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Cardiac testing for coronary artery disease in potential kidney transplant recipients (Review)

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[Diagnostic Test Accuracy Review]

Cardiac testing for coronary artery disease in potential kidney transplant recipients

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ABSTRACT

Background

Patients with chronic kidney disease (CKD) are at increased risk of coronary artery disease (CAD) and adverse cardiac events. Screening for CAD is therefore an important part of preoperative evaluation for kidney transplant candidates. There is significant interest in the role of non-invasive cardiac investigations and their ability to identify patients at high risk of CAD.

Objectives

We investigated the accuracy of non-invasive cardiac screening tests compared with coronary angiography to detect CAD in patients who are potential kidney transplant recipients.

Search methods

MEDLINE and EMBASE searches (inception to November 2010) were performed to identify studies that assessed the diagnostic accuracy of non-invasive screening tests, using coronary angiography as the reference standard. We also conducted citation tracking via Web of Science and handsearched reference lists of identified primary studies and review articles.

Selection criteria

We included in this review all diagnostic cross sectional, cohort and randomised studies of test accuracy that compared the results of any cardiac test with coronary angiography (the reference standard) relating to patients considered as potential candidates for kidney transplantation or kidney-pancreas transplantation at the time diagnostic tests were performed.

Data collection and analysis

We used a hierarchical modelling strategy to produce summary receiver operating characteristic (SROC) curves, and pooled estimates of sensitivity and specificity. Sensitivity analyses to determine test accuracy were performed if only studies that had full verification or applied a threshold of ≥ 70% stenosis on coronary angiography for the diagnosis of significant CAD were included.

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Main results

The following screening investigations included in the meta-analysis were: dobutamine stress echocardiography (DSE) (13 studies), myocardial perfusion scintigraphy (MPS) (nine studies), echocardiography (three studies), exercise stress electrocardiography (two studies), resting electrocardiography (three studies), and one study each of electron beam computed tomography (EBCT), exercise ventriculography, carotid intimal media thickness (CIMT) and digital subtraction fluorography (DSF). Sufficient studies were present to allow hierarchical summary receiver operating characteristic (HSROC) analysis for DSE and MPS. When including all available studies, both DSE and MPS had moderate sensitivity and specificity in detecting coronary artery stenosis in patients who are kidney transplant candidates [DSE (13 studies) - pooled sensitivity 0.79 (95% CI 0.67 to 0.88), pooled specificity 0.89 (95% CI 0.81 to 0.94); MPS (nine studies) - pooled sensitivity 0.74 (95% CI 0.54 to 0.87), pooled specificity 0.70 (95% CI 0.51 to 0.84)]. When limiting to studies which defined coronary artery stenosis using a reference threshold of ≥ 70% stenosis on coronary angiography, there was little change in these pooled estimates of accuracy [DSE (9 studies) - pooled sensitivity 0.76 (95% CI 0.60 to 0.87), specificity 0.88 (95% CI 0.78 to 0.94); MPS (7 studies) - pooled sensitivity 0.67 (95% CI 0.48 to 0.82), pooled specificity 0.77 (95% CI 0.61 to 0.88)]. There was evidence that DSE had improved accuracy over MPS (P = 0.02) when all studies were included in the analysis, but this was not significant when we excluded studies which did not avoid partial verification or use a reference standard threshold of ≥70% stenosis (P = 0.09).

Authors' conclusions

DSE may perform better than MPS but additional studies directly comparing these cardiac screening tests are needed. Absence of significant CAD may not necessarily correlate with cardiac-event free survival following transplantation. Further research should focus on assessing the ability of functional tests to predict postoperative outcome.

PLAIN LANGUAGE SUMMARY

[Summary title]

[Summary text]

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SUMMARY OF FINDINGS

Summary of findings 1. Summary of results

Summary of results: Results of studies on cardiac testing in kidney transplant candidates

Review question: Comparison of non-invasive cardiac screening tests with coronary angiography for the detection of significant CAD in potential kidney transplant recipients

Patient population: Kidney transplant candidates undergoing pre-transplant cardiac evaluation

Setting: Investigations performed in hospital or in an outpatient setting

Geographical location: Studies were conducted in USA (12 studies), Brazil (4 studies), India, (3 studies) the UK (3 studies), Australia (1 study), Canada (1 study), and Spain (1 study)

Index test : Any non- or minimally invasive test used to assess risk of CAD.

Reference standard: Coronary angiography

Included studies: DSE (13 studies; 745 participants), MPS (9 studies; 582 participants), EST (2 studies; 129 participants), EBCT (1 study; 97 participants), DSF (1 study; 86 participants), exercise ventriculography (1 study; 35 participants), CIMT (1 study; 105 participants), resting wall motion abnormality on echocardiography (2 studies; 265 participants), left ventricular dysfunction on echocardiography (1 study; 52 participants), mitral annular calcification on echocardiography (1 study; 125 participants), resting ECG (3 studies; 263 participants).

Limitations

Only DSE and MPS were evaluated in detail, although these also had only a limited number of included comparisons with small sample sizes. No studies were found investigating cardiopulmonary exercise testing, CT coronary angiography, magnetic resonance angiography or cardiac magnetic resonance imaging. Fewer than five studies were found for each of EBCT, resting ECG, conventional echocardiography, exercise ventriculography, DSF and CIMT. Sparse directly comparative data also resulted in low power to detect important differences in accuracy between tests.

Significant heterogeneity was present among studies investigating the same screening test. Although differences in study population characteristics (e.g. prevalence of chest pain) and test application (diagnostic test threshold, criteria for positive test, choice of stress agent and stress protocol, and operator variability) likely contributed to heterogeneity, we were hindered from estimating their contributions because of relatively sparse data, which resulted in low power.

Partial verification, where not all patients who received screening tests also received coronary angiography, occurred in 5/25 comparisons. This may have affected estimates of sensitivity and specificity.

Two different reference standard thresholds (≥ 70% stenosis or ≥ 50% stenosis) were used in the included studies, with most studies only using one reference standard threshold or the other. An overall analysis pooling the results of all studies regardless of threshold may introduce additional heterogeneity due to a threshold effect.

Results

Test	DSE	MPS
Number of studies [all studies]	13	9
Number of participants [all studies]	745	582
Pooled sensitivity (95% CI) [all studies]	0.79 (0.67 to 0.88)	0.74 (0.54 to 0.87)
Pooled specificity (95% CI) [all studies]	0.89 (0.81 to 0.94)	0.70 (0.51 to 0.84)
Number of studies [≥ 70% stenosis]	9	7

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Number of participants [≥ 70% stenosis]	668	517
Pooled sensitivity (95% CI) [≥ 70% stenosis]	0.76 (0.60 to 0.87)	0.67 (0.48 to 0.82)
Pooled specificity (95% CI) [≥ 70% stenosis]	0.88 (0.78 to 0.94)	0.77 (0.61 to 0.88)
Number of false diagnoses of ≤ 70% coronary artery stenosis in a standard population of 100 patients (false negative rate)	24 (13 to 40) per 100	33 (18 to 52) per 100
Number of false diagnoses of ≥ 70% coronary artery stenosis in a standard population of 1000 patients (false positive rate)	12 (6 to 22) per 100	23 (12 to 39) per 100
Positive likelihood ratio [≥ 70% stenosis] (95% CI)	6.44 (3.03 to 13.70)	2.89 (1.39 to 5.99)
Negative likelihood ratio [≥ 70% stenosis] (95% CI)	0.26 (0.13 to 0.50)	0.43 (0.23 to 0.80)
Post test probability after positive screening test result for a patient with low risk (10% to 29% pre test probability) disease	42% to 72%	24% to 54%
Post test probability after positive screening test result for a patient with intermediate risk (30% to 59% pre test probability) disease	73% to 90%	55% to 81%
Post test probability after positive screening test result for a patient with high risk (60% to 90% pre test probability) disease	91% to 98%	81% to 96%
Post test probability after negative screening test result for a patient with low risk (10% to 29% pre test probability) disease	3% to 10%	5% to 15%
Post test probability after negative screening test result for a patient with intermediate risk (30% to 59% pre test probability) disease	10% to 27%	16% to 38%
Post test probability after negative screening test result for a patient with high risk (60% to 90% pre test probability) disease	28% to 70%	39% to 79%

Conclusions and comments

Both tests, especially DSE, have a role as triage tests for intermediate risk transplant candidates, with negative results precluding the need for further evaluation with coronary angiography, thereby avoiding unnecessary risk to patients and potentially reducing healthcare costs.

Given the wide heterogeneity in the estimates for both DSE and MPS, there is still considerable uncertainty in the true post-test probabilities of each test.

Current evidence suggests that, where feasible, DSE should be used as the screening investigation of choice over MPS.

Applicability of tests in clinical practice

Both DSE and MPS have a role as triage tests for the intermediate risk transplant candidates, with negative results reducing the need for further evaluation with coronary angiography. In high risk patients, a positive non-invasive DSE or MPS confirms the high risk of severe CAD, but a negative result does not conclusively rule out severe CAD. In these patients, one may consider proceeding immediately to coronary angiography and avoid using functional tests.

The relatively low sensitivity and specificity of both DSE and MPS however means that they are not perfect triage tests and a significant number of patients will either have their significant CAD missed (false negatives) or be referred in vain for coronary angiography (false positive).

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Despite the shortcomings of the non-invasive tests in their role as triage tests, the very select nature of the population and the unique challenges facing cardiac investigation in this population (particularly, the need to avoid complications arising from an invasive gold standard) and the lack of an alternate better performing test means that we are forced to accept an imperfect triage test.

Functional testing may provide additional prognostic information, although an investigation into this was not included under the scope of this review.

Costs

None of the studies included a cost-effectiveness evaluation. MPS is known to be more expensive than DSE, although both are less expensive than the reference standard, coronary angiography.

CAD - coronary artery disease; CI: confidence interval; CIMT: carotid intimal medial thickness; DSE: Dobutamine stress echocardiography; MPS: Myocardial perfusion scintigraphy

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BACKGROUND

Kidney transplantation remains the best treatment for patients with end-stage kidney disease (ESKD) in terms of prolonging survival and improving quality of life. However, research has shown that transplantation causes significant cardiovascular stress around the time of the operation, and the incidence of myocardial infarction has been estimated to be approximately 5% (Gunnarsson 1984; Lentine 2005). Cardiovascular disease accounts for almost half (40% to 55%) of all deaths following kidney transplantation (Briggs 2001). Screening for coronary artery disease (CAD) is therefore an important part of evaluation for kidney transplantation and a key decision tool to identify which patients need specialised heart imaging tests (coronary angiography) and when. Clinical practice varies considerably in how patients are selected for testing; some centres test only those patients with significant risk factors, others test all kidney transplant candidates; and in which screening test is used (Hofmann 2008). The studies we reviewed used tests such as dobutamine stress echocardiography (DSE), myocardial perfusion scintigraphy (MPS) and stress electrocardiography (EST) versus radiographic tests such as calcium scoring, among others (Hofmann 2008).

Clinical practice guidelines from the American Society of Transplantation (Kasiske 2001), United Kingdom Renal Association (Dudley 2008) and Canadian Society of Transplantation (Knoll 2005) advise cardiac stress testing in potential transplant recipients who have symptoms or significant risk factors, but do not recommend a particular screening test. The guidelines indicate that the test should be determined by local availability and expertise. Although various screening tests for CAD are available, it remains unclear which tests perform best for patients with ESKD.

Target condition being diagnosed

The target condition was significant CAD in potential kidney transplant recipients. We defined significant CAD as the presence of at least 50% stenosis in at least one epicardial coronary artery detected on coronary angiography.

Index test(s)

Any non- or minimally invasive test used to assess risk of CAD. These included:

- Stress echocardiography (using either exercise or pharmacological stress, such as DSE)
- MPS using either exercise or pharmacological stress
- EST
- Electron beam computed tomography (EBCT)
- Resting electrocardiography (ECG)
- Conventional echocardiography
- Exercise ventriculography
- Digital subtraction fluorography (DSF)
- Carotid intimal medial thickness (CIMT)
- Cardiopulmonary exercise testing
- Computed tomography (CT) coronary angiography
- Magnetic resonance angiography
- Cardiac magnetic resonance imaging.

Rationale

Severe CAD is strongly associated with the risk of myocardial infarction (MI) (Alderman 1993; Manoharan 2009). Non-invasive cardiac screening tests may enable identification of kidney transplant candidates who are at high risk of significant CAD. Such tests are therefore useful in triaging patients for coronary angiography, a test that provides confirmation of diagnosis and opportunity for timely intervention (endovascular or open surgical intervention, and aggressive risk factor modification, or both). There is significant controversy about which tests should be used in the screening process (Hofmann 2008). Although coronary angiography is the gold standard for detecting coronary artery stenosis, it is invasive, costly, and carries risk of nephrotoxicity, arrhythmia, MI, stroke and femoral artery injury. Although anatomical depiction derived from coronary angiography is a valuable diagnostic asset, the test does not provide perfusion or contractility information when the heart is under physiological stress. Non-invasive investigations such as DSE and MPS have moderate sensitivity and specificity in detecting significant CAD in the general population (Fleischmann 1998; Schinkel 2003). The applicability of these results in patients with ESKD who are potential kidney transplant recipients is however uncertain. Common comorbidities among patients with chronic kidney disease (CKD) are hypertension, cardiomyopathy, calcific vascular disease and atherosclerosis. Compared with the general population, these comorbidities may influence diagnostic test performance in people with CKD.

OBJECTIVES

We investigated the diagnostic accuracy of non-invasive cardiac screening tests versus coronary angiography in potential kidney transplant recipients. We provided summary estimates of diagnostic accuracy for individual index tests to better understand the utility and limitations of these non-invasive tests.

Secondary objectives

We compared the diagnostic accuracy among different screening tests through:

1. Direct comparison: By analysing the results of studies that assessed diagnostic accuracy of two or more tests in the same population head-to-head.
2. Indirect comparison: By comparing the pooled results of studies that assessed accuracy of screening tests in separate populations.

The ability of screening tests to detect severe coronary artery stenosis (≥ 70% stenosis detected on coronary angiography) was also assessed and compared among different screening tests.

Investigation of sources of heterogeneity

We also investigated if diagnostic accuracy varied among studies with different prevalence of symptomatic chest pain and analysed the effect. For this analysis, we included only studies that used a threshold of ≥ 70% stenosis on coronary angiography for the diagnosis of CAD. To avoid partial verification, we considered effects among study participants who underwent both the index test and coronary angiography. This methodology meant that we were able to avoid partial verification.

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METHODS

Criteria for considering studies for this review

Types of studies

We included all diagnostic cross sectional studies, cohort studies and randomised studies of test accuracy that compared cardiac test accuracy with results obtained from coronary angiography (the reference standard).

Participants

Study participants included all patients who were considered to be potential candidates for kidney transplantation or kidney-pancreas transplantation at the time the diagnostic tests were performed.

Inclusion criteria

We included studies reporting outcomes relating to patients considered to be potential candidates for kidney transplantation or kidney-pancreas transplantation at the time diagnostic tests were performed. To ensure that our review was accessible and succinct, we chose to limit the population to patients with CKD who were considered candidates for kidney transplantation, but included all possible tests used to diagnose CAD.

Exclusion criteria

Studies were excluded if they did not explicitly state that all study participants were candidates for kidney transplantation. We also excluded studies that investigated cardiac test accuracy in patients with ESKD who were not transplant candidates (i.e. they were unselected dialysis patients, not undergoing pre-transplant assessment). Patients with ESKD who are not transplantation candidates differ from patients who are transplant candidates with respect to several key prognostic variables, such as age and fitness for surgery. These differences in the key prognostic variables may result in differences in disease prevalence and test performance. We also excluded studies which investigated patients with features of acute coronary syndrome as our aim was to investigate the performance of cardiac tests in a preoperative screening context. Where it appeared that only some of the study participants were transplantation candidates, we contacted the study authors requesting separate data for only transplantation candidates.

Index tests

Any non- or minimally invasive test used to assess risk of CAD. These included:

- Stress echocardiography (using either exercise or pharmacological stress, e.g. DSE)
- MPS using either exercise or pharmacological stress
- EST
- EBCT
- ECG
- Conventional echocardiography
- Exercise ventriculography
- DSF
- CIMT
- Cardiopulmonary exercise testing
- CT coronary angiography
- Magnetic resonance angiography
- Cardiac magnetic resonance imaging.

Information regarding the various index tests including the type of result produced, if cut-off values were present, and how differences in cut-off points were handled, is provided in Table 1.

Comparator tests

Any of the listed index tests where they were compared with each other versus the reference standard of coronary angiography.

Target conditions

Coronary artery stenosis was defined as at least 50% narrowing in at least one epicardial coronary artery on coronary angiography. We defined severe coronary artery stenosis as ≥ 70% stenosis on coronary angiography.

Reference standards

Coronary angiography.

Search methods for identification of studies

Electronic searches

We searched the following resources.

- MEDLINE (OvidSP) 1950 - 1 November 2010
- EMBASE (OvidSP) 1980 - November 2010, Week 44

A Trials Search Co-ordinator of the Cochrane Renal Group (RM) formulated specific search strategies for the MEDLINE and EMBASE searches (Appendix 1).

Citation tracking was performed using Web of Science. No restrictions were imposed in terms of language of publication or publication status. To maximise the sensitivity of our search, we avoided the use of methodology filters when searching for diagnostic accuracy studies because even the most sensitive filters have been found to miss relevant studies (de Vet 2008; Doust 2005).

Searching other resources

We handsearched the reference lists of all primary studies and reviews identified by the initial search.

Data collection and analysis

Selection of studies

Two authors independently reviewed the search results, first by title and abstract, and where necessary by review of full text of the study report, to determine inclusion or exclusion. Resulting sets of citations for inclusion were also compared. A third author was available to arbitrate final decisions to include or exclude.

Data extraction and management

A standardised data extraction form was used to abstract study design features and results data from each publication. For each study data were extracted independently by two authors. We extracted: year of publication, country of study, study design, clinical setting, definition of CAD (stenosis percentage on coronary angiogram), the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) methodological items (Reitsma 2009), prevalence of cardiovascular risk factors in the study population (percentages of participants on haemodialysis; with ESKD, diabetes

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mellitus (DM), hypertension; who were male; with history of smoking; and symptomatic of heart disease). We also recorded the numbers of true positives, true negatives, false positives and false negatives. These data were then collated in a spreadsheet. A third author was available to adjudicate on disagreements.

Assessment of methodological quality

Methodological quality of included primary studies was assessed by two authors using a modified QUADAS tool (Smidt 2008; Whiting 2003) that included 11 of the 14 mandatory items (representative spectrum, acceptable reference standard, acceptable delay between tests, partial verification avoided, differential verification avoided, incorporation avoided, reference standard results blinded, index test results blinded, relevant clinical information, uninterpretable results explained, withdrawals explained) (Smidt 2008; Whiting 2003). The operational definitions of the QUADAS items are presented in Appendix 2.

Statistical analysis and data synthesis

Extracted data were used to create forest plots of sensitivity and specificity, to depict study-specific estimates of sensitivity and specificity in receiver operating characteristic (ROC) space for each index test, and to investigate:

1. the diagnostic performance of each index test
2. heterogeneity in the diagnostic performance of each index test according to patient characteristics, study design, and study quality factors (identified in Table 2 where sufficient data were available)
3. the relative diagnostic performance of alternate tests based on all available studies that provided data for at least one test, and when the analysis was restricted to studies that provided data for both tests.

Hierarchical summary receiver operating curve (HSROC) models were fitted using the PROC NLMIXED procedure in SAS9.2®. We applied the HSROC model to derive inferences about diagnostic test accuracy and heterogeneity in test performance where sufficient studies (n ≥ 5) for tests were available. The HSROC model used study specific estimates of sensitivity and specificity to estimate the position and shape of the summary curve (Rutter 2001). The curve was defined by three parameters: threshold (the underlying test positivity rate: a proxy for the cut-point that defines a positive test); accuracy (the diagnostic log odds ratio); and shape (the dependence of accuracy on threshold). Each study provided an estimate for threshold and accuracy which were assumed to be random effects in the model. When there was no evidence of an association between accuracy and threshold, the summary curve was considered symmetric and its position defined by a constant diagnostic odds ratio (DOR). The model estimates were used to obtain summary estimates for sensitivity, specificity, positive and negative likelihood ratios, DORs and 95% confidence intervals (CI), and the corresponding 95% confidence region for each index test. The corresponding area under the curve (AUC) was computed from the constant DOR as part of the analysis.

HSROC model results were used to create plots of estimated summary curves, summary points and confidence regions, superimposed on study-specific estimates of sensitivity and specificity.

We provided summary measures of diagnostic accuracy for:

1. all studies regardless of CAD threshold on coronary angiography
2. studies that reported ≥ 70% stenosis threshold for diagnosis of significant CAD on coronary angiography.

Pairwise comparisons of test performance among alternative index tests were performed using data from studies where comparisons between tests were made in the same study population (direct comparison) or in different study populations (indirect comparison). A covariate of test type was included in the modelling to assess if the SROC curves for tests differed in shape, or overall accuracy. When comparing the relative performance of two index tests, we initially assumed equal variances for random effects for the tests, but extended the models to accommodate unequal variances for random effects where required.

In studies reporting multiple tests in the same participants, results were expressed separately for each test component.

Investigations of heterogeneity

Factors that could influence diagnostic accuracy other than true test performance included those relating to methodological quality and study design, characteristics of the underlying population, and characteristics of the index and reference test. We detailed and compared patient inclusion criteria for each included study. We also investigated heterogeneity statistically by:

1. applying separate models to different subgroups
2. adding covariates to the hierarchical model.

Factors such as differences in study population characteristics (e.g. prevalence of chest pain, hypertension and diabetes) and test application (diagnostic test threshold, criteria for positive test, choice of stress agent and stress protocol, and operator variability) were used to explore any heterogeneity discovered in the analysis for each test separately, and to assess the impact of heterogeneity on the relative accuracy across tests.

For index tests such as ECG and echocardiography, where different definitions of an abnormal test were present, only data that had been measured using the same definitions were combined.

Sensitivity analyses

Where differences were present across studies, we controlled for heterogeneity by conducting sensitivity analyses. In particular, we investigated diagnostic accuracy in studies that:

1. aimed to provide both index tests and reference tests to their study population (studies that avoided verification bias)
2. applied a threshold of diagnosis of severe CAD of ≥ 70% stenosis on coronary angiography
3. consisted entirely of asymptomatic individuals (studies that excluded patients who had either symptoms of cardiac disease or a history of ischaemic heart disease).

RESULTS

Results of the search

The results of electronic database and handsearching are outlined in Figure 1. There were no disagreements between authors about either the number of studies eligible for inclusion, nor data results (κ = 1.0). We identified 26 reports of 25 studies (35 comparisons in

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total). Seven studies compared more than one test versus coronary angiography, and were interrogated to contribute data to more than one test comparison (De Lima 2003; Gang 2007; Garcia-Canton 1998; Garg 2000; Sharma 2005; Sharma 2009; Vandenberg 1996). One study was reported twice (Sharma 2005), and one study (Sharples 2004) could not contribute to the meta-analysis because it reported results per coronary vessel, but not per patient. The diagnostic and treatment pathway is presented at the patient level, but including vessel-level analysis lead to inappropriate weighting in the combined analysis, and the potential for bias from clustering of patients' results. The details of all studies included in the meta-analysis are reported in Characteristics of included studies and Table 2.

