

# Relative Effectiveness of Four Preoperative Tests for Predicting Adverse Cardiac Outcomes After Vascular Surgery: A Meta-Analysis

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Various noninvasive tests have been proposed to stratify perioperative cardiovascular risk, including dipyridamole thallium scintigraphy (DTS), ejection fraction estimation by radionuclide ventriculography (RNV), ischemia monitoring by ambulatory electrocardiography (AECG), and dobutamine stress echocardiography (DSE). Which of these tests is most effective for predicting adverse perioperative cardiac outcome? To answer this question, and also to stimulate future studies, we evaluated 56 studies examining one or more of the four tests. We conducted meta-analysis on 20 studies that met the inclusion criteria. Outcome measures evaluated were cardiac death or myocardial infarction occurring during hospital stay or within 1 mo after surgery. Relative risk (RR), which is the probability of adverse cardiac outcome when the test is positive divided by the probability of adverse outcome when the test is negative, was used to combine evidence from different studies. An empirical Bayes

procedure with a normal-normal hierarchic model was then used to obtain a meta-analytic confidence interval for the overall median of the relative risks. The between-study variance was estimated using the method of moments approach described by DerSimonian and Laird (Controlled Clin Trials 1986;7:177-88). Combined (median) RR [95% confidence interval (CI)] and the number of studies included in our meta-analysis for different evaluative tests were as follows: DTS 4.6 (2.1-10.4) ( $n = 6$ ); RNV 3.7 (1.6-8.3) ( $n = 5$ ); AECG 2.7 (1.4-5.1) ( $n = 6$ ), and DSE 6.2 (1.7-22.8) ( $n = 3$ ). We conclude that while DTS, RNV, AECG, and DSE are effective (the 95% CIs are greater than 1.0) in predicting the cardiac outcome after vascular surgery, the data are not definitive in determining the optimal test (95% CIs for RR overlap). Future studies should include DSE, as this test shows great promise for predicting adverse cardiac events after vascular surgery. (Anesth Analg 1994;79:422-33)

Approximately 570,000 patients in the United States undergo vascular surgical procedures annually (1). More than 60% of these patients also undergo an expensive test to evaluate cardiovascular risk. Because of the high prevalence of symptomatic and asymptomatic coronary artery disease (CAD) in these patients (2-4), preoperative evaluation aims to identify those at high risk for cardiac outcome. Identification of patients at increased risk before surgery may allow important alterations in perioperative care. However, given the costs and risks involved, it is not practical to subject all vascular patients to preoperative coronary angiography (CATH). It is also difficult to get meaningful results from conventional exercise electrocardiography because claudication in the

lower extremities of many vascular surgical patients prevents them from achieving an adequate exercise-load. Therefore, interest has increased in cardiac risk stratification by other noninvasive preoperative tests (5). These tests include dipyridamole-thallium scintigraphy (DTS) (2,6-18), estimation of ejection fraction by radionuclide ventriculography (RNV) (2,19-23), and ambulatory electrocardiography (AECG) (8,24-28). Dobutamine stress echocardiography (DSE) has also been used to predict adverse cardiac outcome in patients undergoing vascular surgery (29-33). It is still uncertain which of these tests is best for predicting adverse cardiac outcome, in terms of "effectiveness" (34). Indeed, many patients are subjected to more than one test.

If results of the preoperative noninvasive tests (positive or negative) and adverse cardiac outcome after surgery (presence or absence) are summarized in a  $2 \times 2$  table, then the relative risk (RR) can be computed.

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RR gives an estimate of the predictive value of a particular test. In this case, RR is the probability of an adverse cardiac event when the test is positive divided by the probability of an adverse cardiac event when the test is negative (35). For example, a RR of 10 for a test means that, on average, individuals with a positive test have a 10 times greater risk of developing an adverse cardiac event than patients with a negative test. A RR of 1 implies that risk is similar whether the test is positive or negative. In the present context, RR gives an estimate of the predictive value of a particular test for adverse cardiac outcome. In this study, we tested the hypothesis that a meta-analysis of studies of DTS, RNV, AECG, and DSE, in which we combined RRs from different but similar studies, could determine the relative effectiveness of these four preoperative tests.

