Title: Prognostic value of cardiac tests in potential kidney transplant recipients: a systematic review

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Abbreviations

CI: Confidence interval

DSE: Dobutamine stress echocardiography

ECG: Electrocardiogram

ESKD: End stage kidney disease

MACE: Major adverse cardiac event

MPS: Myocardial perfusion scintigraphy

OR: Odds ratio

RD: Risk difference

RR: Relative risk

RRR: Relative risk ratio

Abstract

Background: Whether abnormal myocardial perfusion scintigraphy (MPS), dobutamine stress echocardiography (DSE) or coronary angiography, performed during preoperative evaluation for potential kidney transplant recipients, predicts future cardiovascular morbidity is unclear. We assessed test performance for predicting all-cause mortality, cardiovascular mortality and major adverse cardiac events (MACE).

Methods: We searched MEDLINE and EMBASE (to February 2014), appraised studies and calculated risk differences (RD) and relative risk ratios (RRR) with 95% confidence intervals using random effects meta-analysis.

Results: 52 studies (7401 participants) contributed data to the meta-analysis. Among the different tests, similar numbers of patients experienced MACE after an abnormal test result compared with a normal result (RD: MPS 20 per 100 patients tested (95% CI: 0.11–0.29), DSE 24 (95% CI: 0.10–0.38) and coronary angiography 20 (95% CI: 0.08–0.32; *P*=0.91). Although there was some evidence that coronary angiography was better at predicting all-cause mortality than MPS (RRR 0.69, 95% CI: 0.49–0.96; *P*=0.03) and DSE (RRR 0.72, 95% CI: 0.50, 1.02; *P*=0.06), non-invasive tests were as good as coronary angiography at predicting cardiovascular mortality (RRR MPS 0.89, 95% CI: 0.38–2.10; *P*=0.78; DSE 1.09, 95% CI: 0.12–10.05; *P*=0.93) and MACE (RRR MPS 1.09, 95% CI: 0.64–1.86; *P*=0.74; DSE 1.56, 95% CI: 0.71–3.45; *P*=0.25).

Conclusions: Non-invasive tests are as good as coronary angiography at predicting future adverse cardiovascular events in advanced chronic kidney disease. However, a substantial number of people with negative test results go on to experience adverse cardiac events.

Introduction

Cardiovascular evaluation is an important part of the preoperative workup of potential kidney transplant candidates. Cardiac tests aim to identify patients at increased risk of future major adverse cardiovascular events (MACE) who may benefit from pre-emptive medical or surgical intervention prior to receiving a transplant. The scarcity of organs available for transplant means that cardiovascular evaluation results inform the best use of a limited resource, by excluding patients with unmodifiable advanced cardiovascular disease and poor long term prognosis (1).

While on the transplant waiting list, and after transplantation, cardiovascular disease is the commonest cause of death. Recent systematic reviews of diagnostic test accuracy have demonstrated that non-invasive functional tests have moderate accuracy in predicting obstructive coronary artery disease in potential kidney transplant recipients (2,3). Non-invasive cardiac tests (e.g. myocardial perfusion scintigraphy, MPS, and dobutamine stress echocardiography, DSE) perform well in predicting cardiovascular events in the general population undergoing major non-cardiac surgery (4-8), but their performance in patients with end-stage kidney disease (ESKD) is unclear. In patients with ESKD, not all cardiovascular events are caused by myocardial ischaemia, with congestive cardiac failure and fatal ventricular arrhythmia being major causes of cardiovascular mortality (9). Patients with ESKD also have a high incidence of cardiomyopathy, hypertension and calcific coronary artery disease (associated with coronary flow reserve abnormalities), all of which may affect cardiac test performance and test results (10-12). Accurately identifying patients with obstructive coronary artery disease may not necessarily identify patients who are at high risk of MACE following transplantation.

Clinical guidelines from the American Heart Association / American College of Cardiology Foundation (13), American Society of Transplantation (14), Canadian Society of Transplantation

(15), and UK Renal Association (16) recommend using a non-invasive test in patients with known coronary artery disease, symptoms of coronary artery disease and in asymptomatic individuals with multiple risk factors for coronary artery disease. Coronary angiography is recommended as a subsequent test in patients with an abnormal non-invasive testing. These guidelines do not specify which non-invasive test should be used, other than that this should be determined by local availability and expertise. Despite this guidance, uncertainty among clinicians means clinical practice varies in deciding which patients to test and which tests to use when evaluating people for kidney transplantation.

We undertook a systematic review to evaluate the prognostic value of cardiac tests in predicting future MACE, cardiovascular mortality and all-cause mortality in patients being considered for kidney transplantation.

Materials and Methods

Search Strategy

Two investigators searched MEDLINE and EMBASE (via OvidSP) from inception to April 30, 2014 without language restriction, using MeSH headings and text word terms for kidney transplantation, chronic kidney disease and index tests (SDC, Materials and Methods). To locate studies not indexed in MEDLINE or EMBASE, we included citation tracking through Web of Science and checked bibliographies of relevant identified studies. Inter-observer agreement was reported using the kappa coefficient.

