Prognostic Value of Myocardial Perfusion Studies in Patients with End-Stage Renal Disease Assessed for Kidney or Kidney-Pancreas Transplantation: A Meta-Analysis

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Abstract. The prognostic utility of myocardial perfusion studies (MPS) such as thallium scintigraphy and dobutamine stress echocardiography (DSE) for stratifying cardiac risk among candidates for kidney or kidney-pancreas transplantation is uncertain. This study is a meta-analysis to determine the prognostic significance of MPS results on future myocardial infarction (MI) and cardiac death (CD) in patients with end-stage renal disease (ESRD) assessed for kidney or kidney-pancreas transplantation. MEDLINE was searched using combinations of MeSH headings and text words for transplantation, coronary artery disease, prognosis, end-stage renal disease, and noninvasive cardiac testing (nuclear scintigraphy and DSE) for primary studies. Studies were included if they reported MPS results and cardiac events in patients assessed for kidney or kidney-pancreas transplantation. Methodologic study quality and outcome data were independently abstracted in duplicate by two researchers. The relative risks (RR) of MI and CD were calculated using a random effects model. Twelve articles met all inclusion criteria; 12 studies reported CD, and 9 reported MI. In eight studies, thallium scintigraphy was used (four with pharmacologic stress, four with exercise stress), whereas four used DSE. When compared with negative tests, positive tests had a significantly increased RR of MI (2.73 [95% CI, 1.25 to 5.97]; $P = 0.01$) and CD (2.92 [95% CI, 1.66 to 5.12]; $P < 0.001$). Subgroup analyses of studies of diabetic patients indicated that positive tests were associated with a RR of CD 3.95 (95% CI, 1.48 to 10.5; $P = 0.006$) and a RR of MI 2.68 (95% CI, 0.95 to 7.57; $P = 0.06$) when compared with negative tests. In studies evaluating mixed populations of diabetic and nondiabetic patients, positive tests were associated with a RR of CD 2.52 (95% CI, 1.25 to 5.08; $P = 0.01$) and with a RR of MI 2.79 (95% CI, 0.85 to 9.21; $P = 0.09$) when compared with a negative test. The presence of reversible defects was associated with an increased risk of MI in diabetic patients and of CD in both subgroups; fixed defects were associated with an increased risk of CD but not MI. It is concluded that positive MPS are useful in identifying patients with significantly increased risk of future MI and CD in both diabetic and nondiabetic ESRD patients.

Cardiovascular disease is common in individuals with end-stage renal disease (ESRD) and accounts for between 40 and 45% of all deaths in these patients (1,2). At the time of initiation of chronic dialysis treatment in 1999, approximately 25% of patients have a history of ischemic heart disease and about 10% have had myocardial infarction (MI) (2,3). Although the rate of death from cardiac disease in ESRD patients in the United States fell in the 8-yr period between 1991 and 1998, the incident rate of MI rose in the second and third years of treatment by 15.7% and 6.8%, respectively (4). In addition, the short-term and long-term prognosis after acute MI in ESRD patients is poor, with 40% of patients dying of cardiac causes at 1 yr and almost 60% by 3 yr (5).

The high rates of serious and fatal coronary artery disease in ESRD patients underscores the need for a systematic approach to the cardiac assessment of individuals being considered for kidney and kidney-pancreas transplantation. Clinical practice guidelines (6,7) and reviews (8,9) have recommended that noninvasive screening tests or coronary angiography be performed based on the individual's estimated risk of CAD. There is agreement that many young patients, including some with diabetes, are at low risk and do not need special investigations (10–12), whereas those with angina or history of MI should undergo cardiac catheterization (8,9). However, for the older asymptomatic patient with either diabetes or other coronary risk factors, myocardial perfusion studies (MPS) such as thallium scintigraphy or DSE have been recommended (6,8,9).

The diagnostic test characteristics of MPS have been studied, and a wide range of sensitivities for the detection of significant coronary artery disease have been reported (as reviewed in references 6 and 7). However, less is known about whether patients with abnormal MPS are at higher risk for future MI or CD. Although a large number of studies using

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MPS or DSE have been reported, the prognostic accuracy of many of the individual reports has been limited by small sample sizes (range, 33 to 189), low event rates (range, 3 to 28 events), and the lack of multivariate analysis. Accordingly, to assess the prognostic utility of MPS, we performed a meta-analysis of 12 studies that reported the rate of MI and cardiac death in ESRD patients assessed for kidney or kidney-pancreas transplantation.