## Methods

Studies evaluating the utility of preoperative DTS, RNV, AECG, or DSE in predicting adverse cardiac outcome after vascular surgery were retrieved. Articles published in English before December 1993 were identified by using a Medline search. We then retrieved the references listed in the identified articles and the reviews of the subject. Abstracts of scientific conferences and unpublished studies were not included.

Our definitions of positive and negative test results for each of the preoperative tests follow:

- DTS: A positive test result is the occurrence of redistribution defect in at least one segment; a negative test result is the absence of redistribution defect or the presence of a fixed defect.
- RNV: A positive test result is an ejection fraction  $\leq 35\%$ ; a negative result is an ejection fraction of  $>35\%$ .
- AECG: A positive test result is the occurrence of ischemia preoperatively as evident by ST-segment depression of  $\geq 1$  mm or ST increase  $\geq 2$  mm after J point (measured at 60 ms) lasting at least 1 min. A negative test result is absence of ischemia.
- DSE: A positive test result is development of new regional wall motion abnormalities (normal to hypokinesis, akinesis, dyskinesis, or wall-thickening changes) or worsening of existing regional wall motion abnormalities (hypokinesis to akinesis, dyskinesis, or wall-thickening changes) in at least one segment on echocardiography during dobutamine infusion. A negative result is no change on echocardiography during dobutamine infusion.

The end-points defining adverse cardiac outcome after vascular surgery were cardiac death or myocardial infarction (MI) occurring during hospital stay or within 1 mo after surgery. In studies in which patients suffered both MI and cardiac death, the latter was taken into account for analysis.

The retrieved articles were studied carefully to identify the studies with a uniform definition of positive and negative test results. The number of patients in each of four categories was noted: test result positive, cardiac event positive; test result negative, cardiac event positive; test result positive, cardiac event negative; and test result negative, cardiac event negative. When the test was evaluated in patients undergoing different types of noncardiac surgery, an attempt was made to separate data for patients undergoing vascular surgery. For each study, RR of developing an adverse cardiac event when the test result was positive versus when the test result was negative was computed (Appendix A).

We examined study design, i.e., patient selection and "blindness" to test result of physicians caring for the patients. Surgical procedures were classified as aortic (aortobifemoral graft or aortic aneurysm surgery), lower extremity vascular surgery, or carotid endarterectomy, and the percentage of patients in each of these categories was noted. Studies were excluded in which treatment was altered by performance of CATH, coronary artery bypass graft (CABG) surgery, or percutaneous transluminal coronary angioplasty (PTCA) based on occurrence of positive test results.

However, in most series, some patients received myocardial revascularization before vascular surgery. Therefore, as part of an alternative analysis, we added those studies in which patients had treatment altered (CABG or PTCA) after positive test results. In most instances, the percentage of patients who received myocardial revascularization before peripheral vascular surgery was small; these patients were excluded from the alternative analysis. If treatment was altered for more than 20% of patients in a series, then the series was excluded. The cutoff level of 20% was arbitrary, but our intention was to avoid bias for low predictive value of a test. Results of the alternative meta-analysis were not considered in reaching final conclusions.

We also noted reports of complications associated with preoperative tests (DTS and DSE studies), the timing of delayed imaging (DTS studies), and the duration of preoperative ischemia monitoring and site of electrode placement (AECG studies). Statistical significance or conclusions about the usefulness of a particular test in predicting adverse cardiac events were noted. Finally, studies were examined to determine whether analysis for other potential risk factors associated with adverse cardiac outcome was performed.

Articles were reviewed carefully for evidence of duplicate publications from the same group of investigators involving the same patients. In such cases, the study with the larger sample size or the one that used our definitions for positive and negative results was selected. Retrospective studies were excluded from the meta-analysis. Each of the studies selected was reviewed at least three times to ensure accurate data transcription.

An empirical Bayes procedure with a normal-normal hierarchic model was used to get a meta-analytic confidence interval for the overall median of RR. The variance between studies was estimated using the method of moments approach described by DerSimonian and Laird (36). Computational details of the meta-analysis appear in Appendix B. For computing RR for an individual study, a value of 0.5 was added to all the cells. This maneuver facilitates computing the RR for studies with no false-negative events (otherwise the calculated RR would be infinite) (37).

