presenting with a prior probability ≥50%. Furthermore, CTCA and CAG assess anatomic CAD stenosis, but do not assess the functional significance of coronary lesions. As a result, there is a potential for stenoses seen on CTCA and CAG that are not flow limiting, and therefore may require further evaluation with functional testing. Functional testing should therefore be regarded as incremental to anatomical imaging in order to determine the clinical significance of stenosis, and the potential benefit of revascularisation and prognosis. Functional testing may be performed using xECG, SE, SPECT, PET, CMRI, CTCA-based FRR estimation or catheter-based invasive FFR measurement, the latter being the current reference standard test. In the future CTCA may allow the assessment of ischaemia using perfusion techniques or virtual FFR measurement, however, these are not yet established procedures. The role of functional testing for less severe stenoses is unclear: in such cases, the results of functional tests may guide the intensity of medical therapy, lifestyle interventions and the frequency of follow up visits. In this respect, more randomised clinical trials and cost-effectiveness research is needed.

In line with a previously performed systematic overview (51), the current systematic review highlights the importance of risk stratification based on prior probability to guide imaging decisions. Ideally, the prior probability is estimated using a risk calculator that incorporates patient characteristics, medical history, risk factors and previous diagnostic test findings (11). At each stage of the diagnostic workup process, new findings are included in the calculator in order to revise the probability which is then used to make the next workup decision. This leads to an individualised and integrated approach, consistent with the current focus on personalised medicine.

Conclusions

In conclusion, the results from this study suggest that CTCA as an initial gatekeeper imaging test is cost-effective under varying assumptions in patients presenting with stable chest pain with a low to intermediate prior probability of CAD. Yet, as seen in the SPARC registry and the PROMISE trial, the limitations of anatomical imaging raise concern that an over-reliance on coronary anatomy may result in excessive invasive CAGs and that the 'oculostenotic reflex' will increase revascularisation procedures. In addition, as has been seen in recent clinical trials (COURAGE, DIAD, FACTOR-64, FAME2, PROMISE), cardiac event rates with optimal medical therapy, even in patients with established CAD, are quite low. Therefore, in low risk patients with suspected CAD, it seems very unlikely that any testing will reduce cardiac events when compared to no testing and appropriate risk factor modification. Thus, no testing is likely more cost-effective than any imaging strategy in low risk patients. However, a strategy of no testing was underrepresented in the included studies. Therefore, in order to be able to firmly conclude that CTCA is the preferred strategy in low risk patients, a randomised trial (with economic sub-studies) comparing CTCA to a no testing strategy in low risk patients would be helpful. Further, the results from this study suggest SE or SPECT to be cost-effective strategies if functional testing is required in patients presenting with stable chest pain with an intermediate prior probability of CAD. However, PET scanning and xECG have not been studied as intensely as other non-invasive functional testing strategies, and should therefore also be evaluated carefully in larger studies to assess its impact on clinical and economical outcomes. For patients

presenting with stable chest pain with a high prior probability the results from this study suggest direct CAG to be the most cost-effective initial strategy. Yet, studies have shown that clinical estimates of prior probability are grossly overinflated in real world application. Therefore, in real life, the group of patients for whom direct CAG is cost-effective compared with CTCA may not actually exist. For this reason, although this study provides a summary of published economic evaluations in the form of a quick reference and allows for easy comparison, the results should be seen as a spur to further research rather than as providing definitive conclusions. Further studies are needed to compare the cost-effectiveness of alternative non-invasive testing approaches, including a no-testing strategy, for patients with stable chest pain symptoms suggestive of CAD.

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Conflict of interest:

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Figure 1.

Complete search: ***Systematic review cost-effectiveness studies***

Database	*n*
Embase.com	3950
Medline (OvidSP)	2877
Web-of-science	117
Cochrane	2037
PubMed as publisher	42
EconLit	10
Total	**8983**