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Figure 1. Flow of studies identified in literature search for systematic review of testing for coronary artery disease in potential kidney transplant recipients * Some studies investigate more than one test and so contribute to more than one test comparison CIMT: carotid intimal medial thickness; DSE: dobutamine stress echocardiography; DSF: digital subtraction fluorography; EBCT: electron beam computed tomography; ECG: resting electrocardiography; Echo/LV: echocardiography (left ventricular dysfunction or cardiomegaly); Echo/MAC: echocardiography (mitral

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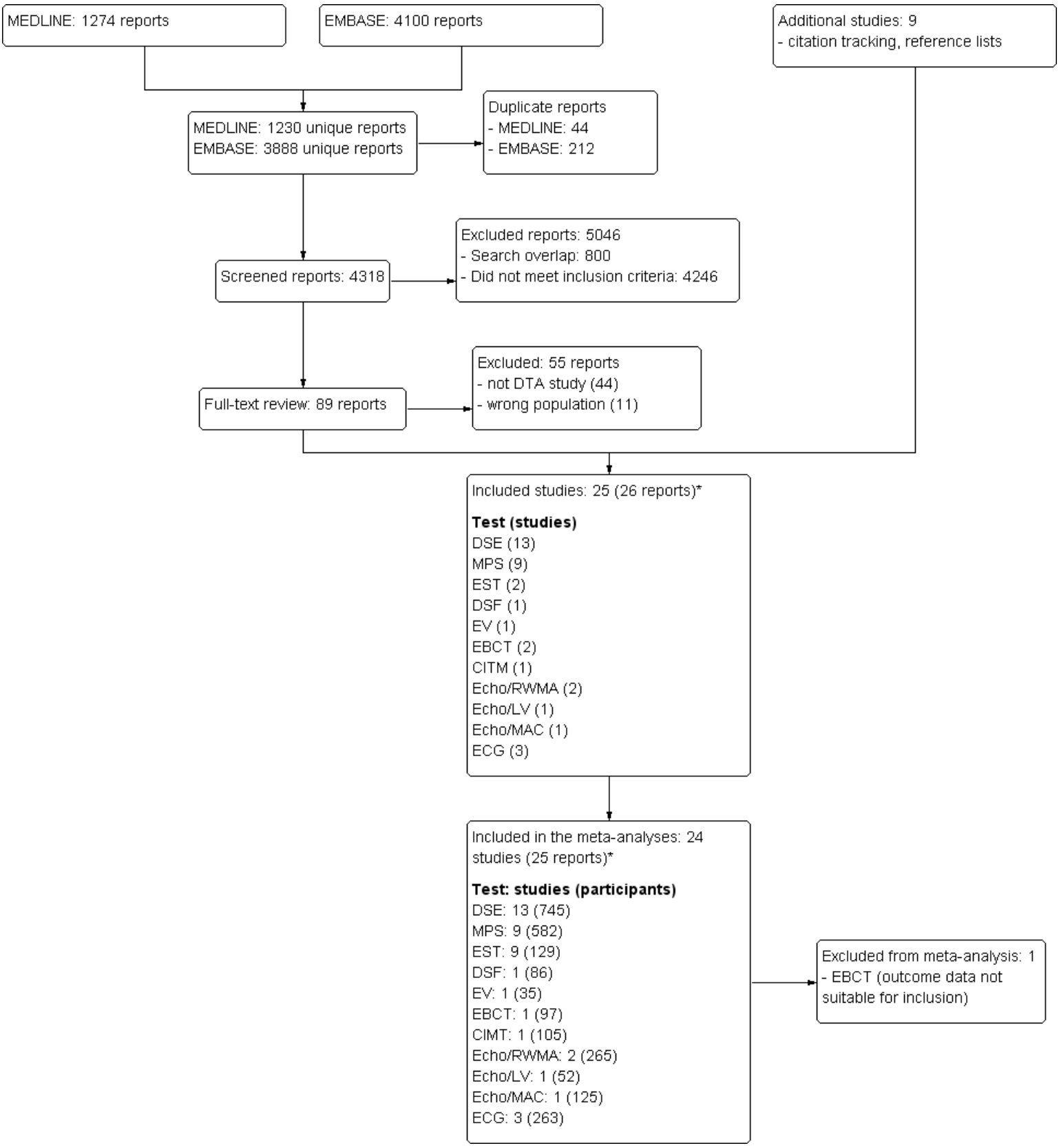
annular calcification); Echo/RWMA: echocardiography (resting wall motion abnormality); EST: exercise stress electrocardiography; EV: exercise ventriculography; MPS: myocardial perfusion scintigraphy



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We identified a further 11 studies (Caglar 2006; Dahan 1995; Dahan 1998; Dahan 2002; De Vriese 2009; Fujimoto 2006; Fukui 2005; Nishimura 2004; Ohtake 2005; Robinson 2007; Schmidt 2001) that reported diagnostic test accuracy in patients with CKD. However, populations in these studies did not consist entirely of patients who were being considered for kidney transplantation - patients on dialysis or with CKD who were not being considered for transplantation were also represented. These studies were excluded from the review because we were unable to obtain separate data for potential kidney transplant recipients only from the authors of these 11 studies. We excluded a total of 55 studies from our review (see Characteristics of excluded studies).

Methodological quality of included studies

Results of the validity assessment are depicted (Figure 2; Figure 3) for the 25 included studies, including Sharples 2004, which could not contribute data. Only 10 included studies provided sufficient information to enable scoring for the 11 nominated QUADAS methodological items. Seven studies satisfied the QUADAS criteria. All included studies satisfied the QUADAS criteria of including study populations that represented the intended target population (potential kidney transplant recipients) and an acceptable reference standard (coronary angiography). Incorporation bias; which occurs when the index test is incorporated in a composite reference standard, often leading to overestimation of diagnostic test accuracy, was not present in any study. No patients were verified with a second or third reference standard because disease status (CAD) was diagnosed only by coronary angiography. Differential verification was therefore also avoided in all studies. The reference standard was not blinded to investigators in three studies that reported coronary angiography being undertaken although results of non-invasive index test were known to the investigators (Brennan 1997; De Lima 2003; Gang 2007). It was unclear if index test results were known at the time of coronary angiography in seven studies (Bennett 1978; Cai 2010; Gowdak 2010; Jassal 2007; Krawczynska 1988; Reis 1995; West 2000). In one study (De Lima 2003, author communication), coronary angiography results were known to investigators who interpreted the index test. It was also unclear if coronary angiography results were known at the time of the index test in eight studies (Bennett 1978; Cai 2010; Gang 2007; Gowdak 2010; Jassal 2007; Krawczynska 1988; Rosario 2010; West 2000). Of the 25 included studies, 20 aimed to provide coronary angiography to all patients who underwent index testing. However, only some participants who underwent index testing proceeded to the reference test in five studies (Bates 1996; Brennan 1997; Cai 2010; Krawczynska 1988; Reis 1995).

Figure 2. Methodological design and reporting quality of studies included in meta-analysis according to risk of bias in quality domains assessed using the Quality Assessment of Diagnostic Accuracy Studies tool: review authors' judgements about each methodological quality item presented as percentages across all included studies

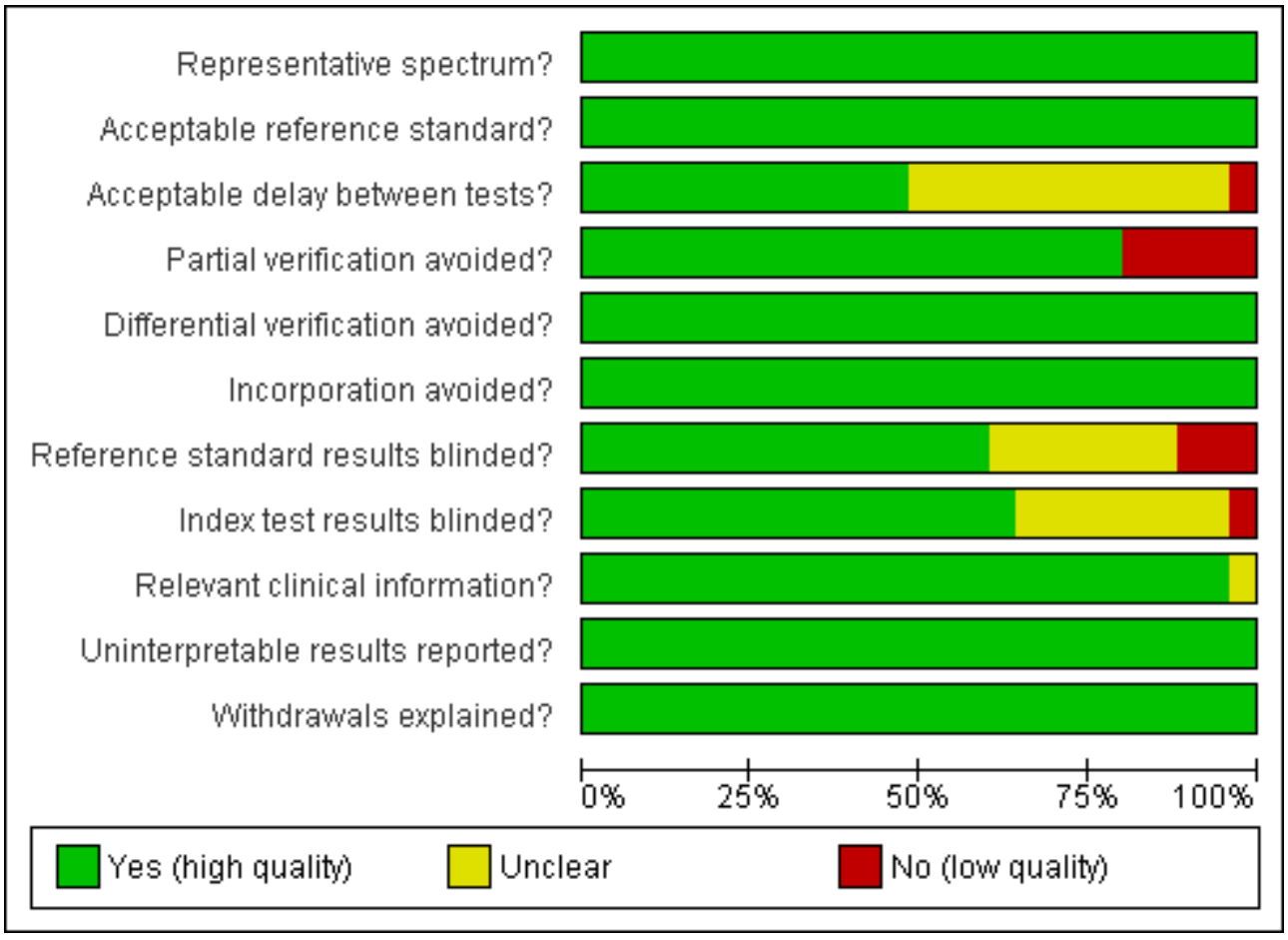

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Figure 3. Methodological quality summary of studies: review authors' judgements about each methodological quality item for each included study using the Quality Assessment of Diagnostic Accuracy Studies tool

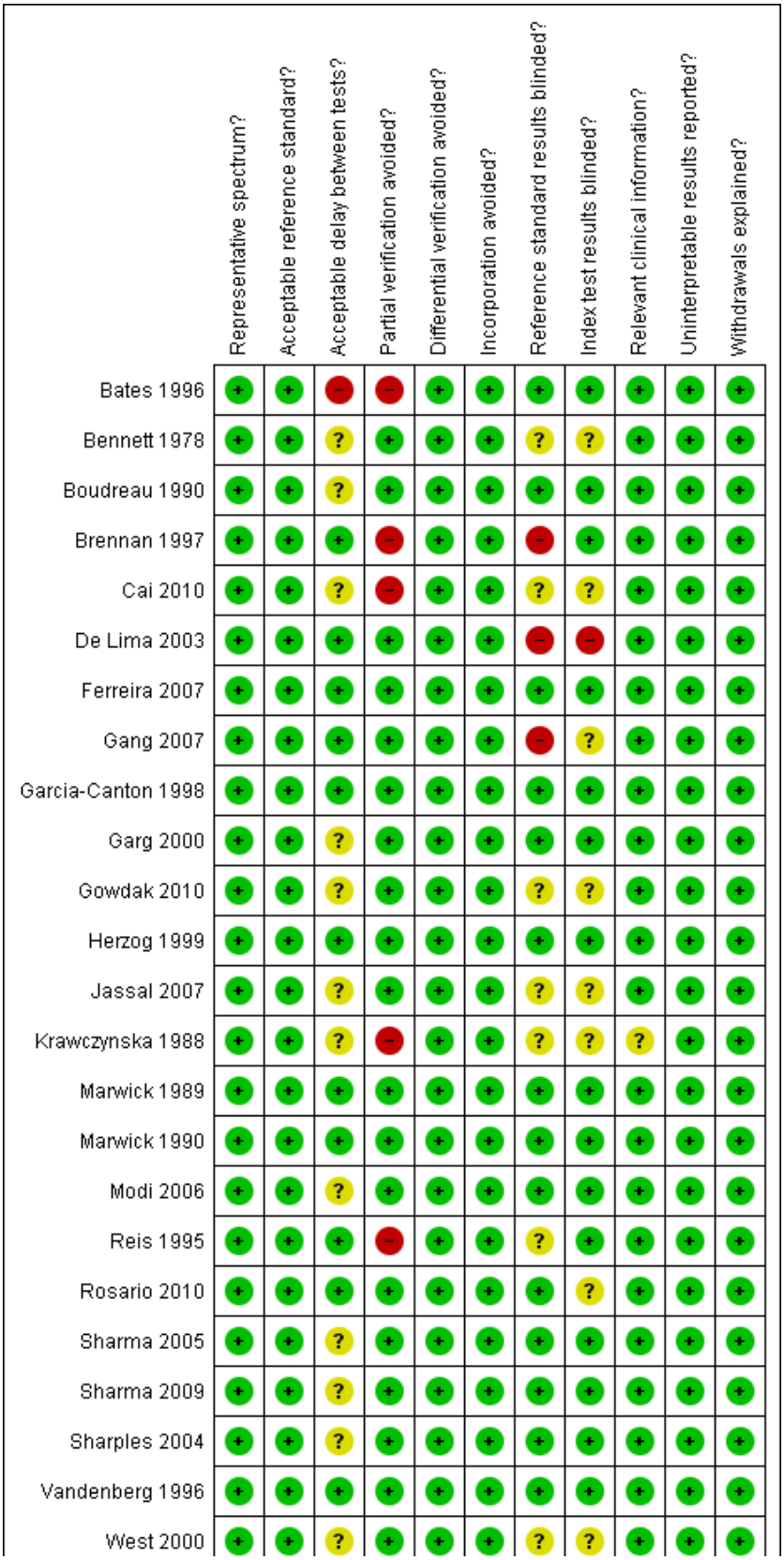

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Figure 3. (Continued)

Findings

We identified 13 studies (745 participants) that evaluated DSE; nine studies (582 participants) of MPS; two exercise EST studies (129 participants), and one study investigated each of EBCT (97 participants), DSF (86 participants), exercise ventriculography (35 participants) and CIMT (105 participants). Two studies (265 participants) investigated the relationship between resting wall motion abnormality on resting transthoracic echocardiography and significant CAD. One study (125 participants) also investigated the relationship between mitral annulus calcification on echocardiography and CAD. Another study (52 participants) investigated the relationship between abnormal echocardiography (left ventricular dysfunction or cardiomegaly) and CAD. Three studies (263 participants) investigated the relationship between abnormal resting ECG and CAD. No studies of diagnostic test accuracy were identified for CT coronary angiography, cardiopulmonary exercise testing, magnetic resonance angiography, or cardiac magnetic resonance imaging.

A forest plot of the study estimates of sensitivity and specificity for each test is shown in Figure 4. Figure 5 depicts the SROC plot of sensitivity and specificity, arranged by test comparison, for all studies (with one exception) identified and included in the meta-analysis. Jassal 2007 was not included because sensitivity could not be calculated due to a lack of patients with CAD.

Figure 4. Accuracy of tests for coronary artery disease versus coronary angiography (forest plot); CIMT: carotid intimal medial thickness; DSE: dobutamine stress echocardiography; DSF: digital subtraction fluorography; EBCT: electron beam computed tomography; ECG: resting electrocardiography; Echo (LV): echocardiography (left ventricular dysfunction or cardiomegaly; Echo (MAC): echocardiography (mitral annular calcification); Echo (RWMA): echocardiography (resting wall motion abnormality); EST: exercise stress electrocardiography; EV: exercise

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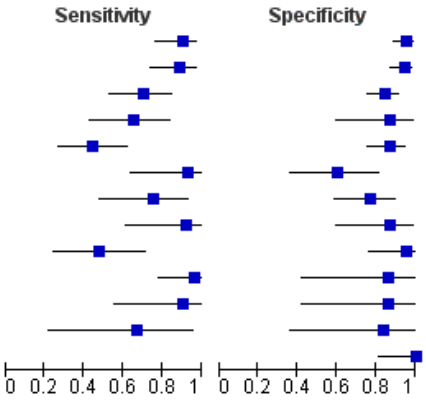
ventriculography; FN: false negative; FP: false positive; MPS: myocardial perfusion scintigraphy; NS: not stated; TN: total negative; TP: total positive

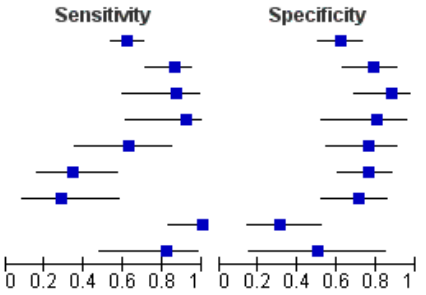
DSE

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Sharma 2009	36	5	4	95	70% or higher	0.90 [0.76, 0.97]	0.95 [0.89, 0.98]
Sharma 2005	32	5	4	84	70% or higher	0.89 [0.74, 0.97]	0.94 [0.87, 0.98]
Ferreira 2007	24	14	10	78	70% or higher	0.71 [0.53, 0.85]	0.85 [0.76, 0.91]
Cai 2010	15	2	8	13	70% or higher	0.65 [0.43, 0.84]	0.87 [0.60, 0.98]
De Lima 2003	15	7	19	48	70% or higher	0.44 [0.27, 0.62]	0.87 [0.76, 0.95]
West 2000	12	8	1	12	70% or higher	0.92 [0.64, 1.00]	0.60 [0.36, 0.81]
Herzog 1999	12	8	4	26	70% or higher	0.75 [0.48, 0.93]	0.76 [0.59, 0.89]
Garcia-Canton 1998	11	2	1	13	70% or higher	0.92 [0.62, 1.00]	0.87 [0.60, 0.98]
Gang 2007	9	1	10	20	70% or higher	0.47 [0.24, 0.71]	0.95 [0.76, 1.00]
Reis 1995	22	1	1	6	50%	0.96 [0.78, 1.00]	0.86 [0.42, 1.00]
Bates 1996	9	1	1	6	50%	0.90 [0.55, 1.00]	0.86 [0.42, 1.00]
Brennan 1997	4	1	2	5	50%	0.67 [0.22, 0.96]	0.83 [0.36, 1.00]
Jassal 2007	0	0	0	18	50%	Not estimable	1.00 [0.81, 1.00]



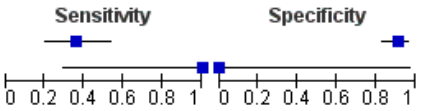
MPS

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Gowdak 2010	85	31	52	51	70% or higher	0.62 [0.53, 0.70]	0.62 [0.51, 0.73]
Boudreau 1990	36	8	6	30	70% or higher	0.86 [0.71, 0.95]	0.79 [0.63, 0.90]
Worthley 2003	13	3	2	22	70% or higher	0.87 [0.60, 0.98]	0.88 [0.69, 0.97]
Garcia-Canton 1998	11	3	1	12	70% or higher	0.92 [0.62, 1.00]	0.80 [0.52, 0.96]
Vandenberg 1996	10	6	6	19	70% or higher	0.63 [0.35, 0.85]	0.76 [0.55, 0.91]
De Lima 2003	8	10	15	32	70% or higher	0.35 [0.16, 0.57]	0.76 [0.61, 0.88]
Marwick 1990	4	9	10	22	70% or higher	0.29 [0.08, 0.58]	0.71 [0.52, 0.86]
Krawczynska 1988	20	18	0	8	50%	1.00 [0.83, 1.00]	0.31 [0.14, 0.52]
Garg 2000	9	4	2	4	50%	0.82 [0.48, 0.98]	0.50 [0.16, 0.84]



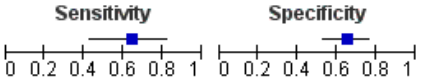
EST

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Sharma 2005	13	8	23	81	70% or higher	0.36 [0.21, 0.54]	0.91 [0.83, 0.96]
Bennett 1978	3	1	0	0	70% or higher	1.00 [0.29, 1.00]	0.00 [0.00, 0.97]



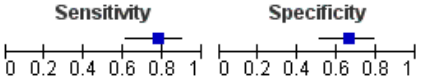
EBCT

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Rosario 2010	16	25	9	47	70% or higher	0.64 [0.43, 0.82]	0.65 [0.53, 0.76]



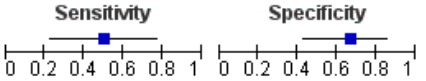
DSF

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Marwick 1989	28	17	8	33	70% or higher	0.78 [0.61, 0.90]	0.66 [0.51, 0.79]



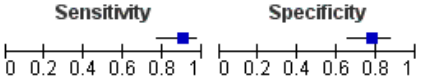
EV

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Vandenberg 1996	7	7	7	14	70% or higher	0.50 [0.23, 0.77]	0.67 [0.43, 0.85]



CIMT

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Modi 2006	38	14	4	49	50%	0.90 [0.77, 0.97]	0.78 [0.66, 0.87]



Echo (RWMA)

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Sharma 2009	13	5	27	95	70% or higher	0.33 [0.19, 0.49]	0.95 [0.89, 0.98]
Sharma 2005	11	4	25	85	70% or higher	0.31 [0.16, 0.48]	0.96 [0.89, 0.99]

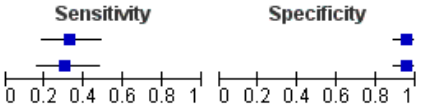


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Figure 4. (Continued)

Sharma 2005	11	4	25	85	70% or higher	0.31 [0.16, 0.48]	0.96 [0.89, 0.99]

Echo (LV)

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Garg 2000	8	5	19	20	50%	0.30 [0.14, 0.50]	0.80 [0.59, 0.93]

Echo (MAC)

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Sharma 2005	22	25	14	64	70% or higher	0.61 [0.43, 0.77]	0.72 [0.61, 0.81]

ECG

Study	TP	FP	FN	TN	%Stenosis	Sensitivity	Specificity
Sharma 2005	27	14	9	75	70% or higher	0.75 [0.58, 0.88]	0.84 [0.75, 0.91]
Gang 2007	9	12	10	9	70% or higher	0.47 [0.24, 0.71]	0.43 [0.22, 0.66]
Garg 2000	51	1	22	24	50%	0.70 [0.58, 0.80]	0.96 [0.80, 1.00]