Materials and Methods

We searched for references included in the National Library of Medicine's MEDLINE database using OVID between 1977 and October 2000. Primary studies were identified using combinations of MeSH headings and textwords for coronary artery disease, transplantation, prognosis, end-stage renal disease (ESRD), stress nuclear scintigraphy, and dobutamine stress echocardiography. Independently, two researchers (CGR and DJT) reviewed the citation list and identified possibly relevant articles. We obtained all articles judged potentially relevant by either reviewer for further evaluation. A manual search of the reference lists of all review and primary articles identified other possibly relevant studies, which we retrieved for further evaluation. We hand-searched published abstracts, for the years 1995 to 2000, from the proceedings of the American Society of Nephrology, the American College of Cardiology, and the American Heart Association and identified other potentially relevant studies.

We used the following criteria to select articles. First, the study population had to include adult patients with chronic renal insufficiency or ESRD assessed for kidney or kidney-pancreas transplantation. Second, myocardial perfusion testing (exposure) had to include either nuclear scintigraphy (thallium or sestamibi) or DSE. The study had to report the outcomes of cardiac death (CD) and/or MI in the cohort of patients according to the MPS result. The minimum sample size was five patients. Disagreements were resolved by discussion and consensus.

The methodologic quality of individual articles is an important consideration for assessing whether the results of a study are biased. In duplicate and independently, two of us (CGR and DJT) used the following criteria (13) to judge the quality of the original articles.

Population. Studies reporting on all patients assessed for transplantation (inception cohort) were classified as consecutive. Studies that excluded some patients from the cohort or the analysis for any reason were considered nonconsecutive. Studies with unclear methods of cohort assembly were classified as unknown.

Exposure. Observers unaware of the clinical status of the patient interpreted the test results (yes/no/uncertain).

Outcome. Clinical outcomes were adjudicated by people unaware of both the test result and the clinical status of the patient (yes/no/unknown). We used the individual studies' definition of CD and MI.

CD and MI were categorized by the MPS result. When data on either or both of these endpoints were not reported, data were requested from the authors. We defined a positive test as either: (*1*) fixed: any baseline abnormality suggestive of noninducible ischemia (fixed defect on nuclear scintigraphy or resting wall motion abnormality on DSE), or (*2*) reversible: imaging changes suggestive of inducible ischemia (reversible perfusion defects on nuclear scintigraphy or new wall motion abnormalities on DSE). Studies were excluded if (*1*) stress ECG abnormalities or inability to achieve target heart rate were considered in their definition of an abnormal test, (*2*) the cardiac events could not be classified according to the stress imaging results. In addition, low-risk patients who did not have stress imaging performed were also excluded from the analysis.

Statistical Analyses

We expressed inter-observer agreement for study selection and individual components of the methodologic quality review as kappa. We calculated the relative risk (RR) and 95% confidence interval (95% CI) for each event using the random effects model (14) using EasyMA 2000 software package (15). To avoid sparse cells and biased estimates when calculating the pooled RR, we used a constant of 0.25 to represent the number of events for studies in which no cardiac events occurred. Annualized event rates are expressed as the number of patients having MI or CD as a proportion of the number of patients at risk divided by the number of patient-years follow-up. One study (16) that did not provide data about duration of follow-up was excluded from these calculations. The events during follow-up were classified according to the baseline MPS result. Comparisons of risk of MI and CD were made between negative test results *versus* positive test results (fixed and reversible combined), negative tests *versus* fixed defects, negative tests *versus* reversible defects, and fixed defects *versus* reversible defects. Sensitivity, specificity, and positive and negative predictive values were calculated using standard methods. We tested for homogeneity using the method of Cochran Q (17).

We planned a prespecified subgroup analysis of diabetic and nondiabetic patients. Five studies were restricted to diabetic patients (16,18–21), five studies contained a mixed population of diabetic and nondiabetic patients (11,22–25), whereas the remaining two studies provided sufficient information to distinguish MPS results and cardiac events for diabetic and nondiabetic patients (12,26). Therefore, we report the primary endpoints according to MPS result in a combined analysis of all studies, and in two sub-groups of patients: (*1*) diabetic patients and (*2*) mixed population of diabetic and nondiabetic patients.

Results

One hundred sixty-six studies were identified using our search strategy, 11 of which were published in English and met all inclusion criteria (11,12,16,18–25). One additional study was identified from references of the primary studies and review articles (26). Of the 12 studies included for analysis, four used DSE, and the other eight studies used myocardial scintigraphy. Of the myocardial scintigraphy studies, four used dipyridamole as a pharmacologic stress agent, and four used exercise.

Six other studies were identified as potentially relevant, but they were excluded for a variety of methodologic reasons. Two studies did not meet the criterion of independent reporting of MI and cardiac death and were excluded (27,28). One abstract was potentially relevant, but it contained insufficient data to classify MI and cardiac death by MPS result (29). The three remaining studies evaluated diabetic transplant candidates using stress-induced ECG abnormalities and/or failure to attain target heart rate in their definition of a positive test (30–32) and were excluded.