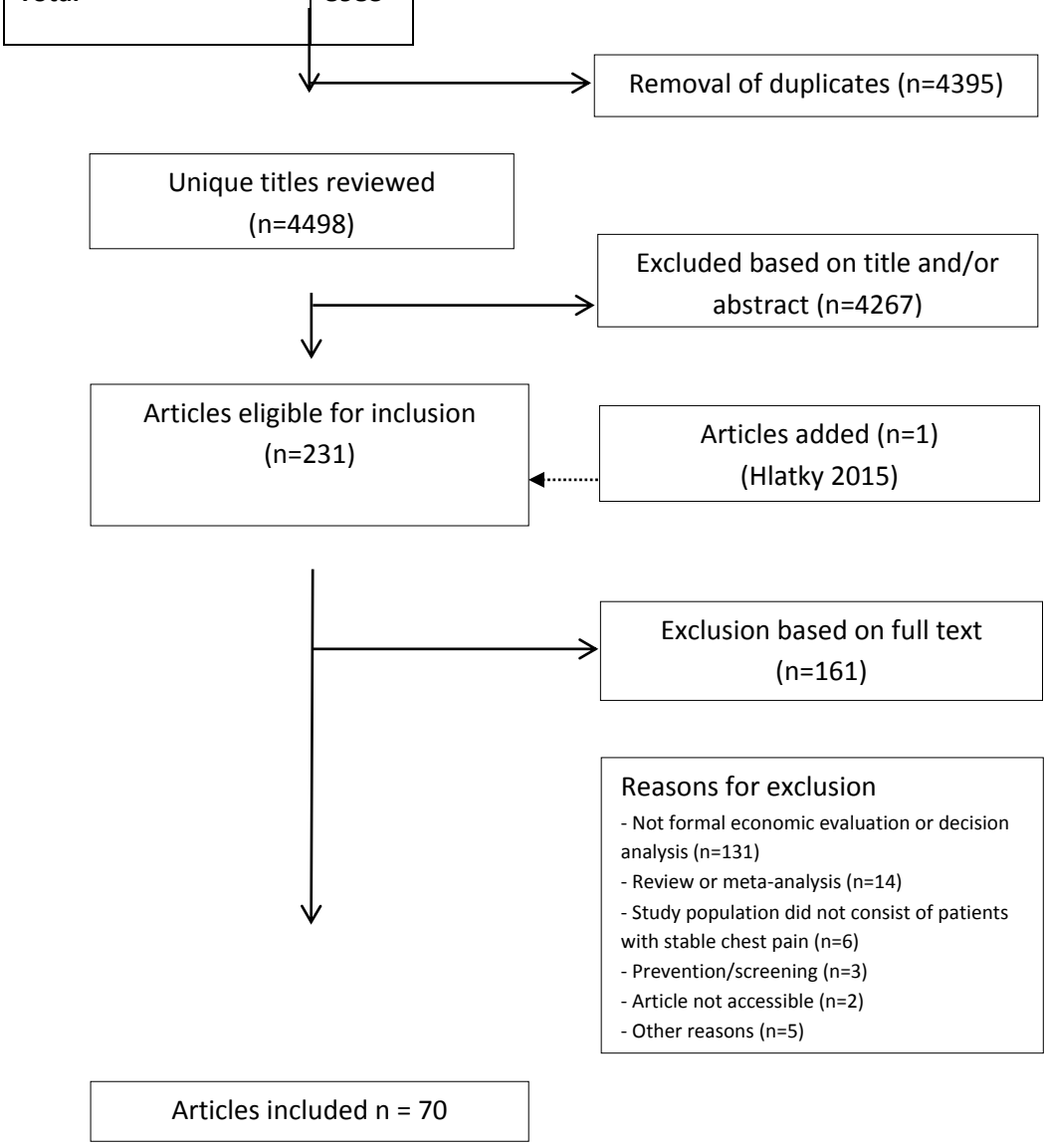


Figure caption

Figure 1: Literature search and selection numbers of articles with respect to economic evaluations and decision modelling for each step of the process are indicated.

Figure 2: Quality assessment of the included economic evaluations and decision models using the modified CHEERS checklist

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18
Amemiya (52)	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	±	-
Genders (5)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kreisz (53)	+	+	+	+	+	+	+	+	+	+	+	±	-	+	+	+	+	±
Ladapo (6)	+	±	+	+	+	+	+	±	+	+	+	+	±	+	+	+	±	±
Min (7)	±	±	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±	-
Genders (54)	+	+	+	+	+	+	+	±	+	+	+	+	+	+	+	+	+	+
Boldt (55)	+	+	+	+	+	+	+	+	+	+	-	±	+	+	+	+	±	±
Iwata (56)	+	+	+	+	+	+	+	±	+	+	-	+	+	±	+	+	±	±
Catalan (57)	±	+	+	+	+	+	+	+	+	+	-	+	+	±	+	+	+	-
Walker (58)	+	+	+	+	+	+	+	+	+	+	±	+	+	+	±	+	+	-
Halpern (59)	+	+	+	+	+	+	+	±	±	+	-	+	+	+	+	+	+	±
Kim (60)	±	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	±
Demir (61)	+	+	+	±	+	+	±	NA	+	+	-	±	+	+	NA	NA	±	-
Min (62)	+	+	+	±	+	+	+	+	+	+	±	±	+	+	+	+	+	±
Patel (63)	+	+	+	±	+	±	±	NA	+	+	-	±	+	+	+	+	±	-
Raggi (64)	+	+	+	+	+	+	+	NA	+	±	-	+	+	+	+	+	+	-
Halpern (65)	+	+	+	+	+	+	+	±	±	+	-	+	+	+	+	+	+	±
Garber (41)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±
Genders (17)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kuntz (43)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Ferreira (19)	+	+	+	+	+	+	+	±	+	±	-	±	+	+	+	+	±	±
Laufer (66)	+	±	+	+	+	±	±	NA	+	±	-	±	+	+	NA	NA	±	±
Thom (67)	+	+	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+	+
Rogers (12)	+	+	+	±	±	+	+	NA	±	+	-	±	+	+	NA	NA	±	-
Kimura (68)	+	+	+	+	±	+	+	+	+	±	-	±	+	+	NA	NA	+	+
Hachamovitch (69)	+	-	+	+	+	+	+	+	-	±	-	±	+	+	+	+	±	+
Patterson (16)	+	+	+	+	+	+	+	+	+	±	-	+	+	+	+	+	+	±
Shaw (70)	+	+	+	+	+	+	+	+	+	±	+	±	+	+	NA	NA	+	±
Hlatky (71)	+	+	+	+	+	+	+	+	+	±	-	+	+	+	+	+	+	±