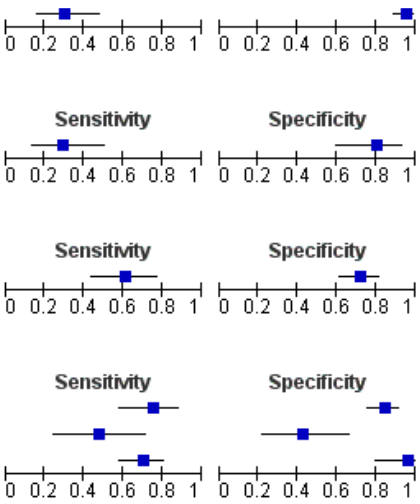

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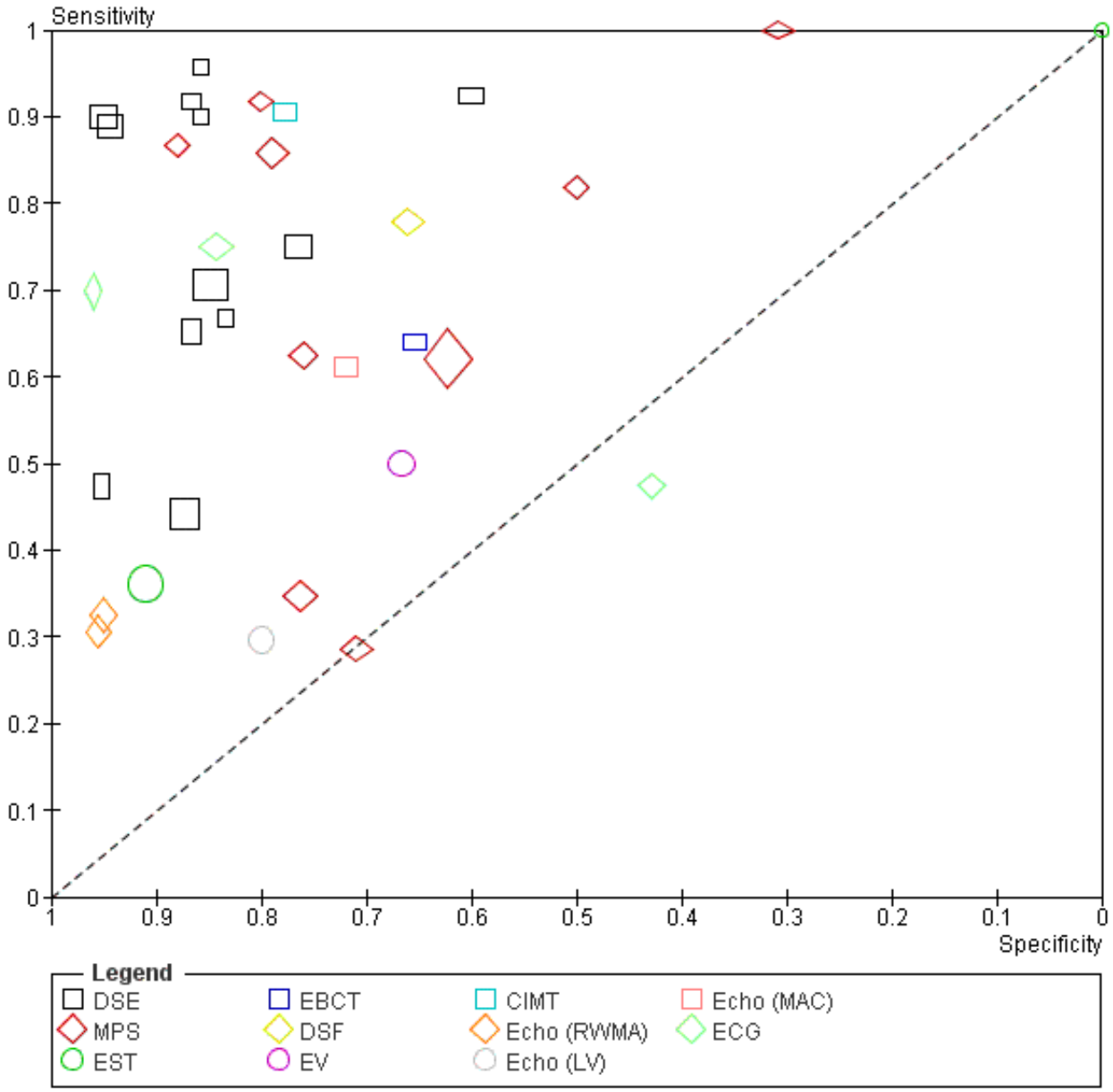
Figure 5. Summary receiver operator curve plot of sensitivity versus specificity for performance of different tests versus coronary angiography. Each symbol represents a study, with the height and width of each symbol being proportional to the inverse standard error of the sensitivity and specificity respectively CIMT: carotid intimal medial thickness; DSE: dobutamine stress echocardiography; DSF: digital subtraction fluorography; EBCT: electron beam computed tomography; ECG: resting electrocardiography; Echo (LV): echocardiography (left ventricular dysfunction or cardiomegaly); Echo (MAC): echocardiography (mitral annular calcification); Echo (RWMA): echocardiography (resting wall motion abnormality); EST: exercise stress electrocardiography; EV: exercise ventriculography; MPS: myocardial perfusion scintigraphy



Dobutamine stress echocardiography (DSE)

DSE was compared with coronary angiography in 13 studies (745 participants) (Bates 1996; Brennan 1997; Cai 2010; De Lima 2003; Ferreira 2007; Gang 2007; Garcia-Canton 1998; Herzog 1999; Jassal 2007; Reis 1995; Sharma 2005; Sharma 2009; West 2000). Using induced wall motion abnormalities during dobutamine stress as a positive result indicating CAD, the sensitivity of DSE varied from 44% to 96% and the specificity from 60% to 100%. Overall, DSE had a DOR of 29.98 (95% CI 12.17 to 73.89) and area under the curve (AUC) of 0.91 (95% CI 0.85 to 0.95). The pooled sensitivity was 0.79 (95% CI 0.67 to 0.88), specificity 0.89 (95% CI 0.81 to 0.94). One study also investigated the relationship between peak systolic

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velocity during DSE for CAD (Sharma 2009). This study reported that ≥ 50% elevation in peak systolic velocity with exercise during DSE was associated with ≥ 70% stenosis on coronary angiography (sensitivity 86%, specificity 88%).

Not all patients who underwent index testing proceeded to have these test results verified by the reference standard. Partial verification was made in three studies (Bates 1996; Brennan 1997; Cai 2010). Furthermore, four studies (Bates 1996; Brennan 1997; Jassal 2007; Reis 1995) used a reference test diagnostic threshold of ≥ 50% stenosis. In the nine studies that used the higher threshold of ≥ 70% stenosis, the pooled sensitivity was 0.76 (95% CI 0.60 to 0.87) and specificity 0.88 (95% CI 0.78 to 0.94) with pooled DOR 23.01 (95% CI 8.08 to 65.51) and AUC 0.90. When only studies that applied a reference standard threshold of ≥ 70% stenosis and avoided partial verification were included, the pooled sensitivity was 0.78 (95% CI 0.59 to 0.89), specificity 0.88 (95% CI 0.76 to 0.94), positive likelihood ratio 6.44 (95% CI 3.03 to 13.70) and negative likelihood ratio 0.26 (95% CI 0.13 to 0.50) with pooled DOR 25.22 (95% CI 7.68 to 82.80) and AUC 0.90.

Overall, there was very strong evidence of heterogeneity among the 13 studies (Figure 6). This remained highly statistically significant even after accounting for differences in reference standard threshold (Figure 7) and partial verification (Figure 8). The remaining studies were similar in the performance of index test and interpretation of test results, but two studies (Sharma 2005; Sharma 2009) were responsible for most of the heterogeneity. There was no statistical evidence of heterogeneity in six studies (De Lima 2003; Ferreira 2007; Gang 2007; Garcia-Canton 1998; Herzog 1999; West 2000). Sharma 2005 and Sharma 2009 differed from other studies in that they originated from a single research group and had the highest proportion of patients who were symptomatic for chest pain. Despite the hypothesis that prevalence of CAD may have accounted for heterogeneity, we could not investigate any relationship between diagnostic accuracy and prevalence of CAD more formally because of the small number of studies, lack of subgrouped patient data, and five studies (Bates 1996; Cai 2010; Garcia-Canton 1998; Jassal 2007; West 2000) did not report proportions of symptomatic patients. Two studies (Bates 1996; Gang 2007) enrolled only patients with DM, and sensitivity was found to range from 47% to 90% and specificity from 86% to 95%.

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Figure 6. Summary receiver operator curve plot of sensitivity versus specificity for performance of different tests versus coronary angiography: Indirect comparison MPS versus DSE. Each symbol represents a study, with the height and width of each symbol being proportional to the inverse standard error of the sensitivity and specificity respectively. The curves represent the summary receiver operator characteristic curves for MPS and DSE. The circles represent the summary estimate of test performance and the zone outline surrounding it represents the 95% confidence region of this summary estimate DSE: dobutamine stress echocardiography; MPS: myocardial perfusion scintigraphy

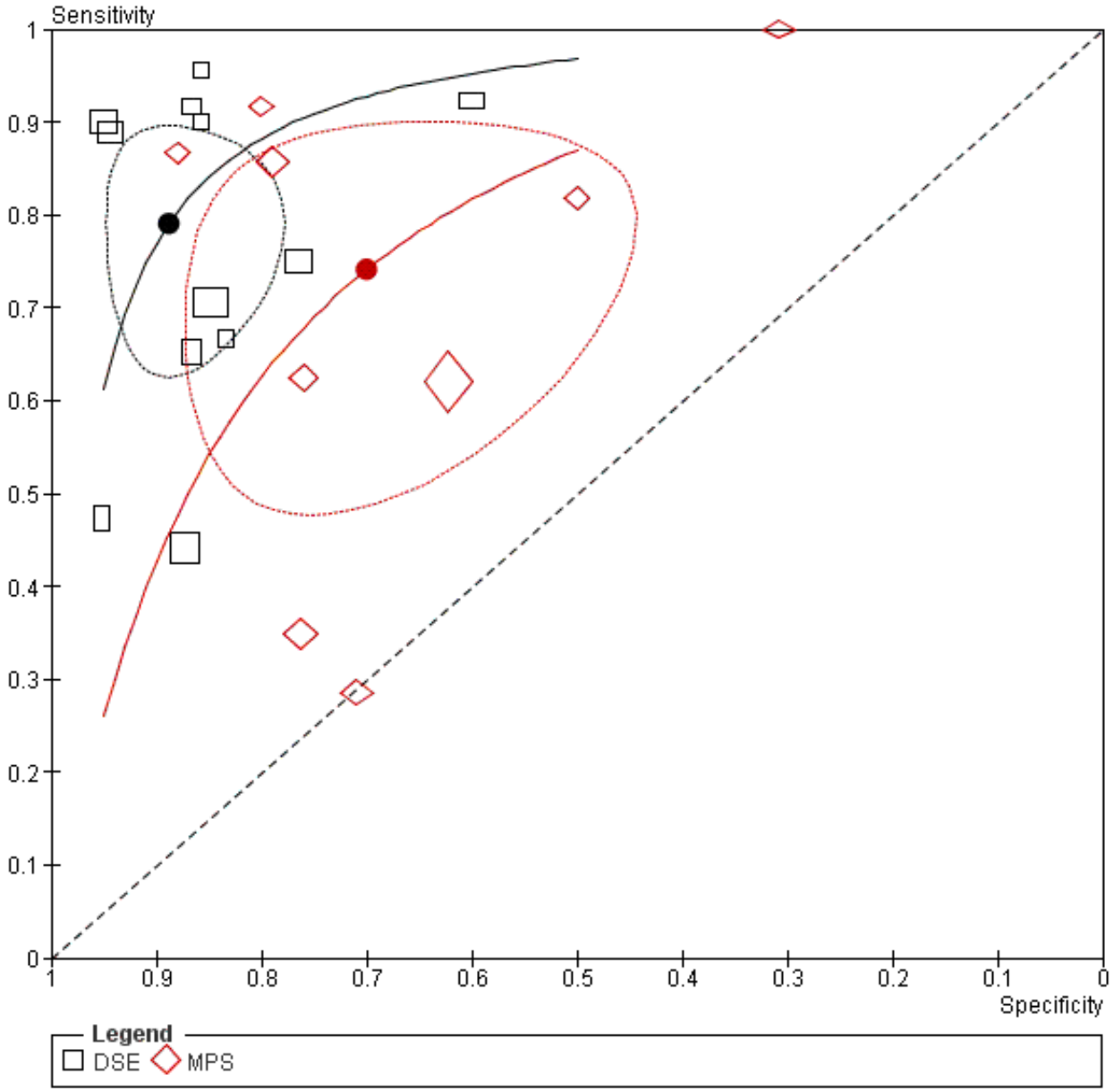

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Figure 7. Summary receiver operator curve plot of sensitivity versus specificity for performance of different tests versus coronary angiography: indirect comparison MPS versus DSE, according to reference standard threshold. Each symbol represents a study, with the height and width of each symbol being proportional to the inverse standard error of the sensitivity and specificity respectively. The curves represent the summary receiver operator characteristic curves for MPS and DSE. The circles represent the summary estimate of test performance and the zone outline surrounding it represents the 95% confidence region of this summary estimate DSE: dobutamine stress echocardiography; MPS: myocardial perfusion scintigraphy

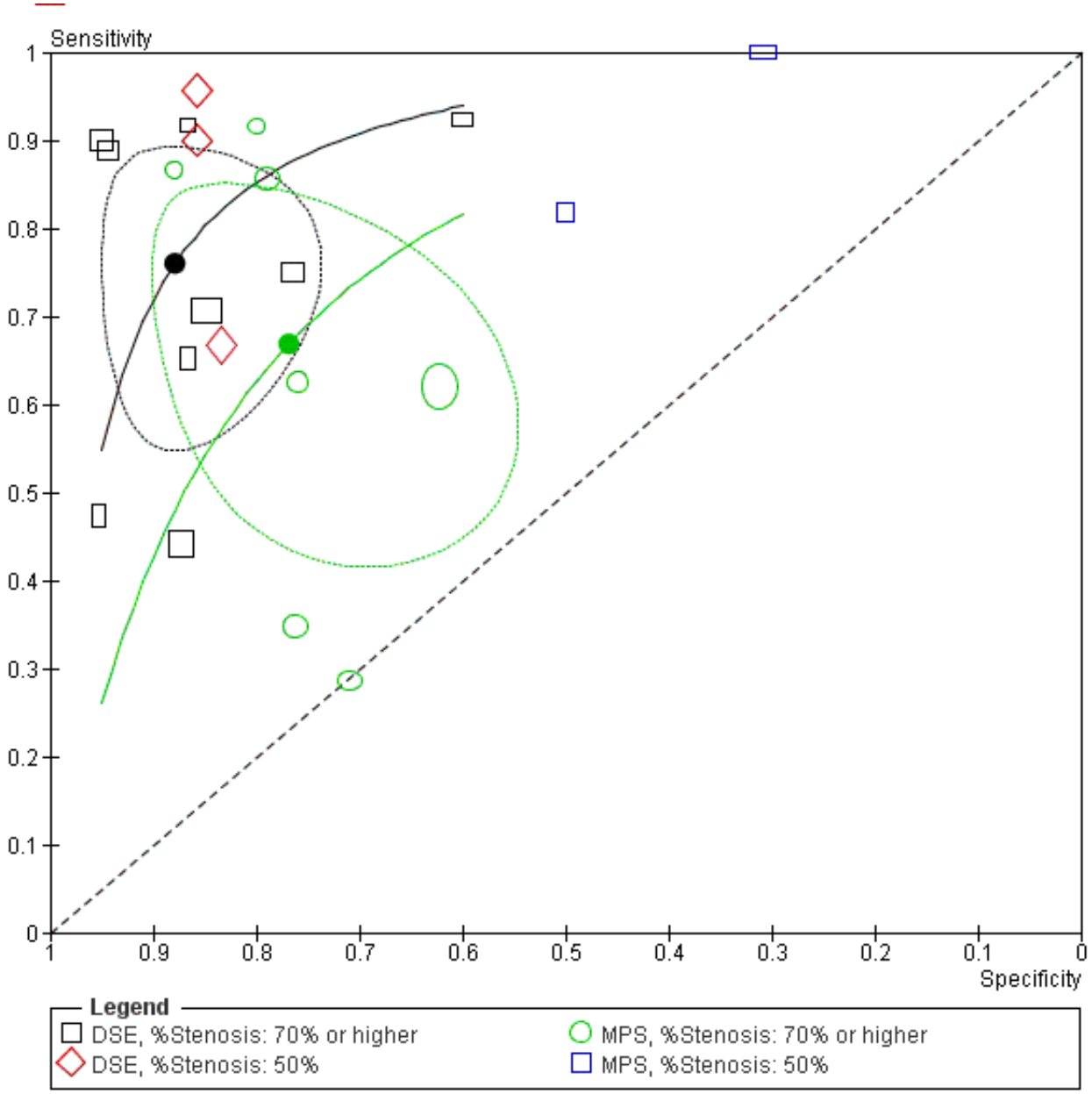

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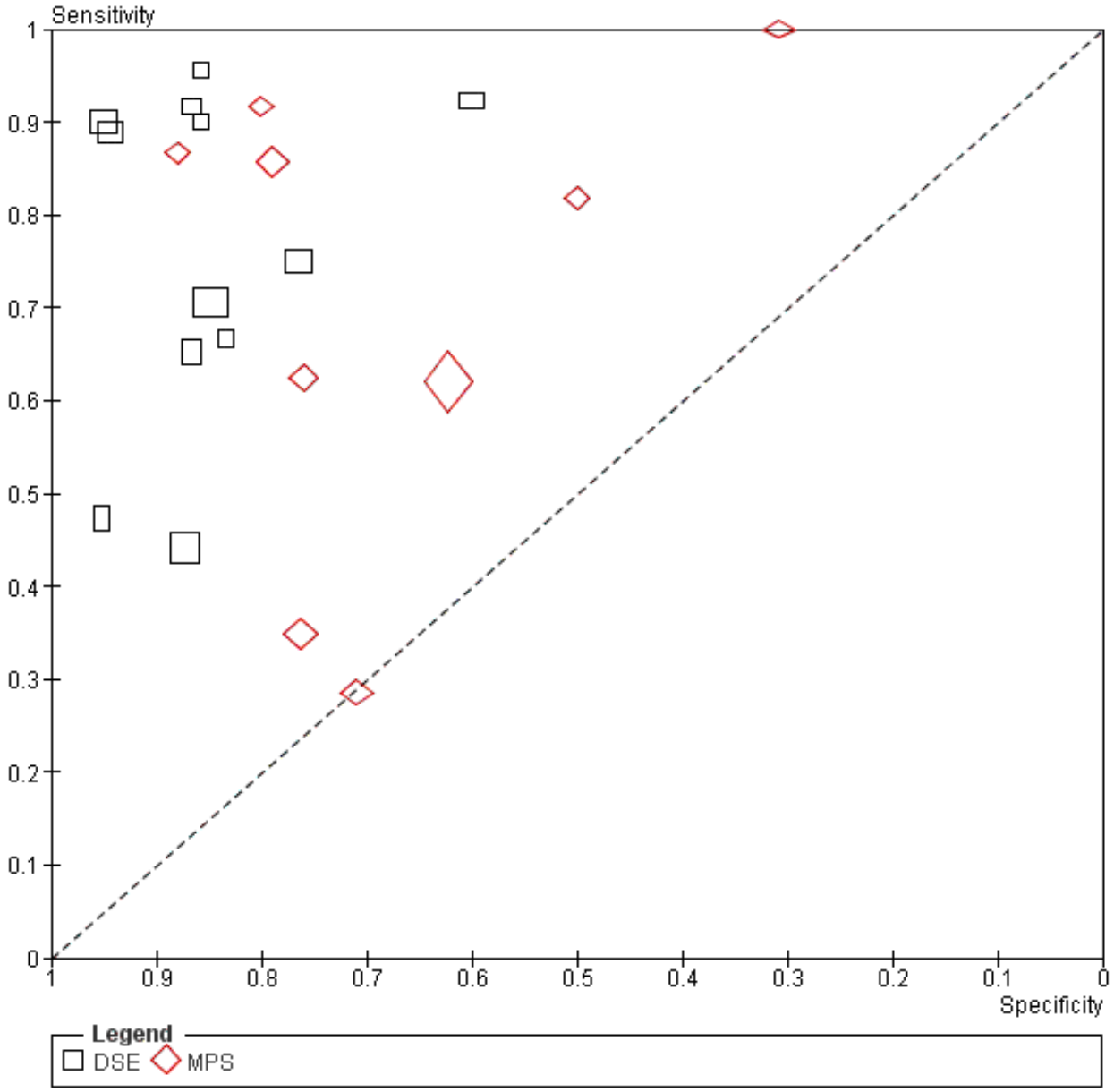
Figure 8. Summary receiver operator curve plot of sensitivity versus specificity for performance of different tests versus coronary angiography: indirect comparison MPS versus DSE, according to presence of partial verification. Each symbol represents a study, with the height and width of each symbol being proportional to the inverse standard error of the sensitivity and specificity respectively. The curves represent the summary receiver operator characteristic curves for MPS and DSE. The circles represent the summary estimate of test performance and the zone outline surrounding it represents the 95% confidence region of this summary estimate DSE: dobutamine stress echocardiography; MPS: myocardial perfusion scintigraphy.



Myocardial perfusion scintigraphy (MPS)

MPS was compared with coronary angiography in nine studies (582 participants) (Boudreau 1990; De Lima 2003; Garcia-Canton 1998; Garg 2000; Gowdak 2010; Krawczynska 1988; Marwick 1990; Vandenberg 1996; Worthley 2003). Sensitivity of MPS varied from 29% to 100% and specificity from 31% to 88%. The pooled summary estimates showed that MPS had a DOR 6.69 (95% CI 2.35 to 19.03) and AUC 0.78 (95% CI 0.64 to 0.88). The pooled sensitivity was 0.74 (95% CI 0.54 to 0.87), and specificity 0.70 (95% CI 0.51 to 0.84).

All but one study (Krawczynska 1988) avoided partial verification bias. Two studies (Garg 2000; Krawczynska 1988) used a threshold of ≥ 50% stenosis and not the reference threshold of ≥ 70% stenosis. When these studies were removed from the analysis, DOR remained unchanged at 6.70 (95% CI 1.84 to 24.41) and AUC 0.78. The pooled

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sensitivity was 0.67 (95% CI 0.48 to 0.82), specificity 0.77 (95% CI 0.61 to 0.88), with positive and negative likelihood ratios of 2.89 (95% CI 1.39 to 5.99) and 0.43 (95% CI 0.23 to 0.80) respectively.

There was very strong evidence of heterogeneity among the nine studies (Figure 6). Heterogeneity remained even after accounting for differences in reference standard threshold (Figure 7) and partial verification (Figure 8). Of the studies that had reference standards of ≥ 70% stenosis and avoided verification bias, four (Boudreau 1990; Garg 2000; Gowdak 2010; Vandenberg 1996) enrolled only patients with DM. Heterogeneity among these four studies of patients with diabetes remained strongly significant, although heterogeneity of the other four studies (De Lima 2003; Garcia-Canton 1998; Marwick 1990; Worthley 2003) decreased when they were excluded. One study (Worthley 2003) that employed tachycardia pacing in some patients to ensure diagnostic MPS had a much higher sensitivity and specificity compared with the other studies and accounted for much of the remaining heterogeneity.

Meaningful investigation into whether prevalence of angina and/or ischaemic heart disease symptoms on diagnostic test performance was not possible as four studies (Garcia-Canton 1998; Garg 2000; Gowdak 2010; Krawczynska 1988) did not provide any information regarding prevalence of angina or ischaemic heart disease symptoms in their study populations.