Table 1 summarizes the characteristics and methodology of the 12 individual studies. The interobserver agreement for consecutive cohort assembly, definition of positive test result, blinding of interpreter of test to clinical status of the patient, and completeness of follow-up were reflected in the following

Table 1. Methodologic review of included primary studies[a]

Study Author, Year (Reference)	Population		Exposure		Outcome	
	Patient Characteristics	Consecutive Cohort Assembly	Definition of (+) Test Result	Blinding of Interpreter to Clinical Information (Y/N)	F/U (mo)	Definition of Cardiac Death
Dobutamine stress echocardiography						
Bates, 1996 (21)	Pre-Tx, T1-DM	No, 53 of 87	Fixed/reversible defects	Not specified	26.7	Not specified
Brennan, 1997 (23)	Pre-Tx, risk of CAD	Y	Not specified	Y, reviewed in duplicate	20	Not specified
Marwick, 1998 (25)	Cardiac risk assessment, 75% pre-Tx	Y	Fixed/reversible defects	Y	38	Cardiac illness prior to terminal event
Herzog, 1999 (24)	Pre-Tx and high risk: DM, ≥2 traditional RFs, can't exercise	No 50 of 68	Inducible ischemia	Y, reviewed in triplicate	22.5	Not specified
Thallium Scintigraphy						
Marwick, 1990 (22)	Pre-Tx, high risk: T1-DM, age >40, CP	Not specified	Fixed/reversible defects	Not specified; reviewer blinded to angiogram results	25	Not specified
Camp, 1990 (18)	Pre-Tx, T1-DM	Not specified	Fixed/reversible defects	Y	11	Includes sudden death
Iqbal, 1991 (19)	Pre-Tx; T1-DM	Y	Fixed/reversible defects	Not specified	14	Not specified
Brown, 1993 (26)	Pre-Tx, high risk and asymptomatic	Not specified	Fixed/reversible defects	Y	48	Not specified
Le, 1994 (12)	Pre-Tx	N, 189 of 196	Fixed/reversible defects	Not specified	47	Not specified
Vandenburg, 1996 (20)	Pre-Tx, T1-DM w/o CAD and had coronary angiogram	N	Fixed/reversible defects	Not specified; blinded to angiogram result	25	Not specified
Mistry, 1998 (16)	Tx patients with Pre-Tx test	N	Fixed/reversible defects	Not specified		Sudden death
Lewis, 1999 (11)	Pre-Tx	N	Fixed/reversible defects	Not specified	38.2	Arrhythmia, CHF, MI, and excluding hyperkalemia

[a] (+), positive; (−), negative; F/U, follow-up; Pre-Tx, pretransplant; T1-DM, type I diabetes mellitus; RF, risk factor; ECG, electrocardiogram; CP, chest pain; CHF, congestive heart failure; MI, myocardial infarction. As noted in Materials and Methods, "fixed" refers to irreversible nuclear scintigraphic defects and resting wall motion abnormalities; "reversible" refers to new scintigraphic or wall motion abnormalities induced by stress.

κ values of 0.68, 0.93, 0.77, 0.96, respectively. Follow-up of patients was over 98% complete in each study.

Combined Analysis

The results of the combined analysis are based on nine studies involving 670 patients reporting on MI (11,16,18–21,23–25) and 12 studies involving 913 patients reporting on CD (11,12,16,18–26).

Risk of Myocardial Infarction

Nine of 388 patients with negative MPS had an MI, whereas 21 of 282 with a positive MPS had an MI, representing an annualized event rate of 1.6% and 4.3% for negative and positive MPS, respectively (Tables 2 and 3). Figure 1A shows the individual study and pooled relative risk (RR) for MI. The RR of MI following a positive test was 2.73 (95% CI, 1.25 to 5.97; $P = 0.01$) when compared with patients with a negative test. No significant heterogeneity existed among individual study results ($P = 0.71$).

When considering the nature of the positive test result (fixed or reversible), the RR of MI was increased in individuals with reversible perfusion defects. In the comparison of reversible defects to normal perfusion images, the RR of MI was 6.19 (95% CI, 1.69 to 22.7; $P < 0.01$; Figure 1B). Similarly, the RR of MI was 7.07 (95% CI, 0.93 to 53.5; $P = 0.058$) when comparing reversible defects to fixed defects (Figure 1D). The RR of MI was not increased in individuals with fixed defects compared with normal perfusion images (RR 1.12 [95% CI, 0.1 to 12.2]; Figure 1C).