We included all cohort studies and randomised controlled trials which reported prognostic outcomes and tested adult potential kidney transplant recipients. Cardiac tests included MPS, DSE, coronary angiography, exercise and resting ECG, electron beam computed tomography, computed tomography coronary angiography, cardiovascular magnetic resonance imaging and cardiopulmonary exercise testing. We excluded studies of patients who were not candidates for a kidney transplant (i.e. unselected dialysis patients not undergoing pre-transplant assessment).

Using a structured template, we extracted details of design, setting, duration, and the outcomes reported in each study. We also recorded which cardiac test was used, the definition of an abnormal cardiac test, and baseline characteristics of the study population. Our outcomes included all-cause mortality, cardiovascular mortality, and MACE. The definition of MACE included cardiovascular death, myocardial infarction, arrhythmia and pulmonary oedema. MACE only included coronary revascularization when it was undertaken following myocardial infarction, or arrhythmias caused by myocardial ischaemia. Cardiovascular death included death from myocardial infarction, arrhythmia and stroke.

Two reviewers independently performed methodological quality assessment of included studies using existing guidelines (17,18). Where possible, we contacted study authors to obtain data not available in published format. This systematic review of prognostic accuracy is an extension of an existing systematic review of diagnostic test accuracy, which had a published protocol (2).

Quantitative Data Synthesis

We calculated pooled risk difference (RD) and relative risk (RR) of an abnormal test predicting each of the pre-specified outcomes, with their 95% confidence intervals (CI) using a random effects model (Review Manager 5.1 (www.revman.com) and tested for heterogeneity using the Cochran Q statistic and I^2 values. We expressed the risk difference as the number of additional patients (per 100 patients tested) with an abnormal test result that developed the outcome compared with those with a normal test result. For each outcome, we produced summary forest plots stratified by cardiac test. We then investigated sources of heterogeneity using subgroup analyses and meta-regression. First, we grouped MPS and DSE studies according to their definition of what an abnormal test was. Specifically, we investigated whether our results varied among studies which classified patients with fixed defects without reversible components as being normal or abnormal. For studies which used coronary angiography, we investigated whether the threshold of stenosis used to diagnose coronary artery disease (≥50% or ≥70%) changed our results. To investigate confounding by multiple study-level characteristics, we then fitted a multivariate-adjusted random-effects meta-regression model for each cardiovascular outcome using SAS9.2 (www.sas.com). We investigated how the likelihood of each outcome varied by which cardiac test was used, the prevalence of coronary artery disease and diabetes mellitus, the positive test rate in the study population and the duration of follow up. Finally, when data were available, we performed multivariate logistic regression to analyse how revascularization or transplantation affected the risk of each pre-

specified cardiovascular outcome. As treatment strategies, perioperative management of patients with cardiovascular risk, transplant age as well as performance of cardiac tests differ over time, and since this also has the potential to affect post-test outcomes, we also performed a sensitivity analysis including studies which were published from 2000 onwards.

Results

Studies Included for Analysis

We included 100 studies (Fig. 1). Outcome data suitable for meta-analysis for individual tests could not be extracted from 48 studies (SDC, References), so 52 studies (7401 participants) were included in data synthesis. Inter-observer agreement for data abstraction and bias assessment was good (kappa=0.87). Characteristics of included studies are presented in Table 1. One research group produced seven studies with overlapping populations (19-25), and so we included only the study which had the largest population of patients to avoid bias by including the same participants more than once. No studies were found evaluating electron beam computed tomography, computed tomography coronary angiography, cardiovascular magnetic resonance imaging and cardiopulmonary exercise testing.

The results of the methodology quality assessment are presented in SDC Fig. 1 and SDC Table 1. Whether the assessors of outcomes or cardiac test results were blinded to test results was reported in only 26 of 52 studies (outcome assessment was blinded in 11 studies, unblinded in 15 studies), and unknown in 26 studies. All studies had a population which was representative of the average patient with ESKD undergoing pre-transplant cardiac evaluation and used appropriate statistical analysis on the outcome data provided.

All-cause Mortality

All-cause mortality was investigated in studies of MPS (11 studies, 1564 participants) (26-36), DSE (five studies, 779 participants) (37-41), and coronary angiography (12 studies, 1839 participants) (22,26,33,40,42-49) (Fig. 2). One study reported all-cause mortality in relation to

exercise ECG (477 participants) (37), and two studies in relation to a resting ECG (667 participants) (37,50). The percentages of patients developing outcomes of interest during the study follow up period, according to test type and test result are presented in Table 2. Seven additional participants in every 100 (95% CI: -0.03–0.18) with an abnormal MPS test result died compared to those with a normal test result. For DSE, 12 additional participants in every 100 (95% CI: 0.06–0.17) with an abnormal test result died, whilst for coronary angiography an additional 15 participants in every 100 (95% CI: 0.07–0.24) with an abnormal test died compared to those with a normal test. Considering the risk of all-cause mortality, there was weak evidence that the prognostic value was better for coronary angiography than MPS (RRR 0.69; 95% CI: 0.49–0.96; *P*=0.03) or DSE (RRR 0.72; 95% CI: 0.50–1.02; *P*=0.06) (Table 3, SDC Fig. 3).