Other tests

- Two studies (129 participants) (Bennett 1978; Sharma 2005) compared EST with coronary angiography. In Bennett 1978, only 4/7 participants were able to achieve an adequate heart rate and had a diagnostic exercise stress test; the three remaining participants underwent non-diagnostic tests due to suboptimal stress capacity. Sensitivity for this study was 1.0 (95% CI 0.29 to 1.0) and specificity 0 (95% CI 0 to 0.97). In Sharma 2005, which enrolled 125 participants, sensitivity was 0.36 (95% CI 0.21 to 0.54) and specificity 0.91 (95% CI 0.83 to 0.96).
- One study (97 participants) (Rosario 2010) compared EBCT with coronary angiography. This study reported that when a calcium score threshold of 1330.72 Agatston units was used as a cut-off point, sensitivity was 0.64 (95% CI 0.43 to 0.82) and specificity 0.65 (95% CI 0.53 to 0.76), using a reference standard threshold of ≥ 70% stenosis to diagnose CAD.
- One study (35 participants) (Vandenberg 1996) compared exercise radionuclide ventriculography with coronary angiography showing a sensitivity of 0.50 (95% CI 0.23 to 0.77) and a specificity of 0.67 (95% CI 0.43 to 0.85)
- One study (86 participants) (Marwick 1989) compared DSF with coronary angiography, showing a sensitivity of 0.78 (95% CI 0.61 to 0.90) and a specificity of 0.68 (95% CI 0.51 to 0.79).
- One study (105 participants) (Modi 2006) compared CIMT with coronary angiography, showing a sensitivity of 0.90 (95% CI 0.77 to 0.97) and a specificity of 0.78 (95% CI 0.66 to 0.87).
- Three studies (Garg 2000; Sharma 2005; Sharma 2009) correlated echocardiography findings with CAD. Two studies (Sharma 2005; Sharma 2009) used resting wall motion abnormality to define an abnormal index test. These studies, which were performed by the same authors on similar populations, had very similar sensitivity and specificity (Sharma 2005 reported sensitivity of 0.31 (95% CI 0.16 to 0.48) and specificity of 0.96 (95% CI 0.89 to 0.99); Sharma 2009 found sensitivity of 0.33 (95% CI 0.19 to 0.49) and specificity of 0.95 (95% CI 0.89 to 0.98)). Sharma 2005 also compared mitral annular calcification and CAD and reported that this echocardiographic finding had a sensitivity of 0.61 (95% CI 0.43 to 0.77) and specificity of 0.72 (95% CI 0.61 to 0.81). Garg 2000 used echocardiographic criteria of left ventricular dysfunction or cardiomegaly to define test positivity, and reported sensitivity of 0.30 (95% CI 0.14 to 0.50) and specificity of 0.80 (95% CI 0.59 to 0.93).
- Three studies (Gang 2007; Garg 2000; Sharma 2005) investigated resting ECG for CAD diagnosis. In these studies, abnormal resting ECG was defined as the presence of pathological Q waves, left ventricular hypertrophy, ST depression ≥ 1 mm, ST elevation ≥ 1 mm, T wave inversion or bundle branch block. However, results differed. Gang 2007 reported sensitivity of 0.47 (95% CI 0.24 to 0.71) and specificity of 0.43 (95% CI 0.22 to 0.66); Garg 2000 identified sensitivity of 0.70 (95% CI 0.58 to 0.80) and specificity of 0.96 (95% CI 0.80 to 1.00), and Sharma 2005 reported sensitivity of 0.75 (95% CI 0.58 to 0.88) and specificity of 0.84 (95% CI 0.75 to 0.91).

Comparative analysis: DSE versus MPS

Garcia-Canton 1998 and De Lima 2003 directly compared DSE and MPS (Figure 9). Both studies reported that DSE had a higher specificity and equivalent or better sensitivity compared with MPS. Each applied reference standard thresholds of ≥ 70% stenosis for diagnosing CAD, and avoided partial verification bias.

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Figure 9. Summary receiver operator curve plot of sensitivity versus specificity for performance of different tests versus coronary angiography: Direct comparison MPS versus DSE. Each symbol represents a study, with the height and width of each symbol being proportional to the inverse standard error of the sensitivity and specificity respectively. The lines connecting paired MPS and DSE studies denote studies which investigated the accuracy of MPS and DSE in the same study population (direct comparison) DSE: dobutamine stress echocardiography; MPS: myocardial perfusion scintigraphy

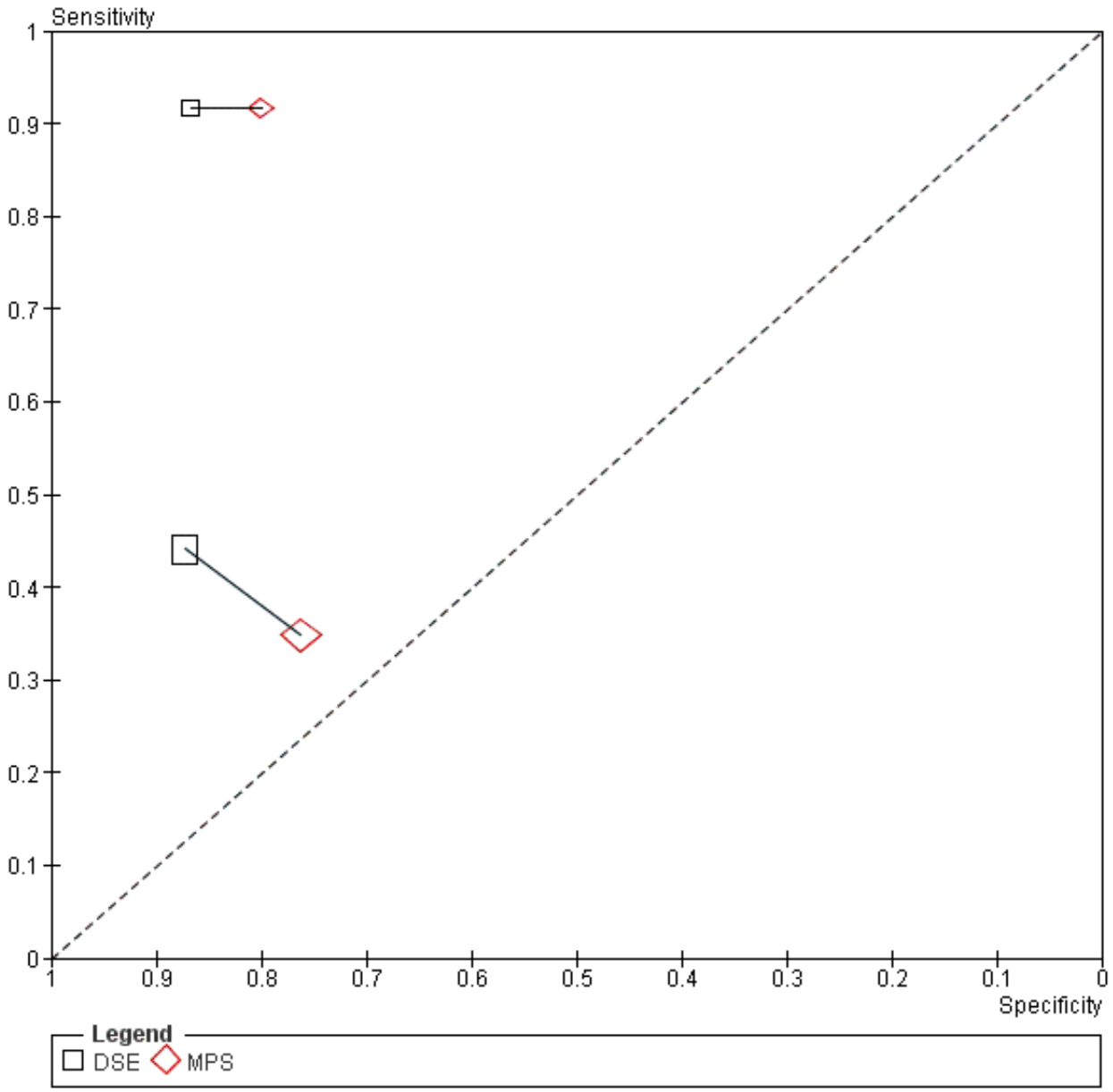

Table 3 and Figure 6 summarise indirect comparison results.

Overall, there was evidence that DSE (13 studies) had better test accuracy than MPS (9 studies) (P = 0.02). Using the results from the earlier analysis, DSE appeared to have a higher pooled sensitivity (DSE: 0.79 (95% CI 0.67 to 0.88) versus MPS: 0.74 (95% CI 0.54 to 0.87) and specificity DSE: 0.89 (95% CI 0.81 to 0.94) versus MPS: 0.70 (95% CI 0.51 to 0.84). The variability in accuracy was smaller for DSE than MPS, demonstrated by the difference in size of the 95% confidence regions in HSROC space. When we included only studies that used definitions of ≥ 70% stenosis on coronary angiography to diagnose severe CAD, DSE (9 studies) had pooled sensitivity and specificity of 0.76 (95% CI 0.60 to 0.87) and 0.88 (95% CI 0.78 to 0.94) respectively. MPS (7 studies) had pooled sensitivity and specificity of 0.67 (95% CI 0.48 to 0.82) and 0.77 (95% CI 0.61 to 0.88) respectively. There was no statistically significant difference between tests (P = 0.09) (Figure 7). When we included only studies where partial verification bias was avoided, DSE (10 studies) had

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pooled sensitivity and specificity of 0.80 (95% CI 0.64 to 0.90) and 0.89 (95% CI 0.79 to 0.95) respectively. MPS (8 studies) had pooled sensitivity and specificity of 0.68 (95% CI 0.51 to 0.81) and 0.75 (95% CI 0.60 to 0.86) respectively. The difference in accuracy between MPS and DSE tests for these studies was statistically significant (P = 0.03) (Figure 8). When only studies that avoided partial verification and had reference thresholds ≥ 70% stenosis on coronary angiography were included in the analysis, there was no evidence of a statistically significant difference between tests (P = 0.09). DSE (8 studies) appeared to have a higher pooled sensitivity: 0.78 (95% CI 0.59 to 0.89) than MPS 0.67 (95% CI 0.48 to 0.82) and DSE specificity: 0.88 (95% CI 0.76 to 0.94) versus 0.77 (95% CI 0.61 to 0.88)] compared with MPS (7 studies), as well as a higher corresponding AUC.

Subgroup analyses

Sparse data, both in terms of numbers of studies and study participants, meant that we were unable to perform meaningful subgroup analyses on the effect of DM or prevalence of angina and symptomatic ischaemic heart disease (IHD) on diagnostic test performance. Only one study (Vandenberg 1996) included a patient population who had no history of angina or IHD. Therefore, a sensitivity analysis of diagnostic accuracy in studies that enrolled only patients who had no symptoms of cardiac disease or history of IHD could not be conducted.

DISCUSSION

Summary of main results

Preliminary findings of comparisons of DSE and MPS versus coronary angiography have been published by our review team (Wang 2011), but this systematic review represents more index tests and several studies that were since identified. Of the many screening tests available, most studies investigated the accuracy of DSE and MPS. Two systematic reviews were conducted that compared DSE and MPS in the general population. These reviews reported that MPS was more sensitive in detecting CAD, but exercise stress echocardiography had higher specificity (Fleischmann 1998; Schinkel 2003). Findings from our review indicate that DSE and MPS have moderate levels of sensitivity and specificity to detect severe coronary artery stenosis.

Our key findings are presented in Summary of findings 1. On direct analysis, DSE had a higher point estimate of sensitivity and specificity compared with MPS. This was statistically significant for both the overall indirect comparison analysis (P = 0.02) and the sensitivity analysis which included only studies that avoided partial verification (P = 0.03). There was no statistical evidence that DSE had higher diagnostic accuracy in the sensitivity analysis which included only studies that avoided partial verification and had reference standard thresholds ≥ 70% stenosis (P = 0.09). However, because results from studies that applied this common threshold were similar to the overall analysis, the lack of statistical significance may have resulted from a reduction of power due to the smaller number of included studies. Although there were few direct comparisons, in two studies that compared DSE and MPS in the same population, DSE had a higher specificity and equivalent or better sensitivity than MPS.

That DSE had a higher specificity than MPS is consistent with the principle that reversible systolic dysfunction (detected by DSE) usually occurs after reversible perfusion abnormalities (detected by MPS). In the general population, MPS should have higher sensitivity but lower specificity than stress echocardiography because systolic dysfunction often occurs only when severe CAD is present. Patients with ESKD often have hypertension, left ventricular hypertrophy and decreased coronary flow reserve, all of which could account for reduced specificity of MPS in kidney transplant candidates (Houghton 1990).

Causes of false negative results in MPS in the general population include balanced triple vessel disease and submaximal heart rate during stress. Although the reason for lower sensitivity in kidney transplant candidates compared with the general population remains unclear, differences in the effect of the stress agent drug among patients with CKD and the general population offers a possible physiological reason for the difference in sensitivity. Dipyridamole, the drug routinely used in MPS, causes vasodilation of coronary blood vessels by promoting accumulation of adenosine, an endogenous vasodilator. Dipyridamole infusion leads to vasodilation of normal coronary arteries, which is interpreted as an appropriate normal increase in cardiac perfusion. The decreased perfusion resulting from reduced vasodilator response of diseased vessels is interpreted as reversible ischaemia. A corresponding rise in heart rate also generally occurs during dipyridamole infusion and is thought to be secondary to vasodilatation, mediated in part by the cardiac nerves. Heart transplant recipients have been shown to have limited vasodilator response to dipyridamole, which has been attributed to increased resting myocardial blood flow in the transplanted heart resulting from increased cardiac workload and cardiac de-innervation (Rechavia 1992). Similarly, patients with CKD (particularly those who have diabetes) may also experience a degree of functional de-innervation as part of an autonomic neuropathy, which would potentially reduce the relative efficacy of dipyridamole. CKD is also invariably associated with arterial calcification and reduced coronary artery flow reserve (Niizuma 2008; Sezer 2007). This may also potentially lead to a decrease in responsiveness to the vasodilating properties of dipyridamole. On the other hand, dobutamine which is commonly used in stress echocardiography, has direct inotropic effects on the cardiac myocyte and potentially may be less affected by the mechanism described.

There was also more variability in the spread of the MPS test results in SROC space compared with DSE. This is probably because MPS is a more subjective test. Several studies of MPS demonstrated considerable inter- and intra-patient result variability, which may limit its diagnostic utility (Akesson 2004; Burkhoff 2001). Variability was also observed in the DSE results, which may be due to unevenness in local expertise to interpret test results across different studies.

Significant heterogeneity was present, which could not be explained by differences in reference threshold and partial verification. Clearly, other factors may have contributed to the clinical heterogeneity in the results. These include differences in study population characteristics (such as prevalence of chest pain, prevalence of diabetes) and test application (diagnostic test threshold, criteria for positive test, choice of stress agent and stress protocol, and operator variability). Limited data from the small numbers of studies and participants meant that we were unable to perform subgroup analyses of the effect of DM and prevalence of angina and IHD on diagnostic performance. Other differences

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across studies may also have played a role. One possible factor was sex of the participants. One study (Gowdak 2010) showed that among patients with diabetes, MPS test performance was influenced by the sex of participants; sensitivity was lower in women (females 56%; males 65%). Accuracy data based on sex was not reported in any of the included studies. Hence, we were unable to determine if the sex of the participant influenced diagnostic accuracy.

Generally, methodological quality was poorly reported. Methodological quality scoring was based on published reports and additional data provided from correspondence with study authors. Unclear reporting of certain methodological issues may not necessarily indicate poor study design; restrictions imposed by journal word limits, or editing, may have precluded reporting all QUADAS items. Several methodological quality items were reported less frequently than others. These included blinding of reference tests (7/25 not reported), blinding of index tests (8/25 not reported), and acceptable delay between tests (12/25 not reported). In addition to the studies where blinding of reference and index tests was uncertain, 3/25 studies reported no blinding of the reference standard; one study reported no blinding of the index test. Therefore, lack of blinding may have affected our results; the overall effect of unblinded reporting of reference and index tests is generally leads to overestimation of diagnostic accuracy (Leeflang 2006).

We did not find any studies that investigated cardiopulmonary exercise testing, CT coronary angiography, magnetic resonance angiography or cardiac magnetic resonance imaging. Fewer than five studies were found for each of EBCT, ECG, conventional echocardiography, exercise ventriculography, DSF and CIMT. This precluded any further meaningful comparisons other than that between DSE and MPS. DSF and exercise ventriculography are seldom used for CAD screening. Nevertheless, results from studies identified for this review (DSF: sensitivity 78%, specificity 66%; exercise ventriculography: sensitivity 50%, specificity 67%) suggest that neither DSF nor exercise ventriculography were likely to be superior to DSE or MPS. EST appeared to have offer high specificity (91%) but poor sensitivity (36%) in the one study that included a sufficient number of participants (Sharma 2005). Resting wall motion abnormality detected on traditional resting transthoracic echocardiography was also found to offer high specificity (95% to 96%) but low sensitivity (31% to 33%). Mitral annular calcification on echocardiography was studied in the same population (Sharma 2005) and this had higher sensitivity (61%) at the expense of lower specificity (72%). The marked variability in sensitivity and specificity of resting ECG confirms that it has no role in triaging patients for CAD. Notwithstanding the limitations posed by few numbers of studies and participants presented, EBCT and calcium scoring methods also appeared to have limited utility in evaluating the cardiac health of potential kidney transplant recipients. This is reflected in the fact that the optimal test performance of EBCT in the only study identified (Rosario 2010) was a calcium score of 1330.72, which is higher than the usual threshold used in the general population. There is also a theoretical disadvantage of calcium scoring methods in potential kidney transplant recipients due to the increased prevalence of arterial calcification in patients with CKD, arising from metabolic bone disease. Although published studies were not identified in this review, other tests that might be expected to have limited application in the pre-transplant setting for patients with CKD include CT coronary angiography (exposure to nephrotoxic IV contrast that could adversely affect any residual kidney function) and magnetic resonance imaging (MRI) or angiography (risk of gadolinium induced nephrogenic systemic fibrosis).

Strengths and weaknesses of the review

A strength of this review was the sensitive electronic search strategy developed that identified both published and unpublished studies. Our search strategy excluded search filters for diagnostic terms because they have limited utility (Leeflang 2006; Ritchie 2007). Other strengths included our analytic approach of combining results from studies with similar methodological characteristics and applying the HSROC model to conduct our analysis. The hierarchical modelling strategy accounted for sampling variability in estimates of sensitivity and specificity (and their correlations) in each study when estimating the random effects. This resulted in accuracy estimates that provided better assessments of underlying common log odds ratios (Macaskill 2003). To ensure that findings were generalisable, we included only studies that investigated only potential kidney transplant recipients. We excluded studies that enrolled participants with ESKD because it could be reasonably anticipated that inclusion of unselected dialysis patients would modify expected differences in underlying prevalence of CAD, and the presence and severity of other comorbidities, as well as differences in clinical rationales for testing. By concentrating on potential transplant candidates our findings may not be generalisable to dialysis or CKD patients who would not benefit from transplantation. Our vigilance in contacting authors to obtain data missing or not reported in studies was rewarded by a satisfying number of responses.

Significant heterogeneity was present among studies that investigated the same screening test. Given that underlying prevalence of disease in a population has potential to alter diagnostic performance (Leeflang 2009), knowledge of the effect of clinical characteristics such as angina or diabetes on diagnostic performance would enable better informed decisions about screening and interpretation of results. Although differences in study population characteristics, such as prevalence of chest pain, and test application (diagnostic test threshold, criteria for positive test, choice of stress agent and stress protocol, and operator variability) were likely to have contributed to heterogeneity, we were hindered in estimating their contributions because of data paucity, which resulted in low power. Consequently, we were unable to derive summary measures of diagnostic performance for specific patient subgroups. Data that were directly comparative were limited and also resulted in low power to detect important differences in accuracy among tests. Incomplete reporting of baseline characteristics and study design features that are necessary for scoring methodological quality was a further limitation that was resolved by contacting study authors to obtain additional data.

Applicability of findings to the review question

Current guidelines for preoperative cardiac evaluation of transplant candidates are unclear about the optimal method of assessment for potential kidney transplant recipients. Patients are often referred for coronary angiography as a result of a positive non-invasive screening test or deemed to be at high risk of CAD. Non-invasive functional tests, such as DSE or MPS, have been used in the general population as a method of triaging patients for coronary

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angiography. Results from our review provide a base to inform clinical decision making that were derived from studies conducted in relevant populations. Table 4 summarises test performance for transplant candidates relative to the general population.

Figure 10 illustrates the applicability of our findings to clinical practice. Patients in the general population who present with stable chest pain for assessment are typically assigned pre-test probabilities of significant CAD of 10% to 29% (low risk), 30% to 59% (intermediate risk) or 60% to 90% (high risk) determined using risk tables (NICE Clinical Guideline 1995). Given the wide heterogeneity in the estimates for both DSE and MPS, there is considerable uncertainty in the true post-test probabilities of each test. However, using the summary estimates in this review, both DSE and MPS may prove useful in ruling out CAD in patients considered to be at low risk for the condition. Patients with positive stress test results warrant additional investigation with coronary angiography. However, the true discriminating value of both tests (especially DSE) is in detecting CAD in intermediate risk patients - a category that includes many potential kidney transplant recipients. Both tests help to classify patients at intermediate risk into either high or low risk categories. When DSE was used, patients at intermediate risk of CAD who tested positive had post-test probability of 73% to 90% (high risk) and those who tested negative were downgraded to low risk (10% to 27%). Both tests, but especially DSE, have roles as triage tests for intermediate risk transplant candidates; negative results can reduce the need for further evaluation with coronary angiography. In high risk patients, a positive non-invasive DSE or MPS test result confirms the high risk of severe CAD, but a negative result does not conclusively rule out severe CAD. These patients can be managed by being referred for coronary angiography, thus avoiding functional tests. Nevertheless, functional testing may provide additional prognostic information, or help to prioritise patients waiting to be referred for coronary angiography in resource-limited areas.

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Figure 10. †Based on the positive and negative likelihood ratios calculated from the systematic review in studies which avoided partial verification and used a reference standard threshold of ≥70% stenosis. DSE had a positive

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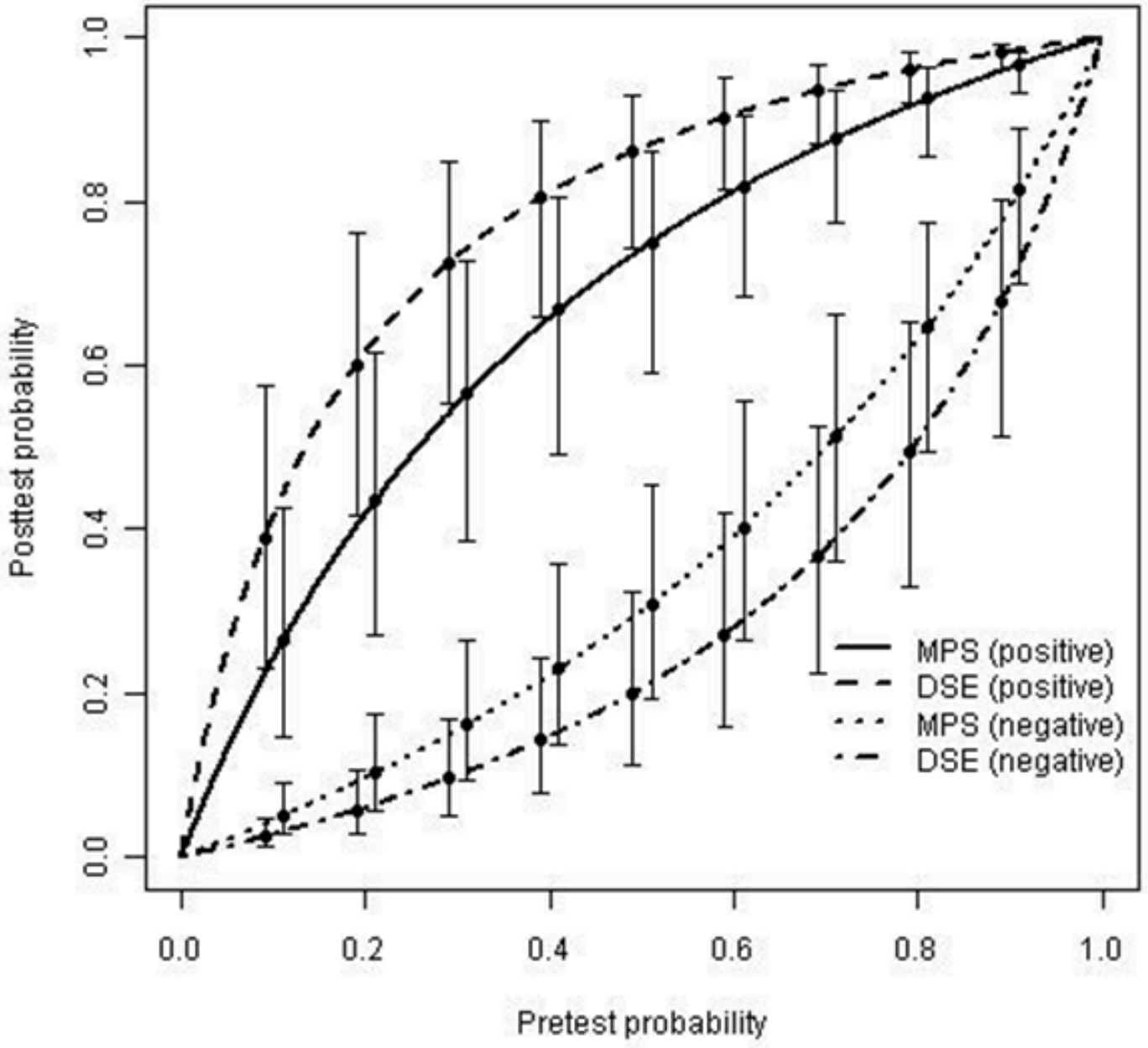
likelihood ratio of 6.44 (95% CI 3.03 to 13.70) and negative likelihood ratio of 0.26 (95% CI 0.13 to 0.50). MPS had a positive likelihood ratio of 2.89 (95% CI 1.39 to 5.99) and negative likelihood ratio of 0.43 (95% CI 0.23 to 0.80).