Risk of Cardiac Death

Sixteen of 505 patients with negative MPS had a CD *versus* 63 of 408 patients with a positive test, representing an annualized event rate of 1.8% and 6.9% for negative and positive MPS, respectively (Tables 2 and 3). Figure 2A shows the individual study and pooled RR of cardiac death. The RR of a CD among patients with a positive test was 2.92 (95% CI, 1.66 to 5.12; $P < 0.001$) compared with patients with a negative test. No significant heterogeneity existed among individual study results ($P = 0.79$)

The presence of both reversible and fixed perfusion abnormalities was associated with an increased risk of CD when compared with normal test results. Patients with reversible defects also had a RR of CD 3.82 (95% CI, 1.83 to 7.94; $P < 0.001$; Figure 2B) compared with patients with normal images. Similarly, the RR of CD was 4.74 (95% CI, 2.26 to 9.92; $P < 0.001$) when patients with fixed defects were compared with those with normal test results (Figure 2C). The RR of CD was not increased in patients with reversible defects compared with those with fixed perfusion defects (RR 0.78 [95% CI, 0.48 to 1.25]; $P = 0.29$; Figure 2D).

If future MI or CD is considered the gold standard against which MPS results are to be applied, the sensitivity of MPS is 0.80 for CD and 0.70 for MI. The specificity is 0.59 for both

Table 2. Cardiac events classified by population type and characteristics of myocardial perfusion abnormality

Study	Reference	Size	Mean F/U (mo)	Test Result (number of subjects)				Cardiac Events Classified by Test Results							
				Positive			Neg	MI				Cardiac Death			
				Fixed	Rev	AbN		Fixed	Rev	AbN	Neg	Fixed	Rev	AbN	Neg
Studies reporting only on patients with diabetes															
Camp, 1990	18	40	11.0	8	9	17	23	0	3	3	0	0	2	2	0
Iqbal, 1991	19	36	14.0	0	12	12	24	0	2	2	0	0	1	1	0
Brown, 1993 (DM)	26	28	48.0	3	11	14	14	—	—	—	—	2	3	5	2
Le, 1994 (DM)	12	57	47	8	24	32	25	—	—	—	—	1	7	8	0
Mistry, 1998	16	176		15	50	65	111	0	3	3	1	0	1	1	0
Totals		337	30.9	34	106	140	197	0	8	8	1	3	14	17	2
Vandenberg, 1996	20	33	25.0	—	—	11	22	—	—	2	2	—	—	0	0
Bates, 1996	21	53	26.7	—	—	20	33	—	—	1	2	—	—	3	1
Totals		86	32.1			31	55			3	4			3	1
Studies reporting on mixed population of patients															
Brown, 1993	26	75	48.0	13	33	46	29	—	—	—	—	7	13	20	1
Le, 1994	12	38	47.0	6	15	21	17	—	—	—	—	3	2	5	2
Marwick, 1998	25	123	38.0	36	36	72	51	0	1	1	1	3	6	9	2
Lewis, 1999	11	112	12.2	17	43	60	52	0	6	6	0	2	3	5	0
Totals		348	32.8	72	127		149	0	7	7	1	15	24	39	5
Marwick, 1990	22	45	25.0	—	—	13	32	—	—	—	—	—	—	1	5
Brennan, 1997	23	47	20.0	—	—	5	42	—	—	1	2	—	—	0	1
Herzog, 1999	24	50	22.5	—	—	20	30	—	—	2	1	—	—	3	2
Totals		142	22.4			38	104			3	3			4	8

MI and CD. The overall incidence of MI was 4.5% and of CD was 8.7%, representing average annualized event rates of 2.8% for MI and 4.3% for CD. The positive predictive value for MI is 7.4% and for CD is 15.4%. The negative predictive value of normal MPS in the combined analysis was 97.7% for MI and 96.9% for CD.

Subgroup Analysis

Diabetic Subgroup. In the diabetic subgroup, data for MI was available in five studies (16,18–21) involving 338 patients and for CD in seven studies (12,16,18–21,26) involving 423 patients.

Five of 213 diabetic patients with a negative MPS had an MI *versus* 11 of 125 diabetic patients with a positive MPS, representing an annualized event rate of 2.4% and 8.4% for negative and positive MPS, respectively. A positive test result was associated with a RR of MI (2.68 [95% CI, 0.95 to 7.57]; $P = 0.06$) of borderline statistical significance when compared with patients with negative test results (Figure 1A, "Diabetics"). However, when studies were analyzed according to the type of the perfusion defect, patients with diabetes assessed for transplantation who had reversible perfusion defects had an RR of MI of 9.29 (95% CI, 1.77 to 48.8) compared with diabetics with normal perfusion images ($P < 0.01$; Figure 1B). Comparisons of the other perfusion defects in the diabetic subgroups (fixed defects *versus* normal tests; reversible *versus* fixed defects) were not statistically significant (Figures 1, C and D).