Cardiovascular Mortality

The ability to predict cardiovascular mortality using MPS (10 studies, 1092 participants) (27,29-33,51-54), DSE (two studies, 202 participants) (55,56), and coronary angiography (seven studies, 220 participants) was also evaluated (20,33,42,48,53,54,56) (SDC Fig. 2). For every 100 patients with an abnormal test, an additional six (CI -0.02–0.13) tested with MPS, 13 (CI -0.01–0.27) tested with DSE and 22 (CI 0.13–0.31) tested by coronary angiography died from cardiovascular disease compared to those participants with a normal test. The RR of cardiovascular mortality did not vary between studies using coronary angiography versus a non-invasive functional test (RRR MPS 0.89; 95% CI: 0.38–2.10; *P*=0.78; DSE 1.09; 95% CI: 0.12–10.05; *P*=0.93, Table 3, SDC Fig. 4).

Major Adverse Cardiac Events

Nineteen studies (2689 participants) reported major adverse cardiovascular events following a MPS (19,24,27,28,30-32,34,35,52,57-65), ten studies (637 participants) following DSE

(21,38,41,55,56,62,66-69), and 17 studies (1947 participants) following coronary angiography (20-24,35,43,48,50,56,60,61,63,64,68,70,71) (Fig. 3). One study (19 participants) reported MACE in relation to the results of an exercise ECG(37,62) and following a resting ECG in another one study (190 participants) (50). MACE following conventional echocardiography was reported in one study (87 participants) (62). For every 100 patients with an abnormal test, an additional 20 (CI 0.11–0.29) tested with MPS, 24 (CI 0.10–0.38) tested with DSE and 20 (CI 0.08–0.32) tested by coronary angiography experienced MACE compared with those participants with a normal test. The RR of MACE did not vary between studies using coronary angiography versus non-invasive tests (RRR MPS 1.09; 95% CI: 0.64–1.86; *P*=0.74; DSE 1.56; 95% CI: 0.71–3.45; *P*=0.25, Table 3, SDC Fig. 5).

We observed significant heterogeneity for MPS, DSE and coronary angiography studies investigating MACE (*P* <0.0001, 0.002 and <0.0001 respectively), MPS studies investigating cardiovascular mortality (*P* <0.0001), and MPS and coronary angiography studies investigating all-cause mortality (*P* <0.0001 for both). For each cardiac test, studies were stratified according to definition of an abnormal test result. Heterogeneity persisted after stratifying studies according to definition of an abnormal test result (SDC Table 2).

Sensitivity analysis and investigation of heterogeneity

As test use has changed over time, a sensitivity analysis was performed on studies published from 2000 onwards, to examine contemporary evidence (Table 4). Overall, although the confidence intervals of the summary estimates were wider, due to reduced power from smaller numbers of included participants, the point estimates were similar to the overall analysis when all studies were included. Heterogeneity largely persisted even in the group of studies published from 2000 onwards.

To evaluate heterogeneity further, we built meta-regression models for each of the specified outcomes. The frequency of abnormal cardiac results in the study population, proportion of patients transplanted during follow up, prevalence of diabetes mellitus, proportion of the study population that was revascularized or transplanted, and median duration of follow-up did not have a significant effect on the RR of any of the pre-specified outcomes (Fig. 4). Six studies investigating coronary angiography presented separate outcome data according to whether or not study participants underwent revascularization (45,46,48,56,63,64). Three studies provided separate data for all-cause mortality according to revascularization status (45,46,48). Using logistic regression random effects models, after accounting for the effect of revascularization, the odds ratio (OR) for all-cause mortality for abnormal coronary angiography was 2.96 (95% CI: 1.25–7.00; *P*=0.01). Four of these studies provided data for MACE (48,56,63,64). The OR for MACE if a patient was found to have significant coronary artery disease on coronary angiography was 16.02 (95% CI: 2.42–105.98; *P*=0.004). Revascularization, however, was associated with a significant reduction of future MACE (OR 0.19; 95% CI: 0.05–0.72; *P*=0.01). Revascularization was also associated with a significant reduction in risk of all-cause mortality (OR 0.28; 95% CI: 0.12–0.64; *P*=0.003).

Fourteen studies presented separate outcome data according to transplantation status (27,29-33,36,45,50,56,57,63,64,70). Transplantation reduced the risk of all-cause mortality (OR 0.19; 95% CI: 0.11–0.33; *P*<0.001) and cardiovascular mortality (OR 0.32; 95% CI: 0.16–0.65; *P*=0.001), but not MACE (OR 0.78; 95% CI: 0.24–2.53; *P*=0.7). Insufficient studies were available to provide separate outcome data according to both transplantation and revascularization status, and therefore we were unable to find their adjusted combined effects on adverse outcome.

Discussion

This current systematic review presents the largest meta-analysis of prognostic data to date for DSE, MPS and coronary angiography in potential kidney transplant recipients. We found that when performed as part of preoperative cardiac screening, the prognostic value of an abnormal DSE or MPS appeared to be at least as good as abnormal coronary angiography for predicting the outcomes cardiovascular mortality and MACE.

Our review describes more mortality and cardiovascular outcomes than an earlier review published in 2003 (72), that focused on MPS, included only twelve studies (with many studies using older stress-perfusion protocols) and only investigated the ability of abnormal test results to predict cardiovascular mortality and myocardial infarction. This earlier review concluded that abnormal MPS was useful in predicting myocardial infarction and cardiac death in patients with ESKD on the basis of a statistically significant elevated RR of adverse outcome for an abnormal test result compared with a normal test (RR cardiac death 2.52, 95% CI: 1.25–5.08; *P*=0.01; RR myocardial infarction 2.79, 95% CI: 0.85–9.21; *P*=0.09). We obtained similar results for mortality outcomes and MACE for MPS, albeit with greater statistical precision due to the much larger number of included studies and participants. Transplantation was associated with improved survival and revascularization was associated with less MACE.