Study	*Item 1*	*Item 2*	*Item 3*	*Item 4*	*Item 5*	*Item 6*	*Item 7*	*Item 8*	*Item 9*	*Item 10*	*Item 11*	*Item 12*	*Item 13*	*Item 14*	*Item 15*	*Item 16*	*Item 17*	*Item 18*
Petrov (72)	+	+	+	+	+	+	+	±	+	±	-	±	+	+	NA	NA	±	±
Nielsen (39)	+	+	+	+	+	+	+	±	+	+	-	±	+	+	NA	NA	+	±
Shaw (73)	+	+	+	+	+	+	+	+	±	+	+	±	+	+	+	+	+	±
Marwick (18)	+	+	+	+	+	+	+	+	+	+	+	±	±	+	NA	NA	+	+
Underwood (46)	+	+	+	+	±	±	+	+	±	+	-	±	±	+	NA	NA	±	+
Wennike (74)	+	+	+	+	+	+	+	NA	±	+	-	-	±	+	NA	NA	±	-
Darlington (75)	+	+	+	+	±	±	+	±	+	+	-	+	+	+	+	+	±	±
Meyer (76)	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-
Tan (34)	+	+	+	+	±	+	±	NA	+	+	-	+	+	+	+	+	+	+
Dewey (33)	+	+	+	+	+	+	+	±	+	+	+	+	+	+	+	+	+	±
Raman (77)	+	+	+	+	+	+	±	+	+	+	-	+	+	+	+	+	+	+
Hlatky (9)	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
Hlatky (36)	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
Zacharias (78)	+	-	+	+	+	±	+	+	+	±	-	±	+	+	NA	NA	±	±
Muzzarelli (79)	+	+	+	+	±	±	+	NA	+	±	-	±	+	+	+	+	±	±
Pilz (80)	±	+	+	+	±	±	-	NA	±	+	-	±	+	+	+	+	-	+
Marwick (81)	+	+	+	+	±	±	+	+	±	±	-	±	+	+	NA	NA	±	+
Lorenzoni (82)	+	+	+	+	+	±	+	+	±	+	+	±	+	+	+	+	±	+
Tardif (83)	+	+	+	+	+	+	+	±	±	+	-	+	+	+	+	+	+	±
Cheng (84)	+	+	+	+	+	±	+	±	±	+	+	+	+	+	+	+	±	+
Cole (85)	+	+	+	+	+	±	+	NA	±	±	-	±	±	+	+	+	±	+

Lee (86)	+	+	+	+	+	+	±	+	+	±	-	+	+	+	+	+	+
Min (87)	+	+	+	+	+	+	+	+	+	±	-	+	+	+	NA	NA	+	+
Moschetti (88)	+	+	+	+	+	±	+	NA	+	+	-	±	+	±	NA	NA	+	+
Moschetti (89)	+	+	+	+	+	+	+	+	±	±	+	±	+	±	+	+	+	+
Min (90)	+	+	+	±	+	±	+	+	±	+	-	±	+	+	+	+	±	+
Mattera (91)	+	+	+	+	+	±	+	±	±	+	-	±	+	+	NA	NA	±	+
Sabharwal (92)	+	+	+	+	+	±	±	±	+	±	-	+	+	+	+	+	±	+
Shaw (93)	+	+	+	+	+	±	+	+	+	+	±	±	+	+	+	+	+	+
Lee (94)	+	+	+	+	+	±	±	-	+	±	+	±	+	+	+	+	±	-
Merhige (95)	+	+	+	+	+	±	+	+	±	±	-	±	+	+	NA	NA	±	-
Rumberger (96)	+	+	+	+	+	+	+	+	±	±	-	+	+	+	+	+	+	±