Cardiac death occurred in 3 of 252 diabetic patients with a negative MPS *versus* 20 of 171 diabetic patients with a positive MPS, representing an annualized event rate of 0.9% and 6.8% for negative and positive MPS, respectively. The RR of CD was (3.95 [95% CI, 1.48 to 10.5]; $P = 0.006$; Figure 2A) in diabetic patients with a positive test when compared with diabetic patients with a negative test. The analysis based on the nature of the perfusion defect revealed that, when compared with those with normal perfusion images, those with reversible perfusion defects had an RR of CD of 3.97 (95% CI, 1.17 to 13.5; $P = 0.03$; Figure 2B), and those with fixed perfusion defects had an RR of CD of 4.70 (95% CI, 1.31 to 16.9; $P = 0.02$; Figure 2C). No increase in risk was observed when comparing fixed *versus* reversible defects in patients with diabetes.

Mixed Population. In the mixed population group, data for MI was available in four studies (11,23–25) involving 332 patients and for CD in 7 studies involving 490 patients (11,12,22–26).

Cardiac death occurred in 13 of 253 patients with negative MPS *versus* 43 of 237 patients with positive MPS, representing an annualized event rate of 2.2% and 7.0% for negative and positive MPS, respectively. A positive test result was associated with an increased RR of CD (2.52 [95% CI, 1.25 to 5.08]; $P = 0.01$; Figure 2A, "Mixed") when compared with those with a negative test. The RR of CD was also significantly increased in patients with reversible (RR, 3.77 [95% CI, 1.40 to 10.2]; $P < 0.01$; Figure 2B) or fixed (RR, 4.76 [95% CI, 1.93 to 11.8]; $P < 0.001$; Figure 2C) perfusion defects when compared with those with normal perfusion images. In these

Table 3. Cardiac events and patient follow-up[a]

Endpoint	Test Result	Total Number of Patients	Number of Events	Patient-Months of Follow-Up	Number of Studies	Events per 100 Patient-Years of FU
All patients						
myocardial Infarction	Positive	217	18	5060	8	4.3
	Fixed defect	61	0	1663.4	3	
	Reversible defect	100	12	2159.6	4	6.7
	Negative	277	8	6107.5	8	1.6
cardiac death	Positive	353	62	10756	11	6.9
	Fixed defect	91	18	3089.4	6	7.0
	Reversible defect	183	37	6104.6	6	7.3
	Negative	394	16	10945.5	11	1.8
Studies reporting only on patients with diabetes						
myocardial Infarction	Positive	60	8	1164	4	8.2
	Fixed defect	8	0	88	1	
	Reversible defect	21	5	267	2	22.5
	Negative	102	4	2020.1	4	2.4
cardiac death	Positive	106	19	3340	6	6.8
	Fixed defect	19	3	608	3	5.9
	Reversible defect	56	13	1923	4	8.1
	Negative	141	3	3867.1	6	0.9
Studies reporting on mixed population of patients with and without diabetes						
myocardial Infarction	Positive	157	10	3896	4	3.1
	Fixed defect	53	0	1575.4	2	
	Reversible defect	79	7	1892.6	2	4.4
	Negative	175	4	4087.4	4	1.2
cardiac death	Positive	237	43	7416	7	7.0
	Fixed defect	72	15	2481.4	4	7.3
	Reversible defect	127	24	4181.6	4	6.9
	Negative	253	13	7078.4	7	2.2

[a] Excludes Reference 16 (Mistry), because duration of follow-up not given.

studies, the risk of future MI was not significantly associated with MPS results.

Table 3 summarizes the event rates in the combined population and in subgroups of diabetic patients and the mixed group of patients. In patients with negative MPS result, 8 of 277 patients followed for 6107.5 patient-months had an MI (average event rate, 1.6%/yr). Cardiac deaths occurred in 16 of 394 patients followed for 10945.5 patient-months (average event rate, 1.8%/yr).

Discussion

The results of this meta-analysis confirm that individuals with abnormal MPS before kidney or kidney-pancreas transplantation are at higher future risk for cardiac events than those individuals with normal tests. Compared with patients with normal tests, those with evidence of inducible ischemia (reversible defects, new wall motion abnormality) have a sixfold increase in the risk of MI and an almost fourfold risk of cardiac death. In addition, patients with noninducible ischemia (fixed defects, resting wall motion abnormality) also have a significantly higher risk of cardiac death (RR, 4.7) but not MI (RR, 1.1). Diabetic patients have a similar pattern of risk, with reversible defects alone strongly associated with MI (RR, 9.3) and both fixed and reversible defects associated with cardiac death (RR, 4.0 to 4.7).