For the first time, our study provides clarity on the ability of MPS, DSE and coronary angiography at predicting adverse cardiac outcomes. These cardiac tests are the most commonly used and so our conclusions provide clinicians robust data in helping decide which test should be used. Our results question the rationale of routinely performing either a non-invasive or an invasive cardiac testing before a kidney transplant as all tests predict outcomes poorly, since a large number of patients with negative test results still have adverse cardiac outcomes, while a substantial proportion of patients with abnormal test results do not have adverse cardiac outcome. Unfortunately, the

included studies did not elaborate further on the characteristics of the patients who had false negative test results, and it is unclear whether this group of patients had a higher incidence of valvular heart disease, atrial fibrillation or pulmonary hypertension, which may have put them at increased risk of adverse events. We acknowledge that no test is perfect, and, in addition, our data does not indicate clear superiority of one non-invasive test over the other. Choice of non-invasive testing is often influenced by other factors such as physician preference and presence of comorbidities that necessitate one test over the other (e.g. MPS is favoured in patients with uncontrolled hypertension or arrhythmia, while DSE is favoured in patients with reversible airways disease or hypotension). Furthermore, underlying differences are likely to exist in the baseline characteristics among the patient populations that underwent MPS and DSE.

In contrast with the earlier review (72), which found that reversible defects were associated with increased risk of cardiac death, we did not find evidence that only reversible defects in MPS or regional wall motion abnormalities on DSE were more predictive of adverse cardiac events than when defining an abnormal test as both fixed and reversible abnormalities. Acute myocardial ischaemia is not the only cause of adverse cardiac outcome in patients with ESKD as arrhythmias and decompensated congestive cardiac failure are also common (9). Peri-operative complications occur more frequently in patients with cardiomyopathy and poor left ventricular systolic function (6), findings which are common in patients with ESKD and which can be diagnosed with both MPS and DSE. This may explain why non-invasive functional tests performed as well as coronary angiography in predicting MACE and cardiovascular mortality, and why DSE and MPS studies that included fixed abnormalities in their definition of an “abnormal test result” were also able to identify patients at increased risk of adverse cardiac outcome.

Cardiovascular complications, sepsis and death from renal failure comprise the major causes of death in the short to medium term following kidney transplantation. Interestingly, there was some

evidence that coronary angiography was better than MPS or DSE at predicting all-cause mortality but equivalent to these non-invasive tests when predicting risk of cardiovascular mortality. This finding should be interpreted with caution as it was of only borderline statistical significance and because estimates of risk of all-cause and cardiovascular mortality were derived from different study populations.

Strengths of this work include a comprehensive search strategy which identified both published and unpublished studies. Our results are also specific to candidates for kidney transplantation because we only included studies of potential kidney transplant recipients and not unselected patients with ESKD. This avoided potential differences in underlying prevalence of coronary artery disease, co-morbidities and clinical rationale for testing which one might expect in studies which included unselected dialysis patients.

Our systematic review had several limitations. The conclusion that the prognostic value of an abnormal DSE or MPS appeared to be at least as good as abnormal coronary angiography for predicting the outcomes cardiovascular mortality and MACE is based on these tests being performed in similar patient populations. The populations described were broadly similar across studies, although studies evaluating coronary angiography had higher event rates for each of the outcomes of interest compared with studies evaluating non-invasive tests (Table 2). It is therefore possible that those undergoing diagnostic coronary angiography may have already had a previous abnormal DSE or MPS, or be otherwise at higher risk. It is possible that the predictive ability of coronary angiography was falsely reduced by subsequent revascularisation after abnormal coronary angiography, as percutaneous coronary interventions or coronary artery bypass surgery may have reduced the risk of future adverse cardiac events compared with what would have been expected according to the natural history of this condition. In the general population, early revascularization can significantly change the natural history of coronary artery disease and affect survival,

especially for left main disease, proximal left anterior descending or severe three-vessel coronary artery disease. However, it is unclear whether this holds true for patients with ESKD. The optimum revascularisation strategy remains unclear in patients with ESKD and obstructive coronary artery disease, as percutaneous coronary intervention is associated with improved early survival, while coronary artery bypass surgery long term survival (73). In the majority of studies, it is unclear whether cardiac events occurred pre- or post-transplant. Few studies presented sufficient data regarding which patients in their cohort received early revascularization following cardiac testing or the type of revascularization strategy, so we could not control for this during analysis. As a result, we were unable to determine whether or not an abnormal test result leading to revascularization affects either wait list or post-transplant mortality or MACE. Several studies provided data on whether or not participants received a kidney transplant and whether or not participants underwent cardiac revascularization but rarely gave data regarding both. We were therefore unable to adjust for the competing effects of revascularisation and transplantation. Unequal numbers of patients underwent MPS, DSE and coronary angiography, with more participants undergoing MPS. The small numbers of participant undergoing DSE may affect the precision of our results, as well as the power to detect any significant difference between MPS and DSE. Duration of follow up varied within and between studies and made comparison of tests difficult. Although we explored the effect of study duration in meta-regression and did not find a relationship between median duration of follow up and outcome, this was performed using study-level data only. An analysis of individual patient level data would potentially allow more subtle differences to be revealed. Because we did not have access to individual patient data, we could not examine the effect of potential confounders of adverse events after a kidney transplant, including the time spent of the transplant waiting list, duration of follow up and whether participants had any heart revascularization before or after their kidney transplant. It was not possible to evaluate whether prognostic test performance differed according to gender as this was invariably not reported in the primary studies identified in this review. A substantial number of studies in this