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18
Shaw (45)	+	+	+	+	+	±	+	+	+	+	+	±	+	+	+	+	+	+
Shreibati (37)	+	+	+	+	+	+	+	±	±	±	-	±	+	+	+	+	±	+
Cheezum (40)	+	+	+	+	+	±	+	+	±	±	-	+	+	+	NA	NA	+	±
Hernández (44)	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Menon (97)	+	+	+	+	+	±	+	±	±	±	-	±	+	+	NA	NA	±	±
Chamuleau (98)	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	±
Stacul (32)	+	+	+	+	±	±	±	+	+	±	-	±	±	+	NA	NA	±	±
Min (38)	+	+	+	+	+	+	+	±	±	+	-	+	+	+	+	+	+	+
Dorenkamp (99)	+	+	+	+	+	±	+	±	±	±	+	+	+	+	+	+	+	±

Figure caption

Figure 2: Quality assessment of the included economic evaluations and decision models using the modified CHEERS checklist

Reviewers judgments of the quality of included economic evaluations and decision models, according to a modified version of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

yes (green/+) indicates high quality or low risk of bias, *no (red/-)* indicates poor quality or high risk of bias, *moderate (orange/±)* indicates moderate quality or moderate risk of bias. *NA (white)* indicates not appropriate/not applicable.

Table 1: Type of sensitivity analysis performed and most important factors influencing the optimal choice of imaging algorithm

Type of Sensitivity analysis	Most important influencing factors	Reference
One-way only	Threshold for PCI ≥70% vs ≥50% stenosis	Hlatky (71)
	Sensitivity to detect severe CAD, Willingness-to-pay threshold	Garber (41)
	Patient managed by interventional cardiologist vs. non-invasive cardiologist	Thom (67)
	Prognosis in patients with FN test results, Nondiagnostic test rate	Lee (94)
	Prior probability of CAD, Test performance, Costs of CAG	Dewey (33)
	Prior probability of CAD, Willingness -to- pay for an additional correct diagnosis	Ferreira (19)
	Prior probability of CAD, Test performance	Dorenkamp (99)
	Prior probability of CAD, Sensitivity of SE	Kim (60)
	Prior probability of CAD, Sensitivity of CMRI, Rate of complications in false-negatives	Moschetti (89)
	Prior probability of CAD, Positivity criterion for CACS	Rumberger (96)
	Prior probability of CAD, (risks of) Radiation exposure in women	Ladapo (6)
	Prior probability of CAD, Test performance, Effective radiation dose	Halpern (59)
	Prior probability of CAD	Raman (77), Boldt (55), Pilz (80), Lee (86), Shaw (73)
	Prevalence of obstructive CAD, Costs of CTCA and CAG	Cole (85)
	Prevalence of CAD	Halpern (65), Patel (63)
	No variables that changed the decision	Shreibati (37), Lorenzoni (82), Shaw (45), Patterson (16)
	Cost data used microcosting analysis vs. reimbursement fees, Treatment time, Overhead costs	Tan (34)
	Costs of CTCA, Costs of CAG, Team experience with CTCA	Catalán (57)
	Costs of CMRI	Iwata (56)
	Costs of FFRct	Hlatky (9)

	Costs of diagnostic tests, Hospitalization, and Medications	Tardif (83)
	CACS cut-point	Raggi (64)
One-way and Two-way	Unit costs of CAG, Sensitivity of CTCA	Cheng (84)
One-way and Bootstrapping	No variables that changed the decision	Hlatky (36)
One-way, Two-way, and Multi-way	Costs of CTCA	Kreisz (53)
One-way and Probabilistic	Test performance, Costs of dual energy CT vs. SPECT	Meyer (76)
	Prior probability of CAD, Test performance, Willingness-to-pay threshold	Hernández (44)
	Probability of CAD, Consequence of a false-positive result	Genders (17)
	Prior probability of CAD, Sensitivity of CTCA	Amemiya (52)
	Prior probability of CAD, CCS grade, Re-identification rate of FN, Costs of CMRI (relative to SPECT)	Walker (58)
	CTCA sensitivity, SPECT sensitivity, CAD prevalence, Costs tests	Min (7)
One-way, Two-way, and Probabilistic	Optimization criterion (i.e. outcome of interest), Prior probability of CAD, Sensitivity/specificity of CTCA	Genders (5)
	Nature and severity of chest pain, Prevalence of CAD, Willingness-to-pay threshold	Kuntz (43)
Probabilistic only	Prior probability of CAD in men	Genders (54)
	Willingness to pay threshold, Costs of FFR, Probability of adverse events	Chamuleau (98)
Multivariable sensitivity analysis and Cox proportional hazards model	No variables that changed the decision	Shaw (93)
Expanding analysis beyond matched cohort	Sample vs. Entire patient population	Min (38)
Subgroup analysis	Prior probability	Sabharwal (92), Hachamovitch (69)
	Known vs. suspected CAD	Muzzarelli (79)
Bootstrapping	No variables that changed the decision	Darlington (75), Min (90), Min (62)
Not performed	Not applicable	Stacul (32),Moschetti (88), Petrov (72), Min (87),