The results of our meta-analysis may be limited by several potential biases. In many studies we included, positive test results led to coronary angiography and may have introduced a verification bias. Verification bias occurs when the screening test result leads to a confirmatory or gold standard test such as a coronary angiogram (33). If the results of coronary angiography led to coronary revascularization, the rate of MI and cardiac death may change and could alter the predictive accuracy of the noninvasive cardiac tests. For example, the results of a randomized controlled trial of surgical revascularization *versus* medical therapy by Manske *et al.* (34) suggest diabetic patients with asymptomatic CAD benefit from pretransplant coronary revascularization. In this study, 26 patients with type I diabetes mellitus, left ventricular ejection fraction >35%, and asymptomatic coronary artery lesions judged to be hemodynamically significant were randomized to medical therapy, consisting of ASA and a calcium channel blocker or revascularization. Nine of thirteen patients in the medical group *versus* 2 of 13 in the revascularization group experienced fatal or nonfatal myocardial infarctions. This study suggests that coronary revascularization in patients with type I diabetes reduces the risk of subsequent cardiac events, and this could result in an underestimate of the risk associated with a positive MPS. The effect of this potential bias on our results cannot be estimated

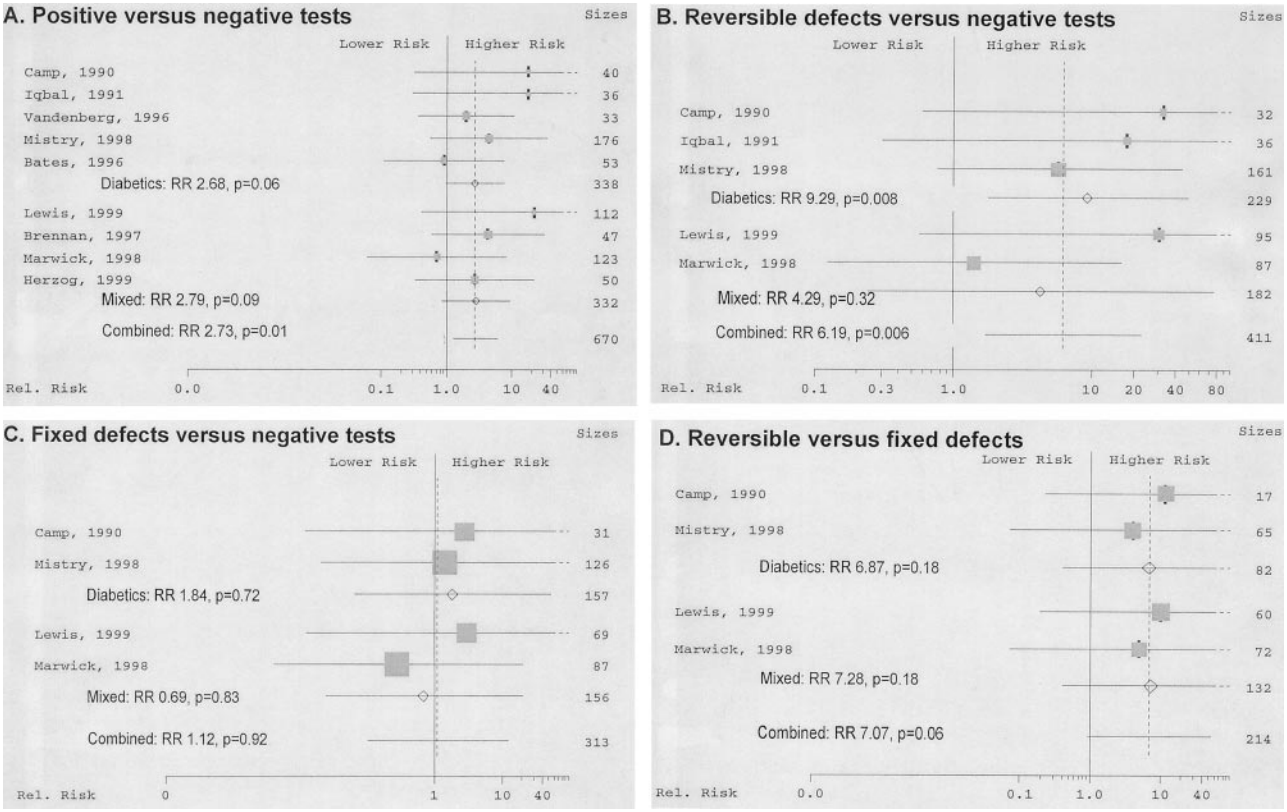

Figure 1. Myocardial infarction. (A) Positive *versus* negative tests; (B) Reversible defects *versus* negative tests; (C) Fixed defects *versus* negative tests; (D) Reversible *versus* fixed defects.

because the numbers of patients treated with revascularization have not been reported in the studies we reviewed.

In nondiabetic patients with ESRD, the effect of verification bias on the predictive accuracy of noninvasive cardiac testing is more difficult to assess. No randomized controlled trial comparing medical therapy *versus* revascularization exists, so optimal treatment strategies are unknown. If verification bias in nondiabetic patients led to angioplasty or bypass procedures, the noninvasive cardiac tests would overestimate the risk of MI and cardiac death if revascularization increased perioperative risk and/or did not improve the long-term prognosis. There is evidence to support this pattern of morbidity and mortality in ESRD patients who are treated with coronary revascularization. In a large observational study of 14,306 diabetic and nondiabetic ESRD patients who had coronary revascularization, in-hospital mortality rate ranged from 5.4 to 12.5%; by 2 yr, 30 to 40% of patients had either died of heart disease or had nonfatal MI (35). These findings suggest that a verification bias could overestimate the accuracy of positive MPS.