review were unblinded, with physicians caring for the patients having access to the results, and this could create significant bias with respect to having imaging results impact on future patient care. The studies included in this analysis also spanned three decades. The fact that the sensitivity analysis including only studies performed after 2000 yields similar results to the overall analysis is reassuring. Nevertheless, test performance, diagnostic accuracy and perioperative management of patients with cardiovascular risk may change in the future with technical advances. Despite these limitations, we believe our work represents the best pragmatic design and most comprehensive overview of the relationship between cardiac test results and subsequent patient outcomes in this population.

DSE requires an intravenous infusion and is both time and labour intensive. Although the diagnostic accuracy of exercise stress echocardiography, which is more easily accessible, is likely similar to that of DSE in the healthy normal population, there is a higher risk of sub-maximal stress and uninterpretable test result with exercise stress testing, especially among patients with renal impairment who may have exercise limitation due to other comorbidities such as peripheral vascular disease, diastolic dysfunction secondary to hypertensive heart disease, fluid overload and pulmonary hypertension. DSE has an advantage over MPS in that it does not involve radiation exposure, and this should be a consideration for patients being considered for kidney transplantation who often require repeated screening investigations due to long waiting lists for transplantation and because they are increased risk of future malignant complications.

In conclusion, non-invasive screening tests appear to be at least as good as coronary angiography at predicting future adverse outcome. Both normal DSE and MPS results are associated with a relatively low risk of future adverse events; a normal non-invasive screening test should therefore reassure both the clinician and patient. Initial investigation with coronary angiography, is not warranted in the absence of a conventional indication or as part of a research study. Future studies

are required to investigate whether or not cardiac evaluation strategies result in lower risk of MACE and improved survival. , and which cardiac test should be offered to patients based on their baseline cardiovascular risk. Given that some patients with negative test results develop adverse cardiac events, further study into the characteristics of patients belonging to this false negative cohort should be performed. Better understanding of this patient group and the mechanisms of adverse cardiac events in patients with normal non-invasive testing and/or coronary angiography may help identify other important preoperative risk factors and potentially reduce the frequency of adverse cardiovascular events in the future.

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Table 1: Characteristics of studies included in the quantitative meta-analysis

Study	Country	Number of patients undergoing test	Definition of abnormal test (% stenosis, type of defect, RWMA)	% patients with known cardiovascular disease	% diabetic	% study population revascularized	% study population transplanted	Median follow up (years)	Outcomes measured
Myocardial perfusion scintigraphy[a]									
Ali 2011 (4)	Qatar	39	Reversible	?	47	1.3	100	5.2	MACE
Arantes 2010 (1)	Brazil	363	Fixed+reversible	30	32	?	0	1.4	MACE
Atkinson 2011 (1)	UK	47	Fixed+reversible	?	23	8.5	38	6.3	ACM
Brown 1989 (2)	USA	65	Reversible	3	55	?	54	1.9	MACE
Camp 1990 (2)	USA	40	Reversible	7.5	100	2.5	52.5	0.9	MACE
Cottier 1990 (6)	Switzerland	70	Fixed+reversible	0	0	0	87	2.3	CVM
Derfler 1991 (2)	Austria	23	Fixed+reversible	17	17	?	100	6	MACE CVM ACM
Feola 2002 (1)	Italy	82	Reversible	2	24	6.1	27	2.4	MACE ACM
Fuster 2000 (1)	Spain	77	Reversible	10	100	1.3	94	?	MACE
Gowdak 2010 (1)	Brazil	234	Reversible	?	45	?	?	2.1	MACE
Holley 1991 (3)	USA	141	Reversible	?	100	0.7	68	3.6	MACE
Le 1994 (3)	USA	95	Reversible	9	60	3.2	43	2.9	CVM ACM
Leonardi 2009 (1)	Italy	302	Reversible	43	6	3.0	55	3.5	CVM ACM
Lewis 2002 (4)	USA	112	Fixed+reversible	10	32	2.7	56	2.3	MACE CVM
Lin 2001 (5)	USA	95	Reversible	17	100	2.1	?	1.0	MACE
Marwick 1990 (2)	USA	45	Fixed + reversible	16	31	?	?	2.1	CVM
Mistry 1990 (2)	USA	176	Reversible	?	100	6.8	100	0.02	MACE
Morrow 1983 (3)	USA	54	Reversible	7	100	?	70	2.5	MACE CVM ACM
Patel 2003 (5)	UK	174	Fixed+reversible	5	28	4.6	100	3.5	MACE CVM ACM
Philipson 1986 (3)	USA	60	Reversible	?	100	?	62	1.0	MACE ACM
Radhakrishnan	USA	505	Reversible	?	?	1.4	?	1.0	MACE