Test	Pre-test probability of coronary artery disease	Post-test Probability (%) after positive result*	Post-test Probability (%) after negative result*
Dobutamine stress echocardiography (DSE)	Low risk (10-29%)	42-72%	3-10%
	Intermediate risk (30-59%)	73-90%	10-27%
	High risk (60-90%)	91-98%	28-70%
Myocardial perfusion scintigraphy (MPS)	Low risk (10-29%)	24-54%	5-15%
	Intermediate risk (30-59%)	55-81%	16-38%
	High risk (60-90%)	81-96%	39-79%

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DSE and MPS are not perfect triage tests and a significant number of patients will either have their significant CAD missed (false negatives) or be referred unnecessarily for coronary angiography (false positives). Furthermore, the imprecision of the likelihood ratios resulting from significant between-study heterogeneity produces significant uncertainty in the post-test probabilities for both positive and negative tests. A negative DSE test would still, in a low risk population, yield a post-test probability of 10% to 27%. However, both the desire to avoid complications arising from routine referral of such patients to an invasive gold standard investigations, and the lack of a more accurate alternative method of screening may or may not convince clinicians to consider such posterior test probabilities to be sufficiently low to excuse an asymptomatic individual from having further invasive investigation.

Our results need to be considered together with the real world limitations of practising medicine. Despite the apparent superiority of DSE over MPS to detect severe CAD, the interaction of many clinical factors often result in different transplant centres preferring one screening test over another. These factors may be institutional, arising from practicalities such as availability and or expertise of one screening modality, but not both, in a transplant centre; or patient-related issues such as lack of cardiorespiratory fitness or mobility for exercise stress testing. DSE requires IV infusion and is not available in all cardiology departments. Many cardiology practices offer exercise stress echocardiography, but we were unable to identify any studies of exercise stress echocardiography in potential kidney transplant recipients. The diagnostic accuracy of exercise stress echocardiography is likely to be similar to DSE, although there is a higher chance of submaximal, and therefore uninterpretable, stress test results in patients who undergo this test. The patient factors that affect physician choice of screening test are less likely to be an issue in a population of potential kidney transplant recipients compared with people who are not transplantation candidates, given that transplantation candidates represent a selected healthier subpopulation of those with CKD. MPS requires the presence of a nuclear medicine department. Although these departments are found in tertiary referral hospitals, they may not be present in smaller hospitals or resource-poor settings.

For this review, we defined coronary artery stenosis as ≥ 50% stenosis, and severe coronary artery stenosis as ≥ 70% stenosis. Although asymptomatic patients with certain high risk coronary lesions (e.g. left main or equivalent disease, and triple vessel CAD, particularly with left ventricular dysfunction) benefit from revascularisation regardless of symptoms (Eagle 2004), the benefit of preoperative revascularisation before transplant surgery remains questionable. Two RCTs (CARP (McFalls 2004) and DECREASE-V (Poldermans 2007)) did not demonstrate any revascularisation benefit in asymptomatic CAD before major vascular surgery. Nevertheless, the diagnosis of angiographically-proven significant CAD in kidney transplant candidates imposes further implications on patient management. These include consideration of need for perioperative beta blockade, antiplatelet agents and anticoagulation. A recent registry study (De Lima 2010) confirmed that in patients with CKD and significant CAD, medical therapy results in adequate long-term event-free survival. However, in this study, a greater cardiac event rate occurred in patients who fulfilled criteria for revascularisation but declined intervention. Nevertheless, the lack of RCTs specifically addressing this question in kidney transplant settings means that uncertainty remains about if failure to perform coronary intervention when necessary results in an accentuated increased risk of adverse events and death.

AUTHORS' CONCLUSIONS

Implications for practice

Of the non-invasive screening tests available to detect CAD in potential kidney transplant candidates, MPS and DSE have been studied in detail. Both tests, especially DSE, have roles as triage tests for transplant candidates with intermediate of CAD. Negative DSE results preclude need for further evaluation using coronary angiography, avoiding unnecessary risk to patients and potentially reducing healthcare costs. Given the wide heterogeneity in the estimates for both DSE and MPS, considerable uncertainty remains concerning the true post-test probabilities of each test. Current evidence suggests that where feasible DSE should be used as the screening investigation of choice.

Implications for research

The ability to identify patients at high risk of CAD may not necessarily enable clinicians to predict cardiac event-free survival following transplantation. In the postoperative period, other factors such as inflammation, sympathetic nervous system activation, hypercoagulability and hypoxia contribute to increased cardiac morbidity and mortality (Yao 2004). Patients with kidney disease have abnormal coronary microcirculation and reduced coronary flow reserve, which may result in cardiac ischaemic events, even in the absence of macrovascular stenoses (Caliskan 2008; Niizuma 2008; Sezer 2007). Future research examining the ability of functional tests to predict postoperative outcome is urgently needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bates 1996

Clinical features and settings	**Clinical features** • Adult patients who developed insulin dependent DM aged ≤ 25 years and underwent DSE before planned kidney or kidney-pancreas transplantation between January 1989 and July 1993. **Setting** • University Hospital, Indianapolis, Indiana, USA.
Participants	• Number: 53 patients had preoperative screening; 17 received both DSE and coronary angiography

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Bates 1996 *(Continued)*

- DM: 100%
- Angina pectoris: Not reported
- Hypertension: 98%
- Sex: 64% male

Study design	Prospective, cohort study
Target condition and reference standard(s)	**CAD on coronary angiography** • defined by ≥ 50% stenosis
Index and comparator tests	**DSE** • Regional wall motion was graded as normal, hypokinetic, akinetic, or dyskinetic using a 16-segment model at rest, low dose, peak dose, and recovery stages, and assigned a coronary vascular distribution. A study was considered abnormal if a wall motion abnormality involving ≥ 2 segments was present at rest or developed during stress.
Follow-up	Patients were followed-up for a mean of 498 ± 425 days (range 2 to 1269) after transplantation.
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Adult patients with insulin-dependent DM being considered for kidney and/or kidney-pancreas transplantation.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold ≥ 50% stenosis.
Acceptable delay between tests? All tests	No	18 patients underwent cardiac catheterisation within 101 ± 263 days (range = 200 days before to 557 days after) of DSE. Interval progression of CAD is possible.
Partial verification avoided? All tests	No	18/53 patients underwent coronary angiography.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Yes	All available catheterisation studies were interpreted by a blinded, experienced angiographer using digital callipers.
Index test results blinded? All tests	Yes	All studies were interpreted by an experienced echocardiographer blinded to the clinical and stress electrocardiogram data.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.

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Bates 1996 *(Continued)*

Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	All patients missing from the final analysis were accounted for.

Bennett 1978

Clinical features and settings	**Clinical features** • Patients with juvenile insulin-dependent DM and ESKD who presented for kidney transplant cardiac evaluation. Eleven patients with evidence of arteriosclerotic heart disease gave their informed consent for coronary arteriogram and left ventricular angiogram. Seven patients had EST. **Setting** • University of Oregon Health Sciences Center, Oregon, USA
Participants	• Number: 4 participants • DM: 100% • Angina pectoris: percentage of patients with angina not reported • Hypertension:, 100% • Sex: 36% male
Study design	Cohort study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Absolute degree of stenosis recorded for each patient.
Index and comparator tests	**EST**
Follow-up	30-38 months, unless death occurred earlier.
Notes	Three of the seven patients had a non-diagnostic stress test due to inadequate rate as a result of fatigue.

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with juvenile insulin-dependent DM and ESKD who presented for kidney transplant cardiac evaluation.
Acceptable reference standard? All tests	Yes	Coronary artery stenosis measured by coronary angiography. Absolute degree of stenosis recorded for each patient.
Acceptable delay between tests? All tests	Unclear	Unclear, but likely to be only short delay between tests.
Partial verification avoided?	Yes	All patients received angiography.

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Bennett 1978 *(Continued)*

All tests		
Differential verification avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.
Incorporation avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	All patients missing from the final analysis were accounted for.

Boudreau 1990

Clinical features and settings	**Clinical features** • Patients with DM type 1 and ESKD who presented for kidney transplant evaluation **Setting** • University of Minnesota Hospital and Clinics, Minnesota, USA
Participants	• Number: 80 • DM type 1: 100% • Angina pectoris: 12.5% patients had history of myocardial infarction • Hypertension: Not reported • Sex: 64% male
Study design	Cross sectional study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Coronary angiograms were analysed by a blinded observer who was unaware of thallium scan results or the patient's history. Quantitative analysis sought to determine the percentage of cross sectional narrowing and absolute cross sectional diameter. The criterion for positive test results was ≥ 70% reduction in cross sectional area.
Index and comparator tests	**Dipyridamole-Tl-201 scintigraphy MPS (40 oral, 40 IV dipyridamole)** • Scans interpreted by consensus of three experienced radiologists who were unaware of angiography results or patient history. Each view was subdivided into five segments, and the stress views (first set of images) examined for areas of reduced activity. Categorisation as 'indeterminate' was not permit-

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Boudreau 1990 *(Continued)*

	ted. Stress segments classified as abnormal were examined for definite, possible, or absent redistribution. Other categories were 'positive' and 'fixed defect'. Mixed defects were defined as areas of partial redistribution in a fixed defect or fixed defects in association with reversible defects. Quantitative analysis, including count profiles and washout rates, was also performed. However, only qualitative results were used to reach the final diagnosis, since normal quantitative values are unavailable for this test in this patient population.
Follow-up	None.
Notes	Patients were reported as being followed-up long-term to assess the risk factors (including the thallium scan) for cardiac events after kidney transplantation, although no published data were available.

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with type 1 DM and ESKD who presented for kidney transplant evaluation.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Unclear	Likely to be a short delay between tests.
Partial verification avoided? All tests	Yes	All participants who underwent the index test also received the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Yes	Coronary angiograms were analysed by a blinded observer (not the person who performed the angiography) who was unaware of the Tl-201 scan results or the patient's history.
Index test results blinded? All tests	Yes	The scans were interpreted by consensus of three experienced radiologists who were unaware of the angiography results or patient history.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	No missing patients.

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Brennan 1997

Clinical features and settings	**Clinical features** • Patients with ESKD at risk of CAD who presented for kidney transplant cardiac evaluation **Setting** • Washington University and Barnes-Jewish Hospital, St. Louis, Missouri, USA
Participants	• Number: 47 • DM: 56% • Hypertension: 90% • Sex: 45% male • Mean age: 51 years • History of smoking: 61% • Hypercholesterolaemia: 15% • Coronary heart failure: 2% • Clinical evidence CAD: 21%
Study design	Cohort study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • The criterion for positive test results was ≥ 50% reduction in cross sectional area.
Index and comparator tests	**DSE** • Two-dimensional echocardiography as part of pretransplant evaluation. Graded infusions of dobutamine were administered (5 to 40 mg/kg/min) until the maximum predicted heart rate was achieved. If needed, IV atropine (0.4 to 2.0 mg) was given to increase heart rate to ˜85% of the maximum predicted heart rate. The test was terminated if patients developed: significant arrhythmia, severe hypertension or hypotension, or had new or worsening baseline segmental wall motion abnormalities in ≥ 2 major coronary perfusion regions. Segmental wall motion was scored according to American Society of Echocardiography recommendations, using lh-segment model. Each segment was graded using a semi-quantitative scoring system (normal or hyperdynamic (1); hypokinesis (2); akinesis (3); dyskinesis (4)). The wall motion score index was derived as an average of the 16 segments. All studies were reviewed independently by 2 experienced echocardiographers who were blinded to the clinical data.
Follow-up	Follow-up (range 3 to 64 months) data were obtained for all 47 participants.
Notes	Of the 47 patients who underwent DSE, all 5 patients who tested positive received coronary angiography. Seven other patients who had negative DSE received coronary angiography. The decision about providing coronary angiography for those who were index test negative was not made on grounds of clinical or high pre-test suspicion (author correspondence).

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with ESKD at risk of CAD who presented for kidney transplant cardiac evaluation.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 50% stenosis.
Acceptable delay between tests? All tests	Yes	Average time from DSE to coronary angiography < 9 months (author correspondence).

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Brennan 1997 *(Continued)*

Partial verification avoided? All tests	No	Of the 47 patients who underwent DSE, 5 who tested positive underwent coronary angiography, and 7 others who had negative DSE results also underwent coronary angiography. The reason that patients who were index test negative underwent coronary angiography was for other than clinical or high pre-test suspicion (author correspondence)
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	No	It is probable that the person who performed the coronary angiogram was aware of the DSE result. However, because later coronary angiograms were performed by an outside institution, this was not necessarily the case (author correspondence).
Index test results blinded? All tests	Yes	All studies were reviewed independently by two experienced echocardiographers who were blinded to the clinical data.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	All patients missing from the final analysis were accounted for.

Cai 2010

Clinical features and settings	**Clinical features** • Patients with ESKD and intermediate to high risk of CAD awaiting kidney transplantation. CAD defined as presence of at least 1 of: age > 50 years, DM, previous MI or stroke, or extracardiac atherosclerosis **Setting** • Geisinger Medical Center, Danville, Pennsylvania, USA
Participants	Patients at intermediate to high risk of CAD underwent DSE 1 to 12 months (median 5 months) before kidney transplantation • Number: 38 • DM: 54% • Angina pectoris: percentage not reported • Hypertension: 86% • Sex: 64% male
Study design	Retrospective cohort study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography**

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Cai 2010 *(Continued)*

- The criterion for positive test results was ≥ 70% reduction in cross sectional area.

Index and comparator tests	**DSE** • Performed according to a standard dobutamine-atropine protocol and included complete resting echo-Doppler cardiography. Incremental doses of dobutamine (5 to 50 mg/kg/min) infused at 3 minute intervals. If the target (85% predicted maximum for age) heart rate was not reached, and in the absence of inducible ischaemia, 0.25 mg IV atropine administered up to a maximum dose of 1 mg. Echocardiographic images were obtained in the standardised parasternal long- and short-axes (mid-ventricular and apical), and in apical 2-, 3-, 4-, and 5-chamber views at each stage, and were stored digitally. DSE end points were defined as development of new or worsening wall motion abnormality (ischaemia), achievement of > 85% of the predicted maximum heart rate for age, severe symptoms of angina or dyspnoea, SBP < 85 mm Hg or > 220 mm Hg or a decrease in SBP > 20 mm Hg from one stage to the next, > 2 mV ST segment depression in at least 2 consecutive leads, or significant arrhythmias (non-sustained/sustained ventricular/supraventricular tachycardia or high-grade atrioventricular block).
Follow-up	Patients were followed up for a mean of 60 months (range 3 to 145 months) after DSE. The time from kidney transplant to follow-up was 1 to 135 months (median 49 months).
Notes	For the purpose of the analysis, only inducible wall motion abnormalities were counted as positive DSE.

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with ESKD and intermediate to high risk of CAD awaiting kidney transplantation.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Unclear	Likely to be short delay between tests.
Partial verification avoided? All tests	No	38 patients (23 with and 15 without inducible ischaemia on DSE) underwent coronary angiography after DSE.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.

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Cai 2010 *(Continued)*

Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	All patients missing from the final analysis were accounted for.

De Lima 2003

Clinical features and settings	**Clinical features** • Patients presenting for pre-transplant cardiac evaluation based on the presence of at least one of the following characteristics: age > 50 years, DM, angina, previous MI or stroke, left ventricular dysfunction, and extracardiac atherosclerosis. Subjects without these characteristics were not studied because they have a low frequency of coronary events. **Setting** • Hospital das Clínicas, University of São Paulo Medical School, Brazil
Participants	• Number: 150 (data from 24 participants excluded: lost to follow-up (5); declined to continue (19)) • DM: 30% • Angina pectoris: 25% • Hypertension: 95% • Sex: 77% male
Study design	Cohort study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • The criterion for positive test results was ≥ 70% reduction in cross sectional area. Invasive and non-invasive testing were analysed independently by 2 experts in the respective methods without previous knowledge of the experimental hypothesis. Disagreement was arbitrated by a third expert.
Index and comparator tests	**DSE** • Stepwise infusion of dobutamine was started at 5 µg/kg/min and increased to 40 µg/kg/min in 3 minute stages. Inducible ischaemia was defined as hypokinesis or as accentuation of the degree of baseline hypokinesis during the infusion. The test was interrupted if SBP or DBP surpassed 220 mm Hg and 120 mm Hg, respectively, or when SBP fell below 90 mm Hg. • Dipyridamole stress testing (single photon emission-computed tomography with technecium-99m methoxyisobutylisonitrite) * Stress was induced by dipyridamole (0.5 mg/kg IV). Fixed perfusion defects were interpreted as evidence of fibrosis; transient hypoperfusion was interpreted as ischaemia.
Follow-up	Five participants were lost to follow-up. Minimum and mean follow-up periods were 6 and 26 months, respectively. The outcome measure was cardiac events, predefined as sudden death, MI, life-threatening arrhythmia, heart failure, pulmonary oedema, unstable angina, and myocardial revascularisation.
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum?	Yes	Kidney transplantation candidates as part of cardiac evaluation.

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De Lima 2003 *(Continued)*

All tests		
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Yes	Interval between tests was 2 to 6 weeks (author correspondence).
Partial verification avoided? All tests	Yes	All participants who underwent an index test also received the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	No	No blinding for outcomes assessment.
Index test results blinded? All tests	No	No blinding for outcomes assessment.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	The number of tests that were submaximal were reported.
Withdrawals explained? All tests	Yes	All patients missing from the final analysis were accounted for.

Ferreira 2007

Clinical features and settings	**Clinical features** • Kidney transplant candidates with diabetic kidney disease or other causes of CKD or ESKD undergoing cardiac evaluation. Examinations performed one day after haemodialysis. **Setting** • Universidade Federal de São Paulo, Escola Paulista de Medicina, Hospital do Rim e Hipertensão e Hospital São Paulo, Brazil
Participants	• Aged > 40 years, who presented with ≥ 2 risk factors • Number: 126 participants • DM: 27% • Angina pectoris: 12% • Hypertension: not reported

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Ferreira 2007 *(Continued)*

	• Sex: 69% male **Exclusion criteria** • Previous history of MI or surgical or percutaneous myocardial revascularization; unstable angina; decompensated CHF; significant aortic stenosis; pulmonary HTN; hypertrophic cardiomyopathy; inadequate echocardiographic window; atropine use restrictions (glaucoma and obstructive uropathy); irregular dialysis regimen.
Study design	Cross sectional study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • The criterion for positive test results was ≥70% reduction in cross-sectional area.
Index and comparator tests	**Dobutamine/atropine stress echocardiography** • Progressive doses of dobutamine 5, 10, 20, 30 and 40 µg/kg/min, with an increment every 3 minutes. In cases when the final objective of the evaluation had not been reached, 0.25 mg/min atropine was added simultaneously after the third minute of the infusion of 40 µg/kg/min of dobutamine, up to a total maximum cumulative dose of 1 mg. The test was considered diagnostic when either 85% of the maximum for age or echocardiographic signs of myocardial ischaemia was reached. The test was considered non-diagnostic when there were inadequate images for the analysis (lack of definition on ≥ 2 myocardial segments); inability to reach target stress, and premature test withdrawal due to limiting side effects without attaining one of the test aims. • Definitions guiding interpretation were: Normal result defined as uniform increase of systolic movement and thickening of the left ventricular wall and consequent reduction of its final systolic volume (global hyperdynamic response); a positive result for myocardial ischaemia was defined as a new alteration of the reversible segmental contractility or worsening of a pre-existing segmental alteration, in ≥ 2 contiguous myocardial segments.
Follow-up	
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with ESKD who were kidney transplant candidates undergoing cardiac evaluation. Examinations performed one day after haemodialysis.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Yes	Not longer than 2 months.
Partial verification avoided? All tests	Yes	All participants who underwent an index test also received the reference standard test.
Differential verification avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.

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Ferreira 2007 *(Continued)*

Incorporation avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.
Reference standard results blinded? All tests	Yes	The measurement bias was controlled through the "blind" interpretation of the test regarding the coronary angiography, which was considered the reference standard.
Index test results blinded? All tests	Yes	The recorded images were later interpreted by two members who were blinded to the patients' clinical data, as independent observers. The discordance was solved by consensus between the two observers.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	Of 148 patients submitted to the test, 135 finished the protocol, which corresponds to a feasibility of 91%. The reasons that led to test interruption were: attaining 85% of maximum CF for age: 121 (81%); limiting side effects: 13 (9%); echocardiographic signs of ischaemia: 10 (7%) and end of the protocol: 4 (3%).
Withdrawals explained? All tests	Yes	Thirteen patients presented an early withdrawal of the protocol due to limiting side effects: 12 (8.5%) due to hypertensive response and 1 (0.5%) due to severe angina.

Gang 2007

Clinical features and settings	**Clinical features** • Patients with DM and ESKD who presented for kidney transplant cardiac evaluation **Setting** • Muljibhai Patel Urological Hospital, Gujarat, India
Participants	• Number: 40 • Type 2 DM: 100% • ESKD: 100% • Angina pectoris: 5% • Hypertension: 92% • Sex: 90% male
Study design	Cross sectional study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Criterion for positive test results was ≥70% reduction in cross sectional area
Index and comparator tests	**DSE** • DSE was performed by recording images in standard parasternal long- and short-axis and apical 4 chamber and 2 chamber views at baseline, and during stepwise infusion of dobutamine in 3 minute stages at 5, 10, 20, 30 and 40 µg/kg/min. Atropine was administered as needed. DSE end points were target heart rate achieved ([220-age]x0.85), maximum drug dose, intolerable angina, new inducible regional wall motion abnormalities in ≥ 2 coronary vascular territories, ventricular tachycardia, supraventricular tachycardia, hypotension and SBP > 240 mm Hg. **Resting ECG**

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Gang 2007 *(Continued)*

	• Abnormal ECG findings included evidence of left ventricular hypertrophy by voltage criteria (8 patients), evidence of underlying ischaemia, or left bundle branch block.
Follow-up	None
Notes	• Patients underwent DSE followed by coronary angiography as a part of kidney transplant evaluation. • Resting ECG was discounted from the analysis as "abnormal ECG". This was a heterogeneous concept that was suggestive of both ischaemic and non-ischaemic (such as left ventricular hypertrophy) results. 12/40 patients (30%) had baseline ECG evidence of left ventricular hypertrophy by voltage criteria, 8 (20%) patients had evidence of underlying ischaemia; one patient (4%) had left bundle branch block. 19 patients had normal ECGs. 9/21 patients whose ECGs were abnormal had significant CAD on angiography.