Four of the twelve studies included in this meta-analysis used exercise instead of pharmacologic stress, which may introduce bias in two ways. First, patients unable to exercise to achieve a target heart rate may have falsely negative MPS. If these patients had a future risk of cardiac events similar to the risk of patients with positive MPS, their inclusion in the normal test group would tend to decrease the relative risk of future cardiac events associated with a positive test, thereby underestimating the true risk associated with a positive MPS. Second, it is unclear whether patients with ESRD selected for pharmacologic stress have exercise capacity that is more limited than patients selected for exercise testing. In the general population, exercise capacity is a powerful independent prognostic factor in men referred for exercise testing (36). Therefore, it is possible that underlying comorbidity, as reflected in ability to exercise, may influence the choice of either pharmacologic or exercise testing, which could result in misleading risk estimates when the results of the two strategies are combined. However, the lack of heterogeneity in the pooled analysis suggests that the results are probably generalizable to both groups' patients.

Several methodologic features of the studies we reviewed limit our understanding of the prognostic accuracy of MPS. First, because we were unable to determine from the primary studies when patients had cardiac events, the usual statistical analysis applied to survival data could not be performed. As a consequence, the findings in Table 3 are limited to a description of the proportions of patients with and without cardiac events according to their MPS test result, and the average event rate per 100 patient-years of follow up. Second, the results of our meta-analysis are based on univariate analyses and are not adjusted for other important prognostic factors such as age, diabetes, and known coronary artery disease. It is therefore important to ask whether the noninvasive test results are still valid when these other prognostic variables are considered.

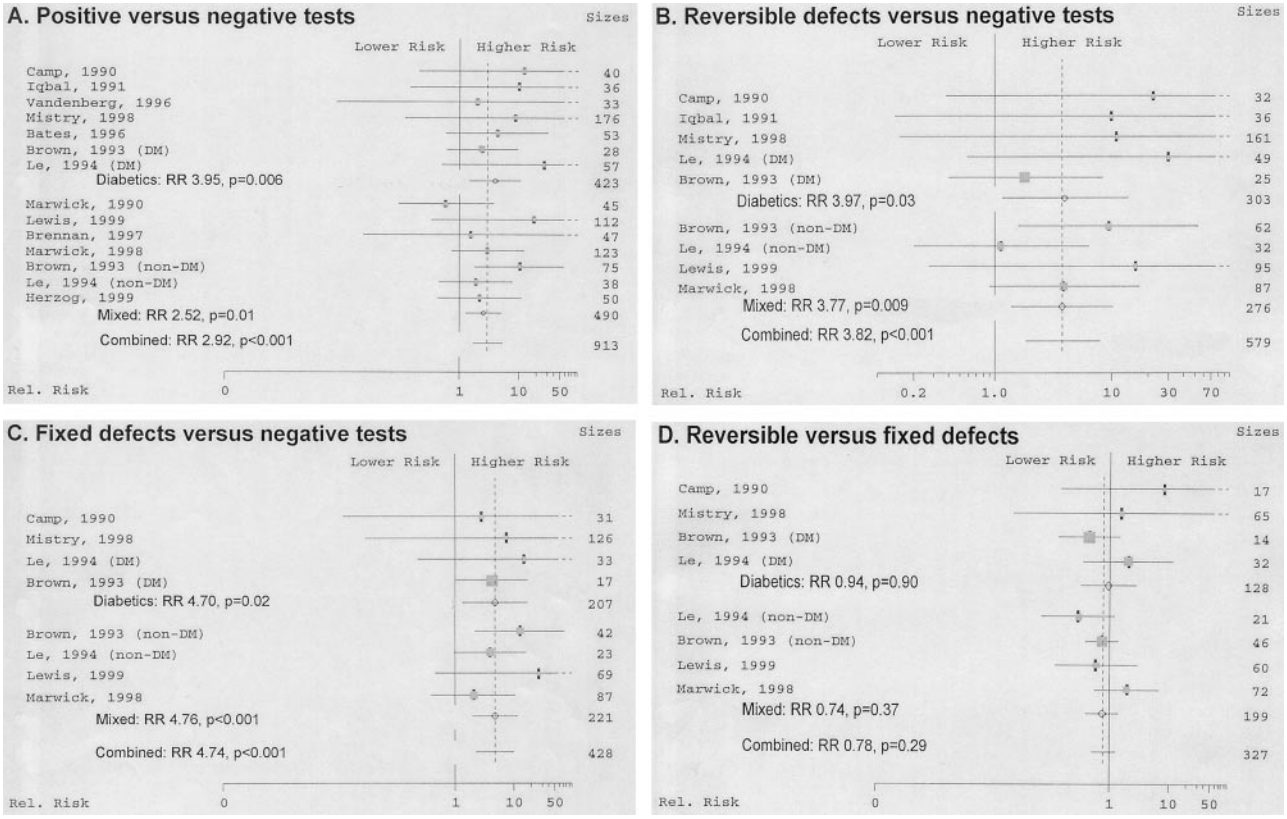

Figure 2. Cardiac death. (A) Positive *versus* negative tests; (B) Reversible defects *versus* negative tests; (C) Fixed defects *versus* negative tests; (D) Reversible *versus* fixed defects.