2012									
Ruparelia 2011 (5)	UK	98	Fixed+reversible	NA	100	3.1	100	1.0	MACE
Stoll 2011	UK	99	Fixed+reversible	?	100	12.1	?	?	MACE ACM
Vandenberg 1996 (4)	USA	41	Fixed+reversible	0	100	9.8	79	2.9	MACE ACM
Venkataraman 2008 (5)	USA	150	Fixed+reversible	NA	66	44.7	0	3.4	ACM
Wong 2008 (5)	UK	126	Reversible	29	42	4.0	33	2.6	CVM
Dobutamine stress echocardiography									
Bates 1996	USA	53	Any RWMA	23	100	7.5	66	2.2	MACE CVM
Bergeron 2007	USA	477	Any RWMA	31	49	?	33	2.3	ACM
Brennan 1997	USA	47	New RWMA	21	56	2.1	?	1.7	MACE ACM
Cortigiani 2004	Italy	71	New RWMA	3	21	4.2	45	3.0	MACE
Cross 1996	USA	72	?	?	?	4.2	?	2.2	MACE
De Lima 2003	Brazil	93	New RWMA	10	30	?	?	4.0	MACE
Herzog 1999	USA	50	New RWMA	16	82	32	44	1.9	MACE
Krotin 2007	Serbia	24	New RWMA	?	?	?	?	?	MACE
Lin 2001	USA	45	New RWMA	17	100	?	?	1.0	MACE
Reis 1995	USA	97	New RWMA	30	64	4.1	26	1.0	ACM
Sharma 2005	UK	125	New RWMA	13	39	12.0	28	1.6	ACM
Tita 2008	USA	149	New RWMA	11	65	0.7	100	2.9	MACE CVM
West 2000	USA	33	Any RWMA	?	?	15.2	?	?	MACE ACM
Coronary angiography									
Ali 2004	Ireland	43	≥70% stenosis	11	13	23.2	100	5.2	MACE
Atkinson 2011	UK	47	≥50% stenosis	?	23	8.5	38	6.3	ACM
Bennett 1978	USA	11	≥70% stenosis	0	100	?	45	1.7	CVM ACM
Braun 1984	USA	100	≥70% stenosis	9	100	?	58	1.9	ACM
De Lima 2003	Brazil	110	≥70% stenosis	10	30	?	?	4.0	MACE
De Lima 2010	Brazil	106	≥70% stenosis	27	32	?	?	0.80	MACE
Enkiri 2010	USA	57	≥70% stenosis	42	61	8.8	51	1.0	ACM
Eschertzhuber 2005	Austria	89	≥50% stenosis	100	?	17.9	100	?	ACM
Fossati 2004	Italy	18	?	?	100	11.1	100	0.05	MACE CVM ACM

Fuster 2000	Spain	12	≥70% stenosis	10	100	8.3	94	?	MACE
Gowdak 2007 CAD	Brazil	301	≥70% stenosis	28	42	?	?	1.8	MACE
Gowdak 2007 NDT	Brazil	288	≥70% stenosis	29	40	?	23	1.8	MACE ACM
Gowdak 2010	Brazil	479	≥70% stenosis	?	45	?	?	2.1	MACE
Herzog 1999	USA	50	≥50% stenosis	16	82	32	44	1.9	MACE
Holley 1991	USA	105	≥50% stenosis	?	100	?	68	3.6	MACE
Kahn 2011	USA	357	≥70% stenosis	21	41	36.0	100	2.9	ACM
Kumar 2011	UK	657	≥70% stenosis	18	47	25.5	43	0.30	ACM
Manske 1997	USA	198	≥50% stenosis ≥75% stenosis	16	100	16.2	81	3.0	MACE
Manske 1992	USA	26	≥75% stenosis	19	100	50	54	1.8	MACE CVM
Marwick 1990	USA	45	≥70% stenosis ≥50% stenosis	16	31	?	?	2.1	CVM
Mistry 1990	USA	42	≥70% stenosis	?	100	?	100	0.02	MACE
Philipson 1986	USA	53	≥50% stenosis	?	100	?	62	1.0	MACE ACM
Ruparelia 2011	UK	98	≥50% stenosis	NA	100	3.1	100	1.0	MACE
Sharma 2005	UK	125	≥70% stenosis	13	39	12	28	1.6	ACM
Tita 2008	USA	12	≥70% stenosis	11	65	8.3	100	2.9	MACE ACM
Vandenberg 1996	USA	37	≥50% stenosis	0	100	9.8	79	2.9	MACE
Wong 2008	UK	19	?	29	42	26.3	33	2.6	CVM
Worthley 2003	Australia	40	≥70% stenosis	18	78	17.5	43	2.3	ACM
Exercise ECG									
Bennett 1978	USA	11	New ECG changes	0	100	?	45	1.7	CVM ACM
Bergeron 2007	USA	477	New ECG changes	31	49	?	33	2.3	ACM
Echocardiography									
Lin 2001	USA	87	Reversible	17	100	?	?	1.0	MACE
Resting ECG									
Ali 2004	Ireland	190	Q waves, ST/T changes, arrhythmia, LVH	11	13	5.3	100	5.2	MACE ACM
Bergeron 2007	USA	477	ST/T changes	31	49	?	33	2.3	ACM
Lin 2001	USA	19	?	17	100	?	?	1.0	MACE

[a] For MPS, the type of stress protocol used is coded: 1=dipyridamole stress, sestamibi; 2=dipyridamole stress, thallium; 3=exercise stress, thallium; 4=multiple stress agents, thallium; 5=multiple stress agents, sestamibi; 6=exercise radionucleotide angiocardiography; RWMA: regional wall motion abnormality; MACE: major adverse cardiac event; ACM: all-cause mortality; CVM: cardiovascular mortality. CAD: Coronary artery disease (journal); NDT: Nephrology, dialysis and transplantation (journal).