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with DM and ESKD who presented for kidney transplant cardiac evaluation.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Yes	DSE and coronary angiography were performed within the same week (author correspondence).
Partial verification avoided? All tests	Yes	All participants who underwent an index test also received the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	No	The person who interpreted the coronary angiogram reports was not blinded to DSE results (author correspondence).
Index test results blinded? All tests	Unclear	All coronary angiograms were performed after DSE, so index tests were likely to be performed without influence from the reference standard.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	No withdrawals reported.

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Garcia-Canton 1998

Clinical features and settings	**Clinical features** • Patients who presented for cardiac evaluation before kidney transplantation underwent DSE and MPS followed by coronary angiography **Setting** • Hospital Universitario Insular de Gran Canaria, Spain
Participants	• Number: 27 • DM: percentage not reported • ESKD: percentage not reported • Angina pectoris: percentage not reported • Hypertension: percentage not reported • Sex: 67% male
Study design	Cross sectional study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Criterion for positive test results was ≥ 70% reduction in cross sectional area.
Index and comparator tests	**DSE** • Stress 99M-Technetium methoxyisobutylisonitrile SPECT
Follow-up	None reported.
Notes	Conference presentation. Unpublished as a study. Additional information obtained from correspondence with authors.

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients who presented for cardiac evaluation before kidney transplantation.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Yes	All coronary angiography was performed from two weeks to three months after the other tests (author correspondence).
Partial verification avoided? All tests	Yes	All participants who underwent the index test also had the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.

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Garcia-Canton 1998 *(Continued)*

Reference standard results blinded? All tests	Yes	Coronary angiography result was reported by a cardiology team member who was unaware of other test results (author correspondence).
Index test results blinded? All tests	Yes	MIBI scan and DSE results were interpreted by clinical and technical experts without knowledge of the other. Both were conducted before coronary angiography.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided concerning the performance and analysis of both the index and reference tests (author correspondence).
Uninterpretable results reported? All tests	Yes	There were no uninterpretable results.
Withdrawals explained? All tests	Yes	There were no withdrawals reported.

Garg 2000

Clinical features and settings	**Clinical features** • Patients with DM who were candidates for kidney transplant **Setting** • Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, India
Participants	• Number: 52 • DM: 100% • Angina pectoris: not reported • Hypertension: 100% • Sex: 88% male • Age (Mean ± SD): 46 ± 6 years
Study design	Cohort study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Criterion for positive test results was ≥ 50 reduction in cross sectional area. Each angiogram was independently reviewed by two experienced cardiologists who were blinded to the clinical data and uninvolved in patient management.
Index and comparator tests	**DSTS** • Patients received400 mg oral dipyridamole and 1.5 mCi Tl-201 injected IV one hour after DSTS. Studies were interpreted qualitatively and quantitatively. Planar thallium was performed in all cases. Normal test results were characterised by: the patient had no chest pain, no significant ST depression in the ECG during stress, and no significant perfusion defect. The test was considered positive if significant defects that were either fixed or reversible were revealed on delayed imaging, based on circumferential count profile analysis. **Echocardiography** • Resting wall motion abnormality

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Garg 2000 *(Continued)*

	Resting ECG • ECGs evaluated for evidence of MI, abnormal ST-T changes, and left ventricular hypertrophy. Evidence of MI was regarded as positive if significant Q waves were present in more than one lead. ST-T segment abnormality was noted as present if ST-segment depression or elevation of at least 1 mm; or inverted T wave in any lead where the QRS complex had a net positive deflection were detected in the absence of bundle branch block and left ventricular hypertrophy.
Follow-up	Survival data are available.
Notes	All patients underwent coronary angiography, echocardiography and resting ECG. 19 patients underwent dipyridamole MPS.

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with DM who were candidates for kidney transplant.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 50% stenosis.
Acceptable delay between tests? All tests	Unclear	Likely to be short delay between tests.
Partial verification avoided? All tests	Yes	All participants who underwent an index test received the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Yes	Each angiogram was independently reviewed by two experienced cardiologists who were blinded to the clinical data and uninvolved in patient management.
Index test results blinded? All tests	Yes	Studies were interpreted qualitatively and quantitatively.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	All patients missing from the final analysis were accounted for.

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Gowdak 2010

Clinical features and settings	**Clinical features** • Patients with DM on dialysis who were candidates for kidney transplant **Setting** • University of São Paulo Medical School, Brazil
Participants	• Number: 219 • DM: 100% • Angina pectoris: not reported • Hypertension: 92% • Sex: 67% male • Mean age: 57 years • Mean duration on dialysis: 36 months
Study design	Cross sectional study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Criterion for positive test results was ≥ 70% reduction in cross sectional area.
Index and comparator tests	**SPECT+ Sestamibi cardiac scintigraphy** • Pharmacological stress induced by dipyridamole.
Follow-up	Data not available.
Notes	Data obtained from poster presented at the European Society of Cardiology conference in 2010 http://spo.escardio.org/AbstractDetails.aspx?id=91377

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with DM who were candidates for kidney transplant.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Unclear	Not reported.
Partial verification avoided? All tests	Yes	All patients underwent coronary angiography.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.

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Gowdak 2010 *(Continued)*

Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	No uninterpretable results present.
Withdrawals explained? All tests	Yes	No withdrawals reported.

Herzog 1999

Clinical features and settings	**Clinical features** Patients referred for kidney transplantation evaluation from June 1992 to January 1995 • ESKD from diabetic kidney disease or other causes • unable to perform treadmill exercise • ≥ 2 CAD risk factors: male; HTN; hypercholesterolaemia (total cholesterol level 240 mg/dL or low-density lipoprotein cholesterol level 160 mg/dL); history of smoking; family history or any evidence suggestive of IHD (angina, effort dyspnoea, previous MI by history or ECG, or abnormal global or regional left ventricular function) **Setting** • Hennepin County Medical Center, Minneapolis, Minnesota, USA
Participants	• Patients were predominantly middle-aged white men. Nearly all patients (92%) were undergoing chronic haemodialysis • Number: 50 • DM: 82% • Angina pectoris: 16% • Hypertension: 94% • Sex: 60% male **Exclusion criteria** • Significant aortic stenosis; unstable angina; inability to obtain informed consent; previous coronary angiography
Study design	Cohort study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Criterion for positive test result was ≥ 70% reduction in cross sectional area by quantitative coronary angiography.
Index and comparator tests	**DSE**

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Herzog 1999 *(Continued)*

- End points for stopping drug infusion were: new inducible wall motion abnormalities involving ≥ 2 coronary artery vascular territories, intolerable patient discomfort, angina with ≥ 2 mm ST segment depression or elevation in a previously normal ECG lead, significant tachyarrhythmia (sustained supraventricular tachycardia or ≥ 3-beat run of ventricular tachycardia), symptomatic severe hypotension, SBP ≥ 240 mm Hg or DBP ≥ 120 mm Hg, attaining target heart rate ([220 - age] × 0.85), or reaching the maximum dose of dobutamine and atropine.
- DSE studies were analysed in digital format independently by three echocardiographers blinded to angiographic data. DSE study was defined as positive for inducible ischaemia when ≥ 1 normal segments developed absolute or relative hypokinesis with stress compared with other segments or an abnormal segment at rest had deterioration of regional systolic thickening with stress. DSE study result was normal if all segments were hyperdynamic with stress. If a resting baseline regional wall motion abnormality was unchanged with stress and all other segments became hyperdynamic, the DSE result was classified as a baseline regional wall motion abnormality with no inducible ischaemia.

Follow-up	Patients were followed up for a mean of 22.5 ± 10.1 months.
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients referred for kidney transplantation evaluation.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Yes	47 patients had angiography within 2 weeks after DSE (median, 2 days; mean, 12.4 ± 41 days); three patients had angiographic studies at 69, 85, and 280 days after DSE (angiography was delayed wound infection (1 patient) and psychosocial reasons (2 patients).
Partial verification avoided? All tests	Yes	All participants who underwent the index test received the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Yes	All lesions occurring in the major coronary artery segments or their proximal branches were visually identified, and an initial qualitative assessment made by a skilled reader blinded to all clinical data.
Index test results blinded? All tests	Yes	All DSE studies were analysed in digital format independently by three echocardiographers blinded to angiographic data.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported?	Yes	No uninterpretable results were present.

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Herzog 1999 *(Continued)*

All tests		
Withdrawals explained? All tests	Yes	55 eligible patients participated; 2 were excluded for unstable angina before scheduled testing; 3 underwent DSE and subsequently declined coronary angiography; 50 patients completed the research protocol. 39/50 patients qualified for DSE by the prespecified inclusion criterion of ESKD secondary to diabetic nephropathy (regardless of exercise capacity). The remaining 11 patients were unable to perform treadmill exercise because of peripheral vascular disease (4 patients), musculoskeletal disease (4 patients), lung disease (1 patient), and generalised fatigue (2 patients).

Jassal 2007

Clinical features and settings	**Clinical features** • Between 2004 and 2006, 30 patients were prospectively evaluated who underwent both DSE and coronary angiography. This population included 12 patients (5 male, mean age 59 ± 13 years) referred to rule out CAD with normal kidney function (Cr < 2.0 mg/dL) and 18 patients (8 male, mean age 55 ± 12 years) with CKD (Cr > 2.0 mg/dL) on haemodialysis referred for pre-renal transplant workup. **Setting** • Boniface General Hospital, Manitoba, Canada
Participants	• Number: 18 • DM: 38% • Angina pectoris: percentage not reported • Hypertension: 77% • Sex: 44% male
Study design	Cross sectional study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Criterion for positive test results was ≥ 50% reduction in cross sectional area.
Index and comparator tests	**DSE** • Beta-adrenergic blocking agents were withdrawn for 24 hours before the study. • Dobutamine was infused at doses of 5, 10, 20, 30, and 40 mg/kg/min for 3 minutes each. Images were analysed using the standard16-segment model
Follow-up	None reported
Notes	Only data for the 18 patients referred for pre-renal transplant workup were considered. Sufficient data in published report to create 2 x 2 table

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients who presented for cardiac evaluation before kidney transplantation.
Acceptable reference standard?	Yes	Coronary angiography with a reference standard threshold of ≥ 50% stenosis.

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Jassal 2007 *(Continued)*

All tests		
Acceptable delay between tests? All tests	Unclear	Likely to be short delay between tests.
Partial verification avoided? All tests	Yes	All participants who underwent the index test also had the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	No uninterpretable results were present.
Withdrawals explained? All tests	Yes	No withdrawals were reported.

Krawczynska 1988

Clinical features and settings	**Clinical features** • 305 patients with ESKD undergoing cardiac assessment prior to kidney transplant **Setting** • Emory University School of Medicine, Georgia, USA
Participants	• Number: 46 • DM: percentage not reported • Angina pectoris: percentage not reported • Hypertension: percentage not reported • Sex: not reported
Study design	Cohort study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Criterion for positive test results was ≥ 50% reduction in cross-sectional area.

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Krawczynska 1988 *(Continued)*

Index and comparator tests	**Thalium-201 Cardiac SPECT** • Stress was induced in 200 patients via exercise, 105 with dipyridamole. Reversible perfusion deficits constituted a positive test.
Follow-up	Postoperative data available for outcomes of death and adverse cardiac events.
Notes	Only available in abstract form (presentation).

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Prerenal transplant cardiac assessment. 305 ESKD patients waiting kidney transplantation.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold ≥ 50% stenosis.
Acceptable delay between tests? All tests	Unclear	Likely to be short delay between tests.
Partial verification avoided? All tests	No	38 patients received both coronary angiography and stress test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Unclear	Not stated in abstract.
Index test results blinded? All tests	Unclear	Not stated in abstract.
Relevant clinical information? All tests	Unclear	Insufficient clinical information provided about performance and analysis of the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	All patients missing from the final analysis were accounted for.

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Marwick 1989

Clinical features and settings	**Clinical features** • ESKD patients undergoing coronary angiography as part of transplant workup over a 2 year period. Patients were selected on the basis of longstanding diabetes history of chest pain or previous MI, or age > 40. **Setting** • Cleveland Clinic, Ohio, USA
Participants	• Number: 86 • DM: 29% • Angina pectoris or IHD: 11% • Hypertension: 36% • Sex: 27% male
Study design	Cross sectional study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • CAD was defined as the presence of ≥ 1 coronary arteries with ≥ 50% diameter stenosis
Index and comparator tests	**DSF** • Results were classified based on the presence or absence of calcification of the coronary arteries
Follow-up	None reported.
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	ESKD patients undergoing cardiac evaluation as part of transplant workup.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 50% stenosis.
Acceptable delay between tests? All tests	Yes	Tests performed at the same time.
Partial verification avoided? All tests	Yes	All participants who underwent an index test received the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded?	Yes	Author correspondence.

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Marwick 1989 *(Continued)*

All tests		
Index test results blinded? All tests	Yes	Author correspondence.
Relevant clinical information? All tests	Yes	Relevant clinical information provided regarding performance and analysis of the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	No withdrawals were reported.

Marwick 1990

Clinical features and settings	**Clinical features** • ESKD patients undergoing coronary angiography as part of transplant workup with longstanding diabetes, history of chest pain or previous MI, or age > 40 **Setting** • Cleveland Clinic, Ohio, USA
Participants	• Number: 45 • DM: 51% • Angina pectoris or IHD: 33% • Hypertension: 81% • Sex: 71% male **Exclusion criteria** • Recent angina or MI
Study design	Cohort study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Each angiogram was independently assessed by a reviewer blinded to fluorographic results. • CAD was defined as presence of ≥ 1 coronary arteries with ≥ 70% diameter stenosis.
Index and comparator tests	**Dipyridamole SPECT Thallium Imaging** • Images were displayed using a semi-quantitative system with a segmented colour scale. Scans were interpreted by an experienced observer without knowledge of catheterisation results, and were classified into groups with normal perfusion, fixed defect or reversible defect.
Follow-up	Follow up over 25 ± 14 months.
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description

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Marwick 1990 *(Continued)*

Representative spectrum? All tests	Yes	ESKD patients undergoing cardiac evaluation as part of transplant workup.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Yes	Thallium scanning was performed within a week of coronary angiography.
Partial verification avoided? All tests	Yes	All participants who received an index test received the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Yes	Author correspondence.
Index test results blinded? All tests	Yes	Author correspondence.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding performance and analysis of the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	No withdrawals were reported.

Modi 2006

Clinical features and settings	**Clinical features** • ESKD patients with hypertension on maintenance dialysis undergoing pre-transplant coronary angiography as per the institutional protocol if they were aged > 40 years to rule out CAD as part of transplant workup **Setting** • Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India
Participants	• Number: 105 • DM: 61/105 (58%) • Hypertension: all were hypertensive • Sex: 102 (97.1%) male

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Modi 2006 *(Continued)*

	• Age (mean ± SD): 51.6 ± 6.2 years (range 38 to 64 years)
Study design	Cross sectional study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • CAD defined as presence of ≥ 1 coronary arteries with ≥ 50% diameter stenosis
Index and comparator tests	**CIMT measurement** • CIMT measurement was conducted on USG B mode 7.5 MHZ probe. At least three readings were taken, and the average of three readings was taken for evaluation. IMT on both sides was calculated and averaged. Plaques were defined as focal widening relative to the adjacent segments, with protrusion into the lumen, composed either of only calcified deposits or a combination of calcification and non-calcified material. The site and extent of lesions were not quantified. • Patients were further divided into two groups according to average CIMT (average IMT > 0.75 mm and those with IMT < 0.75 mm).
Follow-up	None reported.
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	ESKD patients undergoing cardiac evaluation as part of transplant workup.
Acceptable reference standard? All tests	Yes	Yes, coronary angiography with a reference standard threshold of ≥ 50% stenosis.
Acceptable delay between tests? All tests	Unclear	Unclear, but likely to be only short delay between tests.
Partial verification avoided? All tests	Yes	All participants who received an index test received the reference standard test.
Differential verification avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.
Incorporation avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.
Reference standard results blinded? All tests	Yes	Reference standard performed before index test. Therefore it was not influenced by results of index test.
Index test results blinded? All tests	Yes	An operator, who was blinded with respect to the results of the coronary angiography, measured CIMT in all patients prior to coronary angiography and recorded it on videotape. Two independent observers who were blinded to the result of coronary angiography, measured CIMT offline to validate its predictive accuracy as a noninvasive test in predicting the presence or absence of CAD.

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Modi 2006 *(Continued)*

Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	No withdrawals were present.

Reis 1995

Clinical features and settings	**Clinical features** • ESKD patients on dialysis undergoing cardiac evaluation (DSE) as part of transplant workup. Antihypertensive treatment and aggressive DM control were undertaken as clinically indicated **Setting** • University of Michigan, Ann Arbor, Michigan, USA
Participants	• Number: 97 patients underwent screening; only 30 patients received both DSE and coronary angiography • DM: 64% • Angina pectoris or history of IHD: 30% • Hypertension: 96% • Sex: 63% male
Study design	Cohort study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • CAD was defined as presence of ≥ 1 coronary arteries with ≥ 50% stenosis.

Index and comparator tests	**DSE**
	• After completing a resting echocardiogram, stepwise infusion of dobutamine starting at 10 pg/kg/min, and increasing to 20 and a peak of 30 or 40 pg/kg/min in 3-minute stages was initiated.
	• All DSE studies were reviewed by experienced echocardiographers blinded to angiographic data and classified as:
	  • normal response: global increase in contractility, with an associated increase in ejection fraction, implying an absence of significant obstructive CAD (no regional wall motion abnormalities were seen at rest or during DSE).
	  • inducible ischaemia: wall motion abnormalities during DSE in 22 segments in regions that were normal at baseline, implying CAD without prior MI.
	  • fixed response: wall motion abnormality at baseline and no change during DSE implying prior MI without inducible ischaemia.
	  • mixed response: new and/or worsening wall motion abnormality in a patient with a wall motion abnormality at rest, implying prior MI with additional inducible ischaemia.

Follow-up	12 ± 6 months.
Notes	

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Reis 1995 *(Continued)*

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	ESKD patients undergoing cardiac evaluation as part of transplant workup.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 50% stenosis.
Acceptable delay between tests? All tests	Yes	Within 4 months.
Partial verification avoided? All tests	No	Coronary angiography was performed in 30/97 patients.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	All DSE studies were reviewed by experienced echocardiographers blinded to angiographic data.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	All patients missing from the final analysis were accounted for.

Rosario 2010

Clinical features and settings	**Clinical features** • CKD patients in haemodialysis programs referred for kidney coronary angiography as part of a kidney transplant evaluation. The clinical indication for coronary angiography was based on the fact that the patients belonged to the group under high risk for CAD either due to symptoms and/or previous invasive exams that would lead to a suspicion of CVD. **Setting**

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Rosario 2010 *(Continued)*

	• Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.
Participants	• Number: 97 • DM: 38% • Angina pectoris or IHD: 29% • Hypertension: 90% • Sex: 65% male
Study design	Cohort study.
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • CAD defined as presence of ≥ 1 coronary arteries with ≥ 70% diameter stenosis.
Index and comparator tests	**Multi-detector CT exams** • Performed in 16 and 64-column detector-row. Patients' heart rates during examination = 61.1 ± 6.9 bpm. Patients with rates > 70 bpm on arrival for CT scan received IV beta-blocker (metoprolol)to achieve 60 bpm, or the maximum dose (15 mg), since the protocol included associated coronary angiotomography acquisition. Calcium score obtained through prospective acquisition, and synchronised to ECG tracing. Images acquired were 3.0 mm thick, and view field was from 200 to 220 mm for chest axial images covering all cardiac area and allowing visualisation of coronary arteries and possible calcification on coronary artery topography. Images were acquired at a diastolic moment that was defined following patient's heart rate.
Follow-up	Follow-up ongoing.
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	CKD patients already in a haemodialysis program and referred to be submitted to kidney transplant.
Acceptable reference standard? All tests	Yes	Yes, coronary angiography with a reference standard threshold of ≥ 50 and 70% stenosis.
Acceptable delay between tests? All tests	Yes	Time elapsed between Multi-detector CT and coronary angiography was on average 99.03 days, SD 87.65 days, and median 79 days. Minimum interval was 2 days, and maximum interval was 380 days. Only 2 cases exceeded 1 year, and 16 cases had an interval over 6 months.
Partial verification avoided? All tests	Yes	All participants who received an index test received the reference standard test.
Differential verification avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.
Incorporation avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.

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Rosario 2010 *(Continued)*

Reference standard results blinded? All tests	Yes	An observer experienced in QCA technique and who did not participate in the Multi-detector CT analysis - also blind and independent.
Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	No withdrawals were present.

Sharma 2005

Clinical features and settings	**Clinical features** • ESKD patients undergoing cardiac evaluation as part of transplant workup **Setting** • St George's Hospital, London, UK
Participants	• Number: 128 • Dialysis: 54% • Principal cause of ESKD: DM (39 patients) • DM: 39% • Angina pectoris or IHD: 42% • Hypertension: 91% • Sex: 64% male **Exclusion criteria** • Age < 18 years; severe aortic stenosis; unstable angina; inability to consent.
Study design	Cohort study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • CAD defined as the presence of ≥ 1 coronary arteries with ≥ 70% diameter stenosis.
Index and comparator tests	• **Exercise ECG** * Patients had treadmill exercise testing according to standard Bruce protocol to limiting symptoms. The 12 lead ECG was recorded continuously and the following documented: exercise time to limiting symptom, maximal ST segment change, Duke multivariate prognostic score, maximal heart rate, maximal systolic blood pressure, limiting symptoms. The test was stopped if: limiting symptoms (angina, shortness of breath, dizziness, lethargy), ST depression > 3 mm, ventricular tachycardia, drop in blood pressure > 30 mm Hg, SBP rise > 230 mm Hg occurred. Patients were given an angina score: 0 = none, 1 = non-limiting angina, 2 = limiting angina. Duke score was calculated as: total treadmill time (min)-5 X magnitude of maximal ST depression (mm)- 4 X angina index. Horizontal or down sloping ST depression > 1mm measured 80 ms after the J point, and ST elevation > 1 mm measured 40 ms after the J point, were regarded as positive results. The test was described as

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Sharma 2005 *(Continued)*

inconclusive if stopped before 85% predicted heart rate could be achieved with no cardiac symptoms or significant changes at that stage.

- **DSE**
  - An abnormal response was described as the occurrence under stress of hypokinesia, akinesia or dyskinesia in one or more resting normal segments and/or worsening of wall motion in one or more resting hypokinetic segments.
- **Echocardiography**
- **Mitral annular calcification**
  - The presence of mitral annular calcification was defined as an echo dense band visualised throughout systole and diastole, distinguishable from the posterior mitral valve leaflet, and located anterior and parallel to the posterior left ventricular wall on M-mode recordings.
- **Resting wall motion abnormality**
- **Resting ECG**
  - The ECG was considered abnormal if any of the following criteria were met in any of the standard limb leads or precordial leads, except AVR or V1: pathological Q waves, left ventricular hypertrophy by Sokolow–Lyon criteria or Cornell index, ST depression ≥ 1 mm, ST elevation ≥ 1 mm, T wave inversion or bundle branch block (QRS ≥120 ms).