	Marwick (18), Wennike (74), Laufer (66), Merhige (95), Underwood (46), Shaw (70), Nielsen (39), CHeezum (40), Menon (97), Marwick (81), Mattera (91), Zacharias (78), Kimura (68), Rogers (12), Demir (61)

Table 2: Non-invasive imaging tests and imaging algorithms[1] analysed

CTCA-based strategies	Reference	MPS-based strategies	Reference	xECG-based strategies	Reference
ms CTCA±CAG	Dewey (33)	Nuclear perfusion imaging	Tardif (83)	xECG	Shreibati (37), Shaw (70), Nielsen (39), Hachamovitch (69), Marwick (81)
eb CTCA±CAG	Dewey (33)	SPECT±CAG	Genders (17), Raman (77), Rumberger (96), Walker (58), Iwata (56), Boldt (55), Ladapo (6), Min (7), Lee (86), Kuntz (43), Thom (67), Merhige (95), Sabharwal (92), Patterson (16), Shaw (73), Muzzarelli (79), Garber (41), Tan (34), Hernández (44), Hlatky (36), Meyer (76), Shaw (45)	xECG±CTCA±CAG	Ladapo (6), Ferreira (19), Halpern (59)
md CTCA	Min (90), Min (38)	SPECT±CTCA±CAG	Min (7)	xECG±MPS±CAG	Ferreira (19), Underwood (46), Raggi (64)
64s-CTCA±CAG	Kreisz (53), Catalán (57)	MPS±CAG	Shaw (93), Ferreira (19), Underwood (46), Halpern (59), Demir (61)	xECG±CAG	Raman (77), Rumberger (96), Walker (58), Ladapo (6), Dewey (33), Kuntz (43), Marwick (18), Lorenzoni (82), Sabharwal (92), Kim (60), Underwood (46), Patterson (16), Muzzarelli (79), Garber (41), Tan (34), Hernández (44), Halpern (59), Marwick (81)
64s-CTCA	Stacul (32)	MPS±CTCA±CAG	Halpern (59)	xECG±SE±CAG	Lorenzoni (82), Tan (34), Zacharias (78),

[1] See footnotes Table 2. PTCA percutaneous transluminal coronary angioplasty; ph pharmacologic; ms multislice; eb electron-beam; md multidetector; ct computed tomography

					Marwick (81)
ds CTCA±CAG	Dorenkamp (99)	SPECT±PTCA	Chamuleau (98)	xECG±CMRI±CAG	Walker (58)
CTCA	Genders (17), Min (87), Shreibati (37), Min (62), Nielsen (39), Cheezum (40), Darlington (75)[2]	SPECT±FFR±PTCA	Chamuleau (98)	xECG±SPECT±CAG	Raman (77), Walker (58), Genders (54), Muzarelli (79), Tan (34), Hernández (44)
CTCA±CAG	Genders (17), Genders (5), Ladapo (6), Amemiya (52), Min (7), Halpern (65), Lee (86), Ferreira (19), Patel (63), Hlatky (71), Menon (97), Cole (85), Cheng (84), Hlatky (36), Halpern (59), Kimura (68), Rogers (12), Demir (61)	Planar thallium imaging±CAG	Garber (41)	xECG±MPS	Mattera (91)
CTCA±xECG±CAG	Ladapo (6), Halpern (59)	ph SPECT±CAG	Lee (94)	xECG±SE±SPECT±CAG	Tan (34)
CTCA±SE	Genders (17), Rogers (12)	PET±CAG	Merhige (95), Patterson (16), Garber (41), Hlatky (36)		
CTCA±SE±CAG	Genders (17), Halpern (59)	SPECT	Genders (17), Min (87), Min (62), Min (38), Hachamovitch (69), Wennike (74)	**ETT-based strategies**	**Reference**
CTCA±SPECT	Genders (17)	Dual energy CT MPI±CAG	Meyer (76)	ETT±CAG	Rogers (12), Demir (61)
CTCA±SPECT±CAG	Genders (17), Min (7)	MPS	Min (90), Shreibati (37), Shaw (70), Cheezum (40), Mattera (91)	ETT±SE±CAG	Rogers (12)
CTCA±MPS±CAG	Halpern (59)	x-thallium SPECT±CAG	Laufer (66), Kim (60)	ETT±CACS±CAG	Demir (61)