Older age, diabetes, and left ventricular dysfunction and hypertrophy are strongly associated with MI and cardiac death in ESRD patients (5,37,38). However, only 1 of the 12 studies included in this meta-analysis used multivariate analysis to confirm the independent prognostic value of noninvasive tests in predicting cardiac outcomes. Bates and colleagues reported that in 53 patients that a new wall motion abnormality was associated with future cardiac events (odds ratio 12.7) (21). Brown *et al.* (27) found that both reversible defects on thallium scintigraphy and left ventricular dysfunction were independently associated with the combined outcome of future MI or CD. Recently, we have confirmed the findings of these investigators. In a study of 441 consecutive patients being assessed for kidney transplantation, we used a Cox regression analysis to confirm that abnormal thallium/sestamibi test results were still predictive of MI and CD (RR, 2.5) when adjusted for both age and diabetes (39). Similar results were found in a meta-analysis of 15 published reports on preoperative pharmacologic stress risk stratification of patients without kidney disease undergoing vascular surgery (40). Taken together, these findings provide preliminary support that MPS accurately stratify risk in ESRD patients who have multiple risk factors for heart disease.

What are the implications of our findings for the clinician assessing patients for kidney and kidney-pancreas transplantation? First, the combined analysis of any MPS abnormality has adequate sensitivity for future MI or CD (0.70 and 0.80, respectively). Thus, when the average annualized incidence is between 3 to 5%, the negative predictive value exceeds 96%. These values are comparable to MPS test properties in detecting angiographically significant CAD (24). Second, our results also show that evidence of inducible ischemia on MPS is strongly associated with MI and cardiac death in both diabetic and nondiabetic patients, supporting the recommendation that such patients be evaluated with coronary angiography (5–8). Third, we found that patients with non-inducible ischemia were at significantly higher risk for future cardiac death but not MI. However, we could not establish if the higher risk of cardiac death in these patients was related to ongoing ischemia, left ventricular dysfunction, arrhythmias, or a combination of these processes, becuase the studies in our meta-analysis did not control for key prognostic factors. Parfrey *et al.* (41) reported that left ventricular hypertrophy and systolic dysfunction are independent risk factors for *de novo* ischemic heart disease, especially in older patients and those with diabetes. At present, however, it is unknown which demographic and clinical factors are associated with and mediate the higher risk of death from heart disease in patients with non-inducible ischemia. In the absence of other data, and given the higher mortality risk for patients with non-inducible ischemia on MPS, our practice has been to offer cardiac catheterization to these individuals.

Can the clinician be reassured by the finding of a normal MPS in asymptomatic patients who are at higher risk because of older age or diabetes? The patients included in this meta-

analysis, including those with normal tests, all had risk factors for cardiac disease (as the original indication for the MPS). For example, Table 3 shows that among 102 diabetic patients with normal MPS, the incidence of MI was 2.4% per year. Similarly, among 141 diabetic patients with normal MPS, the incidence of CD was 0.9% per year. Although the specificity of MPS for future cardiac events is low, the negative predictive value is high for both MI and CD. These findings indicate a relatively low event rate among high-risk patients with normal tests; however, when compared with young patients without diabetes or other risk factors for CAD, patients with normal MPS still appear to be at higher risk. In two studies that followed low-risk patients, cardiac death occurred in 1 of 94 patients followed for a mean of 48 mo (12) and in none of 72 patients followed for a mean of 12.2 mo (11). These findings suggest that over time, patients who have risk factors and normal MPS still have a higher cardiac risk than previously recognized.

In summary, we performed a meta-analysis of 12 observational studies involving 913 patients assessed with MPS as part of their cardiac evaluation before kidney or kidney-pancreas transplantation. We conclude that in patients with ESRD assessed for transplantation and evaluated using nuclear scintigraphy or DSE, a negative test result is associated with a low event rate for each of MI and cardiac death. Conversely, patients with abnormal myocardial perfusion studies are at higher long-term risk for MI or cardiac death. This was observed for both fixed and reversible perfusion defects. The data from these studies should be useful to clinicians when counseling patients about cardiac risk and making decisions about subsequent cardiac investigations before kidney or kidney-pancreas transplantation.

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