Follow-up	Patients were followed up for 1.32 ± 0.48 years (range 0.19 ± 2.12 years).
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	ESKD patients undergoing cardiac evaluation as part of transplant workup.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Unclear	Likely to be short delay between tests.
Partial verification avoided? All tests	Yes	All participants who underwent the index test received the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Yes	Angiograms were interpreted by two experienced, blinded observers with consensus for disagreement.
Index test results blinded? All tests	Yes	All images were reported offline by two experienced observers blinded to the rest of the study.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding performance and analysis of both the index and reference tests.

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Sharma 2005 *(Continued)*

Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	No withdrawals were reported.

Sharma 2009

Clinical features and settings	**Clinical features** • ESKD patients undergoing cardiac evaluation as part of transplant workup **Setting** • Ealing Hospital NHS Trust, Middlesex, UK
Participants	• Number: 143 • DM: 38% • Angina pectoris or IHD: 27% • Hypertension: 92% • Sex: 64% male **Exclusion criteria** • < 18 years; severe aortic stenosis; unstable angina
Study design	Cohort study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • CAD defined as presence of ≥ 1 coronary arteries with ≥ 70% diameter stenosis
Index and comparator tests	**DSE** • Peak systolic velocity measured by tissue Doppler imaging: The percentage of ischaemic myocardium was calculated from tissue Doppler imaging analysis as the number of ischaemic segments divided by the number of visualised segments. • Conventional visual assessment: Semi-quantitative analysis was performed using a 17-segment model. An abnormal response was described by the occurrence under stress of a new or worsening wall motion abnormality in ≥ 1 left ventricular segment. The severity of ischaemia was determined by the number of ischaemic segments seen during dobutamine stress and by the peak wall motion score index. **Echocardiography** • Resting wall motion abnormality
Follow-up	Mean follow-up was 2.3 ± 0.7 years (range 0.2 to 3.3 years)
Notes	The authors reported that this study population was different from the study results published in 2005. We were able to create 2 x 2 tables using tabulated results from the study.

Table of Methodological Quality

Item	Authors' judgement	Description

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Sharma 2009 *(Continued)*

Representative spectrum? All tests	Yes	ESKD patients undergoing cardiac evaluation as part of transplant workup.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Unclear	Unclear, but likely to be only short delay between tests.
Partial verification avoided? All tests	Yes	All participants who underwent the index test received the reference standard test.
Differential verification avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.
Incorporation avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.
Reference standard results blinded? All tests	Yes	Angiograms were interpreted blindly by two experienced observers and consensus was obtained in discordant cases from a third experienced operator.
Index test results blinded? All tests	Yes	The analysis of conventional and tissue Doppler imaging stress echo data was performed off-line by two independent, experienced observers blinded to clinical and coronary angiography data. Consensus was obtained in discordant cases from a third experienced operator.
Relevant clinical information? All tests	Yes	All patients missing from the final analysis were accounted for.
Uninterpretable results reported? All tests	Yes	No results were reported to be uninterpretable.
Withdrawals explained? All tests	Yes	No withdrawals were reported.

Sharples 2004

Clinical features and settings	**Clinical features** • ESKD patients referred for coronary angiography as part of cardiac work up before kidney transplantation **Setting** • Two inner city renal units in Royal London and St Bartholomew's Hospital, London, UK
Participants	• Number: 18 • DM: percentage not reported • Angina pectoris: percentage not reported

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Sharples 2004 *(Continued)*

- Hypertension: percentage not reported
- Sex: 50% male
- Man age: 53.9 years (range 31 to 73 years)
- Mean time on RRT: 27.4 months (range 4 to 111 months)

Study design	Cross sectional study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • CAD defined as presence of ≥ 1 coronary arteries with at least 50% stenosis.
Index and comparator tests	**EBCT** • Images were performed with a 100-ms scanning time and a single slice thickness of 3 mm. 36 to 40 tomographic slices were obtained for each subject during 2 breath-holding sessions. The degree of coronary artery calcification was calculated by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity for each lesion to yield a lesion-specific calcification score. The proximal segments of the left main stem, left anterior descending, left circumflex and right coronary arteries were examined.
Follow-up	None reported.
Notes	Results reported per vessel, not per patient. Insufficient data to construct meaningful 2 x 2 table. Therefore, study did not contribute data to the meta-analysis.

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	ESKD patients assessed for CAD before kidney transplant.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 75% stenosis.
Acceptable delay between tests? All tests	Unclear	Likely to be short delay between tests.
Partial verification avoided? All tests	Yes	All participants who underwent the index test received the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Yes	Analysis of the coronary angiograms was performed using a digital analysis system operated by a cardiologist blinded to the calcification score.
Index test results blinded? All tests	Yes	The acquired images were scored with the use of Imatron software by a single radiologist blinded to the clinical or angiographic history of the patient.

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Sharples 2004 *(Continued)*

Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	There were no uninterpretable results.
Withdrawals explained? All tests	Yes	There were no withdrawals.

Vandenberg 1996

Clinical features and settings	**Clinical features** • Patients with kidney disease and DM referred for kidney and/or pancreas transplantation from 1988 to 1993 undergoing cardiac evaluation as part of transplant workup with no history of angina, MI, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty; pharmacologic stress thallium scintigraphy and/or exercise radionuclide ventriculography performed as part of the evaluation; and coronary artery angiography performed within 6 months after the radionuclide evaluation (and no cardiac symptoms in the interim period). **Setting** • Cardiovascular Center, University of Iowa College of Medicine, Iowa, USA
Participants	• Number: 47 • DM: 100% • Angina pectoris or IHD: Nil • Hypertension: 74%. 35/74 (74%) * Patients were taking antihypertensive medications, including beta blockers and calcium channel blockers; medications were continued during stress testing • Sex: not reported
Study design	Cohort study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • CAD defined as presence of ≥ 1 coronary arteries with ≥ 75% diameter stenosis. Separate data available for 50% stenosis
Index and comparator tests	**Pharmacologic stress thallium scintigraphy** • IV dipyridamole was infused at a rate of 0.142 mg/kg per min for 4 min. IV adenosine was infused at a rate of 0.14 mg/kg per min for 6 min. Thallium-201 (3 mCi) was injected IV 5 min after the completion of the dipyridamole infusion or 4 min after the beginning of the adenosine infusion. Imaging was performed within 10 min with a gamma-camera. Planar images in anterior and lateral projections were obtained and were followed immediately by single-photon emission CT imaging. Images were interpreted by consensus of two experienced radiologists who were unaware of the angiography results. Test results were considered abnormal if either a fixed or a reversible defect was present. **Exercise radionuclide ventriculography** • Radionuclide ventriculography was performed in 40 patients using a modified in vivo red blood cell-labelling technique with an initial IV injection of 5.1 mg of stannous pyrophosphate, followed by 25 to 30 mCi of technetium-99m pertechnetate. Patients performed semi supine exercise with a bicycle ergometer table during continuous 12-lead ECG monitoring. Exercise was begun at a pedal speed of 50 rpm and a work load of about 50 watts, which was increased by 10 watts every 30 sec to a symp-

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Vandenberg 1996 *(Continued)*

tom-limited maximum. Heart rate and blood pressure were recorded at each exercise level. Images were obtained in the left anterior oblique projection at peak exercise and ejection fraction was calculated from this image. Exercise was considered adequate if the peak rate pressure product was > 20,000 or if the rate pressure product at least doubled from baseline to peak exercise.

- A test result was considered abnormal if any of the following were present:
  * resting ejection fraction of < 50%
  * failure to increase ejection fraction by at least 5 percentage points (in female subjects and in those with a resting ejection fraction of > 60%, the failure to increase ejection fraction was not considered abnormal); or
  * a new wall motion abnormality with exercise

Follow-up	The mean time from thallium scintigraphy to the latest follow-up visit was 35 ± 19 months.
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Renal failure patients undergoing cardiac evaluation as part of transplant workup.
Acceptable reference standard? All tests	Yes	Yes, coronary angiography with a reference standard threshold of ≥75% stenosis.
Acceptable delay between tests? All tests	Yes	Angiography was performed 55 ± 42 days after thallium scintigraphy in 42 patients and 50 ± 45 days after exercise radionuclide ventriculography in 40 patients.
Partial verification avoided? All tests	Yes	All participants who received an index test received the reference standard test.
Differential verification avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.
Incorporation avoided? All tests	Yes	This was not an issue in this study. Disease status (CAD) is diagnosed only through coronary angiography.
Reference standard results blinded? All tests	Yes	Measurements were made by a single observer without knowledge of the results of the imaging tests.
Index test results blinded? All tests	Yes	Images were interpreted by the consensus of two experienced radiologists who were unaware of the angiography results.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of both the index and reference tests.
Uninterpretable results reported? All tests	Yes	Yes. One MPS was technically suboptimal and was therefore not included in the analysis. Exercise ventriculography was suboptimal in five patients and they were not included in the analysis.
Withdrawals explained? All tests	Yes	All patients missing from the final analysis were accounted for.

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West 2000

Clinical features and settings	**Clinical features** • Dialysis-dependent renal transplant candidates evaluated between 1 January l993 and 1 March l995 were screened for cardiac high-risk factors (identified as those with diabetes mellitus, previous MI, age 50 years or more cerebral and/or peripheral vascular disease, CHF, class I or II angina (Canadian Cardiovascular Society classification), and dialysis dependency of more than 5 years). **Setting** • Geisinger Medical Center, Danville, Pennsylvannia, USA
Participants	• Number: 33 • DM: percentage not reported • Angina pectoris or IHD: percentage not reported • Hypertension: percentage not reported • Sex: not reported
Study design	Cohort study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • CAD was defined as the presence of one or more coronary arteries with 70% or greater diameter stenosis, or greater than 50% in left main coronary artery.
Index and comparator tests	**DSE** • DSE was performed the day after dialysis to avoid hypertensive blood pressure response from volume overload. A standardised DSE protocol was used. DSE findings were graded as negative if normal wall motion was present and positive when: * CAD: fixed, inducible, or mixed segmental wall motion abnormalities * Cardiomyopathy: diffuse wall motion abnormalities or * Primary valvular heart disease: severe aortic stenosis, aortic insufficiency, mitral stenosis, or mitral regurgitation secondary to primary leaflet abnormalities were present
Follow-up	Patients were followed up for an unspecified time.
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	ESKD patients undergoing cardiac evaluation as part of transplant workup.
Acceptable reference standard? All tests	Yes	Coronary artery stenosis measured by coronary angiography. CAD defined as the presence of ≥ 1 coronary arteries with ≥ 70% diameter stenosis, or > 50% in left main coronary artery.
Acceptable delay between tests? All tests	Unclear	Likely to be only delay between tests.
Partial verification avoided? All tests	Yes	All participants who underwent the index test received the reference standard test.

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West 2000 *(Continued)*

Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of the index and reference tests.
Uninterpretable results reported? All tests	Yes	There were no uninterpretable results.
Withdrawals explained? All tests	Yes	Nine patients were excluded because of prior coronary angiography (5), class III ± IV angina (3), and refusal to participate in the study (1).

Worthley 2003

Clinical features and settings	**Clinical features** • ESKD patients with multiple risk factors (> 60 years; HTN; DM; history of smoking; family history of CAD; hypercholesterolaemia) undergoing cardiac evaluation as part of transplant workup **Setting** • North Western Adelaide Health Service, University of Adelaide, Australia
Participants	• Number: 40 • DM: 78% • Angina pectoris or IHD: 18% • Hypertension: 98% • Sex: 48% male **Exclusion criteria** • Normal coronary angiography within the preceding 2 years; coronary revascularisation within the last 12 months; evidence of previous Q-wave infarction on ECG at rest; class III to IV angina pectoris at study entry
Study design	Cohort study
Target condition and reference standard(s)	**Coronary artery stenosis measured by coronary angiography** • Angiograms were assessed by 2 cardiologists who were blinded to the perfusion imaging results. A significant coronary stenosis was defined as > 70%
Index and comparator tests	**Tachycardic-stress perfusion imaging**

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Worthley 2003 *(Continued)*

- All patients underwent induction of tachycardiac stress via treadmill exercise or temporary cardiac pacing. Treadmill exercise was performed using the Bruce protocol, on a symptom-limited basis. Exercise was deemed adequate if peak heart rate was > 75% of the theoretic maximal values, or if exercise was terminated because of angina pectoris. Pacing was performed in patients unable to attain adequate stress on treadmill testing. Pacing was performed at the time of cardiac catheterisation, but before coronary angiography. Myocardial imaging was achieved by IV injection of technetium-99m tetrofosmin (400 MBq) 1 minute before termination of tachycardiac stress. Images were acquired on a triple-headed gamma camera with 180° single-photon emission CT. The images were assessed by nuclear cardiologists who were blinded to the cardiac catheterisation results.

Follow-up	Mean follow-up of 28 ± 10 months.
Notes	Informed consent was obtained before study entry.

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	ESKD patients undergoing cardiac evaluation as part of transplant workup.
Acceptable reference standard? All tests	Yes	Coronary angiography with a reference standard threshold of ≥ 70% stenosis.
Acceptable delay between tests? All tests	Yes	Tests were done at the same time (author correspondence).
Partial verification avoided? All tests	Yes	All participants who underwent the index test received the reference standard test.
Differential verification avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Incorporation avoided? All tests	Yes	Disease status (CAD) diagnosed by coronary angiography.
Reference standard results blinded? All tests	Yes	Angiograms were assessed by 2 cardiologists who were blinded to the perfusion imaging results.
Index test results blinded? All tests	Yes	Images were assessed by nuclear cardiologists who were blinded to the cardiac catheterisation results.
Relevant clinical information? All tests	Yes	Relevant clinical information was provided regarding the performance and analysis of the index and reference tests.
Uninterpretable results reported? All tests	Yes	There were no uninterpretable test results.
Withdrawals explained? All tests	Yes	No withdrawals reported.

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bpm: beats per minute; CAD: coronary artery disease; CF: cardiac failure; CHF: congestive heart failure; CIMT: carotid intimal medial thickness; CKD: chronic kidney disease; CVD: cardiovascular disease; DBP: diastolic blood pressure; DM: diabetes mellitus; DSE: dobutamine stress echocardiogram; DSTS: dipyridamole stress thallium scan; EBCT: electron beam computed tomography; ECG: electrocardiogram; ESKD: end-stage kidney disease; HTN: hypertension; IHD: ischaemic heart disease; IMT: intimal media thickness; IV: intravenous; MI: myocardial infarction; MIBI: methoxyisobutyl isonitrile stress; MPS: myocardial perfusion scintigraphy; QCA: quantitative coronary analysis; RRT: renal replacement therapy; RWM: regional wall motion; SBP: systolic blood pressure; ST: sinus tachycardia; WMA: wall motion abnormality

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ali 2004	Coronary angiography not routinely performed on patients in study.
Arantes 2010	Prognostic study; not enough data available to allow for diagnostic accuracy comparison with coronary angiography.
Braun 1984	No index tests for comparison.
Brown 1989	Prognostic study; not enough data available to allow for diagnostic accuracy comparison with coronary angiography.
Caglar 2006	Patient population not consisting of patients who are potential transplant recipients; coronary angiography only provided to patients who tested positive to other tests.
Camp 1990	Coronary angiography not used as reference standard.
Cortigiani 2005	Coronary angiography not used as reference standard.
Cottier 1990	Coronary angiography not routinely performed on patients in study.
Cross 1996	Prognostic study; not enough data available to allow for diagnostic accuracy comparison with coronary angiography.
Dahan 1995	Patient population not entirely consisting of patients who are potential transplant recipients. Separate data for potential transplant recipients not available.
Dahan 1998	Patient population not entirely consisting of patients who are potential transplant recipients. Separate data for potential transplant recipients not available.
Dahan 2002	Patient population not entirely consisting of patients who are potential transplant recipients. Separate data for potential transplant recipients not available.
De Vriese 2009	Patient population not entirely consisting of patients who are potential transplant recipients. Roughly 1/3 of the patients that were included in the study were being evaluated for kidney transplantation. The others consented to have the evaluation as a screening test, because the authors explained to them that the majority of patients with CAD on dialysis are asymptomatic (author communication). Separate data for potential transplant recipients not available.
Derfler 1991	Coronary angiography not used as reference standard.
Dussol 2004	Coronary angiography not routinely performed on patients in study, only performed on patients who were index test positive.
Eschertzhuber 2005	Coronary angiography not routinely performed on patients in study.
Feola 2002	Coronary angiography not used as reference standard.

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Study	Reason for exclusion
Fossati 2004	Data insufficient to construct appropriate 2 x 2 table.
Fujimoto 2006	This was a study of diagnostic accuracy but the patient population did not consist entirely of patients who are potential transplant recipients. Separate data on patients who were potential transplant recipients not available.
Fukui 2005	This was a study of diagnostic accuracy but the patient population did not consist entirely of patients who are potential transplant recipients. Separate data on patients who were potential transplant recipients not available.
Fuster 2000	Coronary angiography not routinely performed on patients in study, only performed on patients who were index test positive.
Holley 1991	Coronary angiography not routinely performed on patients in study; data insufficient to construct appropriate 2 x 2 table.
Iqbal 1991	Coronary angiography not used as reference standard.
Jeloka 2007	Coronary angiography not used as reference standard.
Krotin 2007	Coronary angiography not used as reference standard.
Langford 1997	Coronary angiography not used as reference standard.
Le 1994	Prognostic study; not enough data available to allow for diagnostic accuracy comparison with coronary angiography.
Leonardi 2009	Single centre case experience; not a study of diagnostic accuracy.
Lewis 2002	Prognostic study; not enough data available to allow for diagnostic accuracy comparison with coronary angiography.
Lin 2001	Coronary angiography not used as reference standard.
Ma 2006	Coronary angiography only used in those with high risk scores.
Manske 1997	Data insufficient to construct appropriate 2 x 2 table.
Mao 2010	Coronary angiography not used as reference standard.
Mistry 1998	Coronary angiography not used as reference standard.
Morrow 1983	Coronary angiography not used as reference standard.
Nguyen 2007	Coronary angiography not used as reference standard.
Nishimura 2004	This was a study of diagnostic accuracy but the patient population did not consist entirely of patients who are potential transplant recipients. Separate data on patients who were potential transplant recipients not available.
Ohtake 2005	This was a study of diagnostic accuracy but the patient population did not consist entirely of patients who are potential transplant recipients. Separate data on patients who were potential transplant recipients not available.
Oliveira 2005	Only coronary angiography studied. No other index tests present.

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Study	Reason for exclusion
Patel 2003	Coronary angiography not used as reference standard.
Patel 2008	Coronary angiography not routinely performed on patients in study.
Philipson 1986	Reference standard differentially applied to different treatment groups; unable to construct meaningful 2 x 2 table.
Porter 2003	Coronary angiography not used as reference standard.
Rakhit 2006	Coronary angiography not used as reference standard.
Robinson 2007	This was a study of diagnostic accuracy but the patient population did not consist entirely of patients who are potential transplant recipients. Separate data on patients who were potential transplant recipients not available.
Russell 1993	Prognostic study; not enough data available to enable diagnostic accuracy comparison with coronary angiography.
Schmidt 2001	Patient population not exclusively consisting of patients who are potential transplant recipients; patients were either those who were on long-term RRT, or who had undergone successful renal transplantation. Separate data on patients who were potential transplant recipients not available.
Sharma 2007	Coronary angiography not used as reference standard.
Tita 2008	Coronary angiography not used as reference standard.
Trochu 1991	Coronary angiography not used as reference standard.
Venkataraman 2008	Coronary angiography not used as reference standard.
Weinrauch 1978	Only coronary angiography studied. No index tests for comparison.
Weinrauch 1992	Coronary angiography not used as reference standard.
Witczak 2006	Only coronary angiography studied. No index tests for comparison.
Wong 2008	Coronary angiography not used as reference standard.

DATA

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 DSE	13	745
2 MPS	9	582
3 EST	2	129

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Test	No. of studies	No. of participants
4 EBCT	1	97
5 DSF	1	86
6 EV	1	35
7 CIMT	1	105
8 Echo (RWMA)	2	265
9 Echo (LV)	1	52
10 Echo (MAC)	1	125
11 ECG	3	263

Test 1. DSE.

Test 2. MPS.

Test 3. EST.

Test 4. EBCT.

Test 5. DSF.

Test 6. EV.

Test 7. CIMT.

Test 8. Echo (RWMA).

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Test 9. Echo (LV).

Test 10. Echo (MAC).

Test 11. ECG.

ADDITIONAL TABLES

Table 1. Description of index tests

Test	Description	Advantages	Disadvantages	Type of result	Presence of cut-off values
Screening tests					
MPS *Stress Exercise dipyridamole dobutamine* *Radionucleotide thallium-201 or Tc-99m sestamibi radionucleotide agents*	This compares perfusion of myocardium at rest and after a 'stress' such as exercise or drugs (e.g. dipyridamole). When coronary arteries are normal, 'stress' results in vasodilatation and increased coronary blood flow. However, diseased coronary arteries cannot dilate because they are already maximally dilated and there is no increase in blood flow after a stress. MPS reveals these areas as regions of decreased perfusion. A reversible perfusion defect is a sign of ischaemia. A fixed defect (when there is decreased perfusion before, during and after the stress) is an indicator of infarction. Pharmacological agents overcome limitations of exercise testing in patients with kidney disease	Non-invasive Provides information regarding functional status of myocardium under stress conditions	Neither 100% sensitive nor specific Radiation dose Results subject to interpretation and reader bias False positives due to increase in attenuation artefacts caused by left ventricular hypertrophy False negatives due to balanced ischaemia (e.g. triple vessel disease) More expensive than exercise ECG	Dichotomous (i.e. stress test positive or stress test negative)	None. However, whether a stress test is interpreted as positive or negative depends largely on observer interpretation
DSE *Stress Exercise dobutamine*	Stress echocardiography compares the regional wall motion and thickness of myocardium both at rest and after stress. Regional systolic dysfunction is usually caused by CAD. Pharmacological stress agent overcomes limitations of exercise testing in patients with kidney disease	Non-invasive No radiation dose Provides information regarding functional status of myocardium under stress conditions Provides assessment of ventricular size and function	Neither 100% sensitive nor specific Results subject to interpretation and reader bias Operator dependent Acoustic windows not possible in up to 20% of subjects	Dichotomous (i.e. stress test positive or stress test negative)	None. However, whether a stress test is interpreted as positive or negative depends largely on observer interpretation

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Table 1. Description of index tests *(Continued)*

			Hypertensive response to stress agent possible Cardiomyopathies may also show regional variation in function		
Exercise ECG *Bruce protocol stress ECG*	Patient exercises on a treadmill while connected to an ECG. The level of exercise is increased in progressive stages. The patient's symptoms and blood pressure response are checked repeatedly. Ischaemic ECG changes or angina symptoms brought on by exercise are highly suggestive of underlying CAD	Non-invasive Provides information regarding functional status of myocardium under stress conditions	Neither 100% sensitive nor specific Results subject to interpretation and reader bias Often limited by the inability of CKD patients to achieve an adequate peak exercise workload, development of exercise-induced hypotension High proportion have abnormal baseline ECG (left ventricular hypertrophy)	Dichotomous (i.e. stress test positive or stress test negative)	No. However, whether a stress test is interpreted as positive or negative depends largely on observer interpretation
Coronary artery calcium score EBCT *Multi-detector computed tomography*	Cardiac calcium scoring is a non-invasive test that uses computed tomography to detect the presence of calcium in plaque on the walls of the arteries of the heart (coronary arteries). A calcium score is then derived, calculated as a summation of all calcified lesions in the coronary arteries. The calcium score is then compared with a reference range appropriate to a patient's age and sex. High calcium scores are associated with higher risks of cardiovascular events	Non-invasive	Neither 100% sensitive nor specific Radiation dose	Continuous	There is no uniformly agreed cut-off value at which patients are considered at high risk of CAD. We planned to analyse results by combining data from studies which share identical cut-off values
Echocardiography *Trans-thoracic Trans-oesophageal*	An ultrasound of the heart that enables assessment of structure and function. Impairment in systolic function can result from pre-existing CAD	Provides information regarding myocardial function and regional wall abnormalities, which may suggest pre-existing ischaemia or MI Enables assessment of structure	Neither highly sensitive nor specific Does not provide any information of reversible ischaemia Results subject to interpretation and reader bias	Dichotomous (e.g. presence or absence of resting wall motion abnormality)	None
CT coronary angiography	Specialised form of CT that enables imaging of the heart and computerised reconstruction of coronary arteries, permitting as-	Non-invasive Enables diagnosis of precise location and severity of each	Radiation dose Contrast nephropathy Inability to provide opportunity for immedi-	Dichotomous (i.e. presence or absence of	Yes (i.e. ≥ 50% stenosis or ≥ 70% stenosis)