[2] Triage strategy: neither CTCA nor CAG in the low-risk group, CTCA triage in the intermediate-risk group and CAG in the high-risk group (based on the Duke Clinical Score)

CTCA±CMRI	Genders (17)			ETT±CTCA±CAG	Demir (61)
CTCA±CMRI±CAG	Genders (17)			ETT±ph SE±CAG	Demir (61)
CTCA±CAG±FFRcag	Hlatky (71)			ETT±MPI±CAG	Demir (61)
CTCA±FFRct±CAG	Hlatky (71), Kimura (68)				

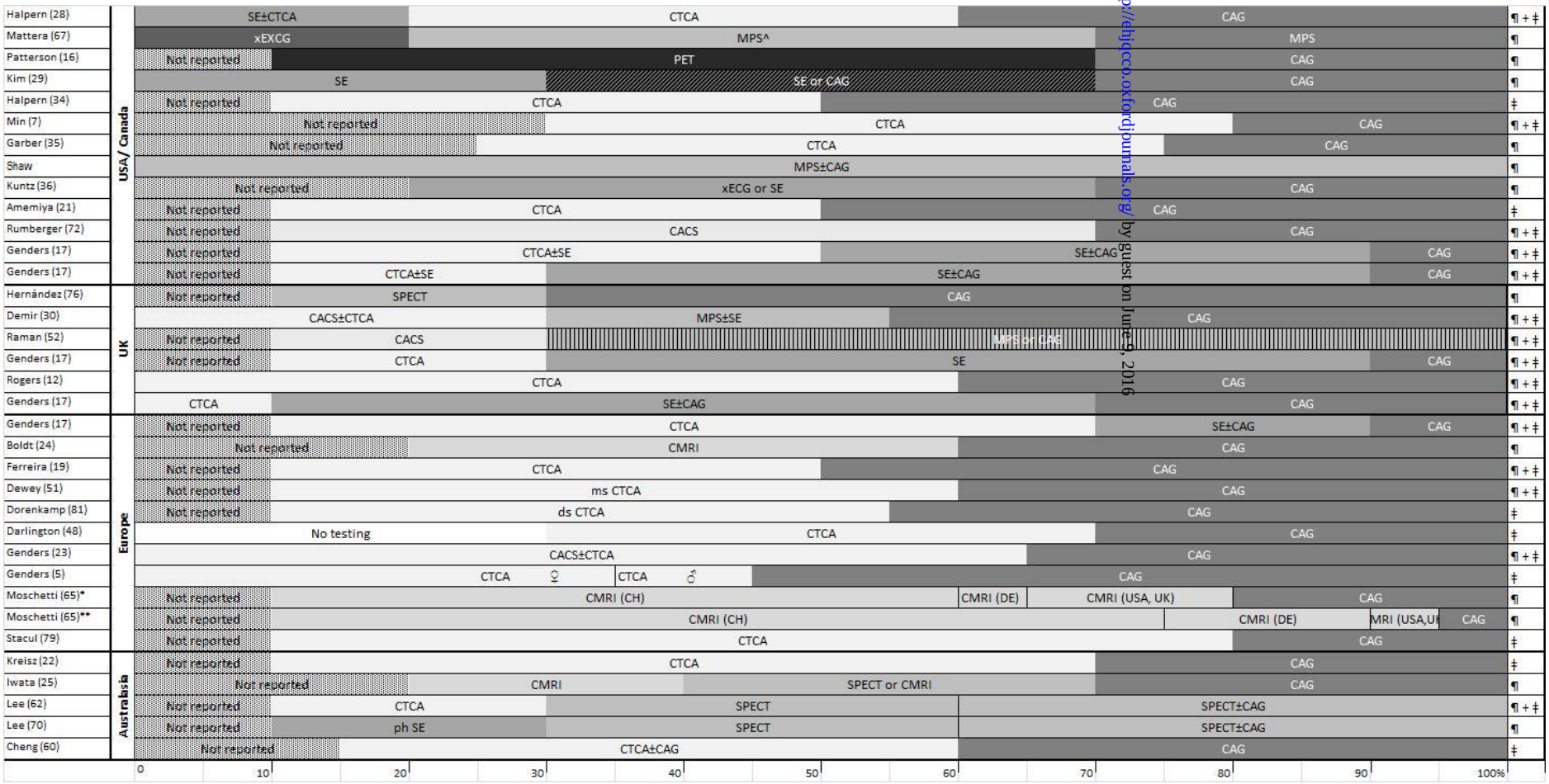
SE-based strategies	**Reference**	**CACS-based strategies**	**Reference**	**CMRI-based strategies**	**Reference**
Contrast SE	Tardif (83)	CACS±CAG	Raman (77), Rumberger (96), Demir (61)	CMRI	Genders (17)
SE	Genders (17), Shreibati (37), Zacharias (78), Marwick(81)	CACS±CTCA±CAG	Genders (54), Ferreira (19)	CMRI±CAG	Genders (17), Walker (58), Iwata (56), Boldt (55), Pilz (80), Petrov (72), Dewey (33), Thom (67)
SE±CAG	Genders (17), Rumberger (96), Ladapo (6), Dewey (33), Ferreira (19), Kuntz (43), Marwick (18), Halpern (59), Lorenzoni (82), Laufer (66), Thom (67), Kim (60), Shaw (73), Garber (41), Tan (34), Wennike (74), Marwick (81), Zacharias (78)	CACS+SPECT±CAG	Raman (77)	CMRI+SE/CTCA/SPECT	Moschetti (88)
ph SE±CAG	Lee (94), Demir (61)	CACS±xECG±CAG	Raggi (64)	CMRI+CAG and FFR	Moschetti (89)
exercise SE±CAG	Lee (94)	CACS±xECG±MPI±CAG	Raggi (64)		