Table 2: Percentages of patients developing outcome of interest, stratified by test type and test result

Outcome	Test	% patients with abnormal test results who develop outcome during follow up (per 100 tested, 95% CI)	% patients with normal test results who develop outcome during follow up (per 100 tested, 95% CI)	% of patients who develop outcome during follow up from the total number of patients tested (per 100 tested, 95% CI)
All-cause mortality	MPS studies	28.0 (14.8, 41.2)	18.2 (11.5, 25.0)	23.4 (15.1, 31.64)
	DSE studies	19.6 (0.08, 39.0)	9.4 (0, 20.6)	12.8 (0, 27.8)
	Coronary angiography studies	33.3 (21.8, 44.7)	13.4 (7.7, 19.0)	22.2 (15.4, 29.0)
Cardiovascular mortality	MPS studies	11.2 (5.4, 17.0)	4.4 (2.0, 6.8)	7.8 (4.8, 10.8)
	DSE studies	16.4 (3.2, 29.7)	4.5 (1.4, 7.6)	6.4 (3.0, 9.7)
	Coronary angiography studies	24.9 (16.2, 33.5)	4.1 (0.3, 7.9)	14.5 (9.3, 19.7)
Major adverse cardiac event	MPS studies	19.0 (12.3, 25.6)	3.9 (2.1, 5.6)	9.7 (6.6, 12.8)
	DSE studies	31.6 (17.7, 45.5)	6.3 (4.2, 8.4)	11.1 (7.6, 14.6)
	Coronary angiography studies	32.2 (19.6, 44.8)	8.5 (4.2, 12.8)	20.7 (13.0, 28.4)

Table 3: Summary of results

	Studies	Risk Difference (95%CI) per 100 tested	Risk Ratio (95%CI)	Relative Risk Ratio (95%CI)	P value Relative Risk Ratio
All-cause mortality					
MPS (all studies)	11	7.0 (-3.0, 18)	1.47 (1.16, 1.88)	0.69 (0.49, 0.96)	0.03
Reversible defects only	6	1.0 (-6.0, 7.0)	1.22 (0.82, 1.81)		
Fixed+reversible defects	5	14 (-1.0, 29)	1.65 (1.22, 2.25)		
DSE (all studies)	5	12 (6.0, 17)	2.09 (1.12, 3.92)	0.72 (0.50, 1.02)	0.06
Reversible defects only	3	9.0 (1.0, 17)	4.45 (1.54, 12.90)		
Fixed+reversible defects	2	14 (6.0, 22)	1.48 (1.19-1.84)		
Coronary angiography (all studies)	12	15 (7.0, 24)	2.07 (1.45, 2.95)	-	-
Abnormal test defined as ≥50% stenosis[a]	4	25 (-16, 66)	2.15 (0.92, 5.00)		
Abnormal test defined as ≥70% stenosis[a]	9	12 (5.0, 19)	1.90 (1.27, 2.85)		
Cardiovascular mortality					
MPS (all studies)	10	6.0 (-2.0, 13)	2.23 (1.38, 3.62)	0.89 (0.38, 2.10)	0.78
Reversible defects only	5	6.0 (1.0, 11)	2.16 (1.11, 4.22)		
Fixed+reversible defects	5	8.0 (-9.0, 25)	2.26 (0.90, 5.66)		
DSE (all studies)	2	13(-1.0, 27)	4.24 (1.28, 14.09)	1.09 (0.12, 10.05)	0.93
Reversible defects only	1	12 (-5.0, 29)	3.97 (0.95, 16.67)		
Fixed+reversible defects	1	15 (-10, 40)	4.95 (0.55, 44.40)		
Coronary angiography (all studies)	7	22 (13, 31)	3.00 (1.56, 5.78)	-	-
Abnormal test defined as ≥50% stenosis[a]	3	26 (13, 39)	5.55 (0.73, 42.23)		
Abnormal test defined as ≥70% stenosis[a]	6	25 (14, 36)	2.45 (1.28, 4.70)		
Major adverse cardiac event					
MPS (all studies)	18	20 (11, 29)	3.64 (2.21, 5.99)	1.09 (0.64, 1.86)	0.74
Reversible defects only	11	27 (13, 41)	5.64 (2.41, 13.21)		
Fixed+reversible defects	7	12 (1.0, 23)	2.60 (1.75, 3.88)		
DSE (all studies)	10	24 (10, 38)	4.62 (2.74, 7.79)	1.56 (0.71, 3.45)	0.25
Reversible defects only[b]	7	24 (4.0, 45)	3.91 (1.88, 8.16)		
Fixed+reversible defects[b]	2	24 (-9.0, 56)	6.38 (1.76, 23.10)		
Coronary angiography (all studies)	13	20 (8.0, 32)	2.83 (1.82, 4.42)	-	-
Abnormal test defined as ≥50% stenosis	4	17 (-9.0, 44)	3.63 (2.09, 6.30)		
Abnormal test defined as ≥70% stenosis	9	25 (12, 38)	2.73 (1.73, 4.30)		