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Table 1. Description of index tests *(Continued)*

	sessment of the lumen and vessel walls	lesion as opposed to vascular territory affected, as is the case for most functional tests. Assesses not only the lumen of the vessel but also the wall. It can also demonstrate soft atheromatous plaques, which cannot be demonstrated on conventional coronary angiography	ate intervention (as opposed to coronary angiography)	significant CAD)	We planned to manage the issue of different cut points by involving an analysis that included: • All studies regardless of threshold of CAD on coronary angiography (these will include both studies which have ≥ 50% stenosis and ≥ 70% stenosis • Only studies which had ≥ 70% stenosis threshold
Cardiac magnetic resonance imaging	MRI of the heart that enables evaluation of its structure and function	Non-invasive No radiation dose Enables assessment of structure of myocardium High spatial resolution means low inter-observer variability	Neither highly sensitive nor specific	Dichotomous (e.g. presence or absence of left ventricular systolic dysfunction)	None
Resting ECG	Transthoracic interpretation of the electrical activity of the heart over time captured and externally recorded by skin electrodes	Provides information regarding the electrical function of the myocardium, which may suggest pre-existing ischaemia, left ventricular hypertrophy or arrhythmias	Neither sensitive nor specific Does not provide any information of reversible ischaemia	Dichotomous (i.e. presence or absence of certain ECG features)	None
CIMT	Measurement of the thickness of artery walls, usually by external ultrasound, to detect both the presence and to track the progression of atherosclerotic disease in humans. Used as a surrogate marker for atherosclerosis	Non-invasive	Neither highly sensitive nor specific Does not provide any information on cardiac function	Continuous	Yes. This will vary depending on the institution (e.g. 0.75 mm)
Cardiopulmonary exercise testing	Evaluates both cardiac and pulmonary function. Cardiac function is evaluated in terms of aerobic capacity and respiratory function. The subject is exercised on a bicycle ergometer or treadmill. The	Non-invasive measurement of ventricular function, respiratory function and cellular function via measurement of gas ex-	Not commonly performed	Dichotomous (e.g. stress ECG positive or stress ECG negative; pres-	Yes, although these will vary for different variables and for different institutions

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Table 1. Description of index tests *(Continued)*

	test enables calculation of maximal aerobic capacity and the point during exercise where anaerobic metabolism is used to supplement aerobic metabolism as a source of energy. These can be measured via gas exchange data	change, as well as detection of myocardial ischaemia Excellent method of evaluating fitness and operative fitness		ence or absence of cardiac failure) and Continuous (e.g. measurement of the maximum aerobic capacity and anaerobic threshold)	
DSF	Used to detect coronary artery calcification. Digital subtraction improves resolution of conventional fluoroscopic methods	Non-invasive Non exercise	Not commonly used Radiation dose	Dichotomous (i.e. presence or absence of calcification)	None
Exercise radionucleotide ventriculography	Technique for a combined assessment of exercise capacity and an evaluation of ventricular size and performance		Not commonly used Radiation dose	Dichotomous (i.e. stress test positive or stress test negative)	None. However, whether a stress test is interpreted as positive or negative depends largely on observer interpretation
Reference standard					
Coronary angiography	Coronary catheterisation is an invasive procedure to access the coronary circulation and blood filled chambers of the heart using a catheter. It can be performed for both diagnostic and interventional (treatment) purposes. It assesses the diameter of coronary artery lumens, heart chamber size and heart muscle contraction performance	Gold standard for detecting CAD. Enables diagnosis of precise location and severity of each lesion Intervention (PTCA) possible during procedure	High cost Lack of sensitivity to intramural coronary atherosclerosis Risk of complications Intravenous contrast media may worsen kidney function Little information on function Radiation dose Results subject to interpretation and reader bias, although to a lesser extent than functional tests	Dichotomous (i.e. presence or absence of significant CAD)	Yes (i.e. ≥ 50% stenosis or ≥ 70% stenosis). We managed the issue of different cut points by involving an analysis which included: • All studies regardless of threshold of CAD on coronary angiography (these will include both studies which have ≥ 50% stenosis and ≥ 70% stenosis • Only studies which had ≥

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Table 1. Description of index tests *(Continued)*

	70% stenosis threshold

CAD: coronary artery disease; CIMT: carotid intimal medial thickness; CT: computed tomography; ECG: electrocardiograph; MPS: myocardial perfusion scintigraphy; MRI: magnetic resonance imaging; PTAC: percutaneous transluminal coronary angioplasty

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Table 2. Characteristics of included studies

Study	Country	Partici-pants	Diabetic patients (%)	Angina (%)	Hyper-tensive (%)	Male (%)	Reference threshold (% steno-sis)	TP	FP	FN	TN
Dobutamine stress echocardiography (DSE)											
Bates 1996	USA	17	100	NA	98	64	50	9	1	1	6
Brennan 1997	USA	12	56	21	90	45	50	4	1	2	5
Cai 2010	USA	38	54	NA	86	64	70	15	2	8	13
De Lima 2003	Brazil	89	30	25	95	77	70	15	7	19	48
Ferreira 2007	Brazil	126	27	12	NA	69	70	24	14	10	78
Gang 2007	India	40	100	5	92	90	70	9	1	10	20
Garcia-Canton 1998	Spain	27	NA	NA	NA	67	70	11	2	1	13
Herzog 1999	USA	50	82	16	94	60	70	12	8	4	26
Jassal 2007	Canada	18	38	NA	77	44	50	0	0	0	18
Reis 1995	USA	30	64	30	96	63	50	22	1	1	6
Sharma 2005	UK	125	39	42	91	64	70	32	5	4	84
Sharma 2009	UK	140	38	27	92	64	70	36	5	4	95
West 2000	USA	33	NA	NA	NA	NA	70	12	8	1	12
Myocardial perfusion scintigraphy (MPS)											
Boudreau 1990	USA	80	100	12.5	NA	64	70	36	8	6	30
De Lima 2003	Brazil	65	30	25	95	77	70	8	10	15	32
Garcia-Canton 1998	Spain	27	NA	NA	NA	67	70	11	3	1	12
Garg 2000	India	19	100	NA	100	88	50	9	4	2	4

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Table 2. Characteristics of included studies *(Continued)*

Gowdak 2010	Brazil	219	100	NA	92	69	70	85	31	52	51
Krawczynska 1988	USA	46	NA	NA	NA	NA	50	20	18	0	8
Marwick 1990	USA	45	51	33	81	71	70	4	9	10	22
Vandenberg 1996	USA	41	100	0	NA	NA	75	10	6	6	19
Worthley 2003	Australia	40	78	18	98	48	70	13	3	2	22
Stress electrocardiography (EST)											
Bennett 1978	USA	4	100	NA	100	36	70	3	1	0	0
Sharma 2005	UK	125	39	42	91	64	70	13	8	23	81
Electron beam computed tomography (EBCT)											
Rosario 2010	Brazil	97	38	29	90	65	70	16	25	9	47
Sharples 2004	UK	18	NA	NA	NA	50	75	*	*	*	*
Digital subtraction fluorography (DSF)											
Marwick 1989	USA	86	29	11	36	27	70	28	17	8	33
Exercise ventriculography											
Vandenberg 1996	USA	35	100	0	NA	NA	75	7	7	7	14
Carotid intimal media thickness (CIMT)											
Modi 2006	India	105	58	24	100	NA	97	38	14	4	49
Echocardiography (resting wall motion abnormality)											
Sharma 2005	UK	125	39	42	91	64	70	11	4	25	85
Sharma 2009	UK	140	38	27	92	64	70	13	5	27	95
Echocardiography (cardiomegaly or LV dysfunction)											

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Table 2. Characteristics of included studies *(Continued)*

Garg 2000	India	19	100	NA	100	88	50	8	5	19	20
Echocardiography (mitral annular calcification)											
Sharma 2005	UK	125	39	42	91	64	70	22	25	14	64
Resting ECG (pathological Q waves, left ventricular hypertrophy, ST depression ≥ 1 mm, ST elevation ≥ 1 mm, T wave inversion or bundle branch block)											
Gang 2007	India	40	100	5	92	90	70	9	12	10	9
Garg 2000	India	98	100	NA	100	88	50	51	1	22	24
Sharma 2005	UK	125	39	42	91	64	70	27	14	9	75

FN: false negative; FP: false positive; NA: not available; TN: total negative; TP: total positive
* Study unable to contribute data to meta-analysis as it reported results per coronary vessel, and not per patient

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Table 3. Comparison of summary estimates of test performance for dobutamine stress echocardiography (DSE) and myocardial perfusion scintigraphy (MPS)

Test	Studies (N)	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic odds ratio (95% CI)	AUC	P value for difference in accuracy*
Overall results: including all studies						
MPS	9	0.74 (0.54 to 0.87)	0.70 (0.51 to 0.84)	6.69 (2.35 to 19.03)	0.78	0.02
DSE	13	0.79 (0.67 to 0.88)	0.89 (0.81 to 0.94)	29.98 (12.17 to 73.89)	0.91	
Only including studies where reference standard threshold ≥ 70% coronary artery stenosis on coronary angiography						
MPS	7	0.67 (0.48 to 0.82)	0.77 (0.61 to 0.88)	6.70 (1.84 to 24.41)	0.78	0.09
DSE	9	0.76 (0.60 to 0.87)	0.88 (0.78 to 0.94)	23.01 (8.08 to 65.51)	0.90	
Only including studies where partial verification was avoided						
MPS	8	0.68 (0.51 to 0.81)	0.75 (0.60 to 0.86)	6.45 (2.12 to 19.64)	0.78	0.03
DSE	9	0.80 (0.64 to 0.90)	0.89 (0.79 to 0.95)	34.28 (11.10 to 105.93)	0.92	
Only including studies which avoided partial verification and had reference standard threshold ≥ 70% coronary artery stenosis on coronary angiography						
MPS	7	0.67 (0.48 to 0.82)	0.77 (0.61 to 0.88)	6.70 (1.84 to 24.41)	0.78	0.09
DSE	8	0.78 (0.59 to 0.89)	0.88 (0.76 to 0.94)	25.22 (7.68 to 82.80)	0.90	

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AUC: area under the curve; CI: confidence interval; DSE: dobutamine stress echocardiography; MPS: myocardial perfusion scintigraphy
* P values for this variable were calculated using the likelihood ratio test in SAS (PROC NLMIXED), and represented the final P value obtained from a backward elimination approach used to eliminate non-significant terms from the original hierarchical model.

Table 4. Comparison of systematic reviews studying the test performance of myocardial perfusion scintigraphy and dobutamine stress echocardiography

Review	Population	DSE		MPS	
		Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Cochrane review	Kidney transplant candidates only	0.79 (0.67 to 0.88)	0.89 (0.81 to 0.94)	0.74 (0.54 to 0.87)	0.70 (0.51 to 0.84)
Fleischmann 1998	General population	0.85 (0.83 to 0.87)	0.77 (0.74 to 0.80)	0.87 (0.86 to 0.88)	0.64 (0.60 to 0.68)
Schinkel 2003	General population	0.80 (NS)	0.86 (NS)	0.84 (NS)	0.77 (NS)

DSE: dobutamine stress echocardiography; MPS; myocardial perfusion scintigraphy; NS - not stated

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
MEDLINE	1. Kidney Transplantation/ 2. Pancreas Transplantation/ 3. (kidney and pancreas and (transplant$ or graft$)).tw. 4. Kidney Failure/ 5. Kidney Failure, Chronic/ 6. (chronic kidney or chronic renal).tw. 7. (endstage kidney or endstage renal).tw. 8. (end stage kidney or end stage renal).tw. 9. (ESRD or ESKD or ESRF or ESKF).tw. 10.exp Renal Dialysis/ 11.dialysis.tw. 12.(hemodialysis or haemodialysis).tw. 13.(hemodiafilt$ or haemodiafilt$).tw. 14.(hemofilt$ or haemofilt$).tw. 15.(PD or CAPD or CCPD or APD).tw. 16.or/1-15 17.Coronary Disease/ 18.Coronary Artery Disease/ 19.Coronary Stenosis/ 20.(coronary arter$ and stenos$).tw. 21.coronary stenos$.tw. 22.coronary atherosclerosis$.tw.

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(Continued)

23.coronary arterioscleros$.tw.
24.(coronary adj5 disease).tw.
25.CAD.tw.
26.or/17-25
27.and/16,26
28.exp Echocardiography/
29.echocardiogr$.tw.
30.echo.tw.
31.Dipyridamole/du [Diagnostic Use]
32.Dobutamine/du [Diagnostic Use]
33.Adenosine/du [Diagnostic Use]
34.Imaging, Three Dimensional/
35.exp Tomography, Emission-Computed/
36.exp Tomography, X-ray Computed/
37.SPECT.tw.
38.Thallium Radioisotopes/du [Diagnostic Use]
39.Nucleosides/
40.Technetium Tc 99m Sestamibi/du [Diagnostic Use]
41.((sestamibi or cardiolite or dipyridamole or persantin) adj3 (scan$ or stud$)).tw.
42.(thallium adj3 (scan$ or stud$)).tw.
43.electron beam tomograph$.tw.
44.EBT.tw.
45.(comput$ adj2 tomograph$).tw.
46.ct scan$.tw.
47.cat scan$.tw.
48.Magnetic Resonance Imaging/
49.Magnetic Resonance Angiography/
50.Diffusion Magnetic Resonance Imaging/
51.Echo-Planar Imaging/
52.(echo-planar or echoplanar).tw.
53.Coronary Angiography/
54.Angiography/
55.MRI.tw.
56.magnetic resonance.tw.
57.MRA.tw.
58.angiogr$.tw.
59.coronary catheteri?ation.tw.
60.(CA or CC).tw.
61.(Fluoroscopy/ or fluoroscopy.tw.) and (Angiography, Digital Subtraction/ or Subtraction Technique/ or digital subtraction.tw.)
62.exp Troponin/du [Diagnostic Use]
63.calcium scor$.tw.
64.Clinical Enzyme Tests/
65.cardiac enzyme$.tw.
66.exp Perfusion Imaging/
67.perfusion imaging.tw.
68.perfusion stud$.tw.
69.perfusion scintigra$.tw.
70.Exercise Test/
71.Radionuclide Ventriculography/
72.Physical Exertion/

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(Continued)

	73.stress test$.tw. 74.exercise.tw. 75.ventriculogra$.tw. 76.treadmill.tw. 77.bicycle.tw. 78.Risk Assessment/ 79.risk stratification.tw. 80.risk algorithm.tw. 81.exp Carotid Arteries/ and exp Ultrasonography/ 82.exp Carotid Arteries/us 83.(carotid adj2 (ultrasound or ultrasonogra$)).tw. 84.Carotid Arteries/ and (Tunica Intima/ and Tunica Media/) 85.(carotid media$ intima$ thickness or carotid intima$ media$ thickness).tw. 86.or/28-85 87.and/27,86
EMBASE	1. exp Kidney Transplantation/ 2. Kidney Failure/ 3. Chronic Kidney Failure/ 4. Chronic Kidney Disease/ 5. (kidney and pancreas and (transplant$ or graft$)).tw. 6. (chronic kidney or chronic renal).tw. 7. (endstage kidney or endstage renal).tw. 8. (end stage kidney or end stage renal).tw. 9. (ESRD or ESKD or ESRF or ESKF).tw. 10.exp Renal Replacement Therapy/ 11.dialysis.tw. 12.(hemodialysis or haemodialysis).tw. 13.(hemofilt$ or haemofilt$).tw. 14.(hemodiafilt$ or haemodiafilt).tw. 15.(PD or CAPD or CCPD or APD).tw. 16.or/1-15 17.Heart Disease/ 18.Cardiovascular Disease/ 19.Coronary Artery Disease/ 20.Coronary Artery Atherosclerosis/ 21.Coronary Artery Obstruction/ 22.(coronary arter$ adj5 stenosis).tw. 23.coronary atheroscleros$.tw. 24.coronary arterioscleros$.tw. 25.(coronary adj5 disease).tw. 26.CAD.tw. 27.or/17-26 28.Angiography/ 29.exp Cardiography/ 30.exp Computer Assisted Tomography/ 31.Arteriography/ 32.exp Heart Function Test/ 33.Xeroradiography/ 34.Tomography/ 35.exp Emission Tomography/ 36.Magnetic Resonance Angiography/

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(Continued)

37.Nuclear Magnetic Resonance Imaging/
38.Radiography/
39.Contrast Radiography/
40.Radioisotope Diagnosis/
41.(Fluoroscopy/ or fluoroscopy.tw.) and (Digital Subtraction Angiography/ or digital subtraction.tw.)
42.exp Heart Scintiscanning/
43.Risk Assessment/
44.Carotid Artery/ and (Ultrasound/ or Echography/)
45.Carotid Artery/ and ((Intima/ and Media/) or (Artery Intima/ and Artery Media/))
46.echocardiogr$.tw.
47.echo.tw.
48.(echo-planar or echoplanar).tw.
49.SPECT.tw.
50.nucleoside$.tw.
51.((sestamibi or cardiolite or dipyridamole or persantin or thallium) adj3 (scan$ or stud$)).tw.
52.electron beam tomograph$.tw.
53.EBT.tw.
54.(comput$ adj2 tomograph$).tw.
55.ct scan$.tw.
56.cat scan$.tw.
57.MRA.tw.
58.MRI.tw.
59.magnetic resonance.tw.
60.angiogr$.tw.
61.coronary catheteri?ation.tw.
62.((dobutamine or adenosine) adj3 stress).tw.
63.troponin.tw.
64.calcium scor$.tw.
65.cardiac enzyme$.tw.
66.perfusion imaging.tw.
67.perfusion stud$.tw.
68.perfusion scintigra$.tw.
69.stress test$.tw.
70.exercise.tw.
71.treadmill.tw.
72.bicycle.tw.
73.risk stratification.tw.
74.risk algorithm.tw.
75.(carotid adj2 (ultrasound or ultrasonogra$)).tw.
76.(carotid adj2 (media$ intima$ thickness or intima$ media$ thickness)).tw.
77.or/28-76
78.and/16,27,77

Appendix 2. QUADAS methodological items and operational definitions

Methodological variable	Operational definition/information required from each study

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(Continued)

1. Representative spectrum (*spectrum bias*)	When included patients did not represent the intended targeted population, this may have led to an under- or overestimation of diagnostic accuracy depending on the difference between the targeted and included populations. The target spectrum in our review was patients with renal failure who were candidates for kidney transplantation. This was scored 'yes' if study participants included only patients with kidney disease who were considered to be candidates for kidney transplantation
2. Acceptable reference standard	An imperfect reference standard may have resulted in misclassification of disease positives and disease negatives. For the purpose of this review, studies had an acceptable reference standard if they used coronary angiography as the reference standard
3. Acceptable delay between tests (*disease progression bias*)	Disease may have progressed to a more advanced stage (i.e. greater degree of coronary artery stenosis) if a significant time interval between index and reference tests was observed, thereby leading to disease progression bias. This was scored as 'yes' if the delay between test was short (i.e. less than three months)
4. Partial verification avoided (*verification bias*)	Partial verification bias usually leads to an overestimation of sensitivity, although its effect on specificity varies. This item was scored 'yes' if all patients who received the index test were also evaluated by the reference standard
5. Differential verification avoided	This was scored 'yes' if no patients were verified with a second or third reference standard
6. Incorporation avoided (*incorporation bias*)	This bias usually leads to an overestimation of diagnostic test accuracy. Incorporation bias was deemed to have existed if the index test was incorporated in a composite reference standard. Studies were scored 'yes' if their classification of disease status did not directly involve the results of the index test
7. Reference standard results blinded (*information bias*)	When the reference standard was interpreted knowing the index test results, this may have led to the overestimation of diagnostic test accuracy. Studies were scored 'yes' if blinding of the reference standard was explicitly stated in the article or if this was acknowledged by authors in subsequent personal communication. Otherwise, the studies were marked 'unclear', unless blinding was explicitly stated to be absent
8. Index test results blinded (*information bias*)	When the index test results were interpreted without the knowledge of results of the reference standard, or with more information than in practice, this may have resulted in bias, usually leading to an overestimation of diagnostic accuracy. This item was scored 'yes' if blinding of the index test was explicitly stated in the article or if this was acknowledged by authors in subsequent personal communication. Otherwise, the studies were marked 'unclear', unless blinding was explicitly stated to be absent
9. Relevant clinical information (*information bias*)	The availability of clinical data during interpretation of test results may have affected estimates of test performance. This item was scored 'yes' if the data available during the study of diagnostic test accuracy was the same as that which would have been available in normal clinical practice
10. Uninterpretable results explained	This item was scored 'yes' if uninterpretable results were explained or if there were no uninterpretable results present. This item was scored 'no' if uninterpretable results were found but not explained
11. Withdrawals explained	Excluding patients from the study may have led to an overestimation of diagnostic accuracy. This item was scored 'yes' if withdrawals were explained or if there were no withdrawals from the study. This item was scored 'no' if there were withdrawals from the study, but these were unexplained

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CONTRIBUTIONS OF AUTHORS

- Louis W Wang: Designed and co-ordinated the review, collected data, undertook searches, screened search results, organised study retrieval, screened retrieved studies against inclusion criteria, appraised study quality, extracted data, corresponded with study authors to obtain additional information, data management, entry, analysis and interpretation, review writing.
- Angela C Webster: Designed and co-ordinated the review, corresponded with study authors to obtain additional information, analysed and interpreted data, review writing, provided general advice on the review, performed previous work that was the foundation of the current study, provided methodological and clinical perspectives (transplant physician).
- Magid A Fahim: Data collection, undertook searches, screened search results, screened retrieved studies against inclusion criteria, appraised study quality, data extraction.
- Ruth Mitchell: Designed search strategies, undertook searches.
- Andrew Hayen: Designed the statistical methodology, analysed and interpreted data.
- Laura Baines: Performed previous research that formed the foundation of the current review, provided a clinical perspective (nephrology).
- Stephen Lord: Performed previous research that formed the foundation of the current review, provided a clinical perspective (cardiology).
- Jonathan C Craig: Provided methodological and clinical perspectives, and general advice on the review.

DECLARATIONS OF INTEREST

- Laura Baines: None known
- Jonathan C Craig: None known
- Magid A Fahim: None known
- Andrew Hayen: None known
- Stephen Lord: None Known
- Ruth L Mitchell: During the time I have been an author on this review my salary has been supported through a grant from the Cochrane Collaboration for work on the Cochrane register of diagnostic test accuracy studies.
- Louis W Wang: None known.
- Angela C Webster: None known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Sparsity of data, both in terms of numbers of studies and participants, meant that we were unable to perform meaningful subgroup analyses of the effect of DM or prevalence of angina and symptomatic ischaemic heart disease on diagnostic test performance.

NOTES

An earlier version of this review was published in the *American Journal of Kidney Diseases* (Wang 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

*Kidney Transplantation; Coronary Angiography [*standards]; Coronary Artery Disease [*diagnosis] [etiology]; Heart Function Tests [*methods] [standards]; Kidney Failure, Chronic [*complications]; Pancreas Transplantation; Reference Standards

MeSH check words

Humans

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