SE±SPECT±CAG	Tan (34)	CACS±CTCA	Rogers (12)	
SE±CTCA± CAG	Halpern (59)			

CAG/FFR	Reference	No testing	Reference
CAG	Genders (17), Kreisz (53), Stacul (32), Catalán (57), Shaw (93), Raman (77), Rumberger (96), Walker (58), Boldt (55), Pilz (80), Petrov (72), Genders (5), Ladapo (6), Amemiya (52), Moschetti (88), Min (7), Halpern (65), Dorenkamp (99), Dewey (33), Ferreira (19), Kuntz (43), Thom (67), Shaw (93), Kim (60), Underwood (46), Patterson (16), Patel (63), Menon (97), Garber (41), Tan (34), Hernández (44), Cole (85), Cheng (84), Wennike (74), Hlatky (9), Hlatky (71), Zacharias (78), Halpern (59), Tan (68), Demir (61), Darlington (75), Shaw (45), Marwick (81)	No testing	Genders (17), Ladapo (6), Amemiya (52), Ferreira (19), Kuntz (43), Kim (60), Meyer (76), Wennike (74), Halpern (59), Zacharias (78)
CAG±FFRcag	Moschetti (89), Halpern (71), Kimura (68)		
FFR±PTCA	Chamuleau (98)		
FFRct	Hlatky (9)		

See footnotes: Table 5

Table 3: Suggested initial imaging test given prior probability by country of analysis***



Imaging algorithms compared

Reference	CACS	ETT	ETT± CACS	ETT± CTCA	ETT± ph SE	ETT± MPS	xECG	ph SE	exerc. SE	SE	MPS	PET	CMRI	planar th. Imaging	ph SPECT	SPECT
Halpern (28)							√*			√*	√*					
Mattera (67)											√					
Patterson (16)							√*					√*				√*
Kim (29)							√*			√*						√*
Halpern (34)																
Min (7)																√*
Garber (35)							√*			√*		√*		√*		√*
Shaw											√*					
Kuntz (36)							√*			√*						√*
Amemiya (21)																
Rumberger (72)	√*						√*			√*						√*
Genders (17)										√ / √*			√ / √*			√ / √*
Genders (17)										√ / √*			√ / √*			√ / √*
Hernández (76)							√*									√*
Demir (30)	√*	√*	√*	√*	√*	√*		√*			√*					
Raman (52)	√*						√*									√*
Genders (17)										√ / √*			√ / √*			√ / √*
Rogers (12)		√*														
Genders (17)										√ / √*			√ / √*			√ / √*
Genders (17)										√ / √*			√ / √*			√ / √*
Boldt (24)													√*			√*
Ferreira (19)										√*	√*					
Dewey (51)							√*			√*			√*			
Dorenkamp (81)																
Darlington (48)																
Genders (23)																
Genders (5)																
Moschetti (65)*													√`			
Moschetti (65)**													√`			
Stacul (79)																
Kreisz (22)																
Iwata (25)													√*			√*
Lee (62)																√*
Lee (70)								√*	√*						√*	
Cheng (60)																