[a] Bennett 1978 and Marwick 1990 reported data for both ≥50% stenosis and ≥70% stenosis test thresholds. Wong 2008 did not report the threshold of stenosis used in the study.
[b] Cross 1996 did not report the definition of an abnormal test result. It therefore was excluded from the analysis

Table 4: Sensitivity analysis only including studies published from 2000 onwards

All-cause mortality	# Studies	# Patients	RR (95%CI)	RD (95%CI) per 100 tested	Heterogeneity P value (I^2)	P value for difference
MPS (all studies)	**7**	**1496**	**1.51 (0.99, 2.31)**	**5.0 (-4.0, 14)**	**0.29 (19)**	
Reversible defects only	3	925	0.63 (0.24, 1.62)	-3.0 (-11, 6.0)	0.75 (0)	0.04
Fixed+reversible defects	4	571	1.78 (1.28, 2.46)	14 (-1.0, 29)	0.62 (0)	
DSE (all studies)	**3**	**812**	**5.07 (1.25, 20.59)**	**11 (1.0, 21)**	**0.90 (0)**	
Reversible defects only	1	112	5.95 (1.21, 29.28)	11 (0, 23)	0.45 (0)	0.66
Fixed+reversible defects	2	700	1.48 (1.19, 1.84)	14 (6.0, 22)	0.54 (0)	
Coronary angiography (all studies)	**8**	**1900**	**2.13 (1.33, 3.38)**	**12 (3.0, 21)**	**<0.0001 (80)**	
Abnormal test defined as ≥50% stenosis	2	166	0.81 (0.05, 12.63)	19 (-45, 83)	<0.0001 (96)	0.81
Abnormal test defined as ≥70% stenosis	6	1734	2.32 (1.33, 4.07)	11 (4.0, 18)	0.02 (62)	
Cardiovascular mortality	**# Studies**	**# Patients**	**RR (95%CI)**	**RD (95%CI) per 100 tested**	**Heterogeneity P value (I^2)**	**P value for difference**
MPS (all studies)	**4**	**751**	**2.99 (0.90, 9.90)**	**6.0 (-6.0, 18)**	**<0.0001 (90)**	
Reversible defects only	2	299	4.44 (1.27, 15.56)	8.0 (2.0, 13)	0.78 (0)	0.46
Fixed+reversible defects	2	452	1.15 (0.04, 33.28)	5.0 (-23, 37)	<0.0001 (95)	
DSE (all studies)	**1**	**158**	**3.97 (0.95, 16.67)**	**15 (-10, 40)**	**NA**	
Reversible defects only	0	0	-	-	-	NA
Fixed+reversible defects	1	158	3.97 (0.95, 16.67)	15 (-10, 40)	NA	
Coronary angiography (all studies)	**3**	**160**	**2.97 (1.27, 6.91)**	**18 (5.0, 31)**	**0.52 (0)**	
Abnormal test defined as ≥50% stenosis	0	0	-	-	-	NA
Abnormal test defined as ≥70% stenosis	3	160	2.97 (1.27, 6.91)	18 (5.0, 31)	0.52 (0)	
MACE	**# Studies**	**# Patients**	**RR (95%CI)**	**RD (95%CI) per 100 tested**	**Heterogeneity P value (I)**	**P value for difference**
MPS (all studies)	**11**	**2058**	**3.79 (1.84, 7.82)**	**13 (3.0, 23)**	**<0.0001 (94)**	
Reversible defects only	6	1133	7.11 (1.55, 32.59)	19 (-1.0, 38)	<0.0001 (94)	0.38
Fixed+reversible defects	5	925	2.86 (1.54, 5.31)	9 (-2.0, 19)	<0.0001 (87)	
DSE (all studies)	**6**	**466**	**3.97 (1.61, 9.74)**	**25 (1.0, 48)**	**0.0004 (78)**	
Reversible defects only	5	431	3.99 (1.46, 10.94)	29 (-3.0, 60)	0.0004 (80)	0.91
Fixed+reversible defects	1	35	3.33 (0.17, 64.33)	10 (-7.0, 27)	NA	
Coronary angiography (all studies)	**6**	**739**	**1.93 (1.45, 2.57)**	**22 (3.0, 41)**	**<0.01 (67)**	
Abnormal test defined as ≥50% stenosis	0	0	-	-	-	NA
Abnormal test defined as ≥70% stenosis	6	739	1.93 (1.45, 2.57)	22 (3.0, 41)	<0.01 (67)	

Figure Legends

Figure 1

Identification and inclusion of study reports.

Figure 2

Risk difference of all-cause mortality after an abnormal test result compared with a normal result.

Figure 3

Risk difference of MACE after an abnormal test result compared with a normal result.

Figure 4

The effect of characteristics of the included studies on the relative risk of outcomes: examination of sources of heterogeneity using meta-regression analysis.