Reference	ms CTCA	eb CTCA	ds CTCA	64s CTCA	CTCA	CTCA± xECG	CACS± CTCA	CACS± SPECT	CTCA± SE	CTCA± MPS	CTCA± SPECT	CTCA± CMRI	xECG± CTCA	SE± CTCA	MPS± CTCA	SPECT± CTCA
Halpern (28)					√*	√*			√*	√*			√*	√*	√*	
Mattera (67)																
Patterson (16)																
Kim (29)																
Halpern (34)					√*											
Min (7)					√*						√*					√*
Garber (35)																
Shaw																
Kuntz (36)																
Amemiya (21)					√*											
Rumberger (72)																
Genders (17)					√ / √*				√ / √*		√ / √*	√ / √*				
Genders (17)					√ / √*				√ / √*		√ / √*	√ / √*				
Hernández (76)																
Demir (30)					√*											
Raman (52)																
Genders (17)					√ / √*				√ / √*		√ / √*	√ / √*				
Rogers (12)							√ / √*		√							
Genders (17)					√ / √*				√ / √*		√ / √*	√ / √*				
Genders (17)					√ / √*				√ / √*		√ / √*	√ / √*				
Boldt (24)																
Ferreira (19)					√*		√*						√*			
Dewey (51)	√*	√*														
Dorenkamp (81)			√*													
Darlington (48)					√											
Genders (23)							√*									
Genders (5)					√*											
Moschetti (65)*																
Moschetti (65)**																
Stacul (79)				√												
Kreisz (22)				√*												
Iwata (25)																
Lee (62)					√*											
Lee (70)																
Cheng (60)					√*											

Reference	xECG± MPS	xECG± SPECT	xECG± SE	xECG±SE± SPECT	SE± SPECT	CAG	CAG± FFR	Med. Therap	No tetst	Prior prob ref. case	Gender ref. case pop.	Mean age ref. case (years)
Halpern (28)						√			√	1% - 60%	♂ + ♀	NR
Mattera (67)	√									0% -70%	♂ + ♀	55±12
Patterson (16)						√				10%-100%	♂ + ♀	50
Kim (29)						√			√	6%-71%	♀	55
Halpern (34)						√				NR	♂ + ♀	NR
Min (7)						√				30%	♂	55
Garber (35)						√				50%	♂	55
Shaw						√				0-15%, 15%-60%, >60%	♀	66±11
Kuntz (36)						√			√	18%, 71%, 95%	♂	55
Amemiya (21)						√		√	√	50%	♂	60
Rumberger (72)						√				NR	♂ + ♀	NR
Genders (17)						√			√	30%	♂	60
Genders (17)						√			√	30%	♀	60
Hernández (76)		√*				√				10.50%	♂ + ♀	60
Demir (30)						√				NR	♂ + ♀	A:60±12, B:58±11
Raman (52)						√				10.50%	♂ + ♀	NR
Genders (17)						√			√	30%	♂	60
Rogers (12)										10%-60%	♂ + ♀	55±9, 52±8, 50±10
Genders (17)						√			√	30%	♀	60
Genders (17)						√			√	30%	♂ + ♀	60
Boldt (24)						√				50%	♂ + ♀	NR
Ferreira (19)	√*					√			√	30%	♂ + ♀	NR
Dewey (51)						√				10%-50%	♂ + ♀	NR
Dorenkamp (81)						√				NR	♂ + ♀	58±8
Darlington (48)						√			√	NR	♂ + ♀	NR
Genders (23)		√*								NR	♂ + ♀	56±10
Genders (5)						√				79% (♂), 65% (♀)	♂ + ♀	60
Moschetti (65)*							√			10%-100%	♂ + ♀	NR
Moschetti (65)**							√			10%-100%	♂ + ♀	NR
Stacul (79)						√				10%-100%	NR	NR
Kreisz (22)						√				10%-90%	♂ + ♀	NR
Iwata (25)										35%	♂ + ♀	NR
Lee (62)										10%-90%	♂ + ♀	62±10
Lee (70)										10%-100%	♂ + ♀	NR
Cheng (60)						√				39%	♂ + ♀	NR

Caption Table 3

*** Only studies reporting the comparative cost-effectiveness of different imaging strategies for patients with stable chest pain at different prior probabilities of CAD.

^ Only MPI when abnormal xECG

√* Imaging strategy ±CAG

√` FFR if CMRI intermediate, CAG if CMRI positive

* All tests performed as outpatient tests

** CAG performed as inpatient test

¶ Compared only functional testing

‡ Compared only anatomical testing

¶ + ‡ Compared both functional and anatomical testing

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