## Results

The total number of articles retrieved for each test was: 28 DTS, 10 RNV, 12 AECG, and 6 DSE. Ultimately, 20 studies contributed to the meta-analysis: six studies of DTS (8-10,13,15,16), five studies of RNV (19-23), six studies of AECG monitoring for preoperative ischemia (8,24-28), and three studies of DSE (30,31,33). In addition to these studies, five DTS studies (11,12,14,17,18) and one DSE (32) study became eligible for the alternative meta-analysis. A list of the studies excluded from our meta-analysis and the reasons for exclusion can be obtained from the authors. The demographic and other relevant data for DTS, RNV, AECG, and DSE studies are given in Table 1. Only four studies, one of DTS (9), one of AECG (28), and two of DSE (30,31), met the design criteria of recruiting consecutive patients presenting for vascular surgery and of blinding physicians caring for patients to the test results.

In AECG studies, the duration of preoperative ischemia monitoring and the sites of electrode placement varied between studies. Electrode placement allowed monitoring of leads  $V_1$ ,  $V_5$ , and aVF for 48 h (8), leads  $V_1$  and  $V_5$  for 12 h (25), leads  $CC_5$  and  $CM_5$  for 24 h (26), lead  $CM_5$  for 18 h (27), unspecified leads for 24 h (24), and bipolar leads for 48 h (28). In DTS studies, the timing of delayed imaging was reported at 3-4 h in five studies and at 2 h in one study (8). Complications associated with DTS testing were reported in eight studies. Complications included chest pain, ST depression on electrocardiogram, headache, nausea, and dizziness; they occurred in 57 of 702 (8.1%) patients. Complications were reported in two DSE studies (30,31). In one study ( $n = 131$  patients) (31), one patient

developed ventricular fibrillation at the peak dose of dobutamine infusion and was resuscitated, and another patient developed paroxysmal atrial tachycardia that responded to metoprolol. In another DSE study ( $n = 75$  patients) (30), complications were as follows: hypertension in three patients, atrial fibrillation in one, increased left ventricular outflow tract gradient in one, and restlessness in one.

In five studies of DTS (11,12,14,17,18) and one study of DSE (32), which were included in the alternative analysis, CATH was performed as a result of a positive test. In five DTS studies ( $n = 362$  patients), 20 patients underwent CABG and three patients underwent PTCA before vascular surgery. None of these patients developed an adverse cardiac event after vascular surgery. But in one study (17) ( $n = 100$  patients), 11 patients with positive DTS test results underwent CATH, and six of these patients underwent CABG. A cerebrovascular accident and two deaths followed CATH and one death followed CABG. In one DSE study (32), CATH was performed in 19 of 23 patients with positive DSE result. Of these 19 patients, 13 underwent myocardial revascularization procedures (CABG in 10 and PTCA in three) followed by vascular surgery. None of these patients had an adverse cardiac event after vascular surgery.

RR and 95% confidence interval (CI) for different studies of each test as well as the combined (median) RR are presented graphically on a logarithmic scale (38) in Figure 1. Results of alternative meta-analysis are presented in Figure 2. On these graphs, the studies are arranged in chronologic order of publication. For all the tests except DSE, there was a bias for better predictive value in the early studies.

Combined (median) RR (95% CI) and the number of studies included in our meta-analysis for different evaluative tests were as follows:

Test	RR (95% CIs) from primary meta-analysis (Figure 1) <sup>a</sup>	RR (95% CIs) from alternative meta-analysis (Figure 2) <sup>b</sup>
DTS	4.6 (2.1-10.4) ( $n = 6$ )	5.2 (2.3-11.6) ( $n = 11$ )
RNV	3.7 (1.6-8.3) ( $n = 5$ )	3.7 (1.6-8.3) ( $n = 5$ )
AECG	2.7 (1.4-5.1) ( $n = 6$ )	2.7 (1.4-5.1) ( $n = 6$ )
DSE	6.2 (1.7-22.8) ( $n = 3$ )	8.1 (2.5-26.4) ( $n = 4$ )

<sup>a</sup> Final conclusions were based on data from this analysis.

<sup>b</sup> Includes studies where treatment was altered based on positive test results (see Methods for details).

The relative effectiveness of these four tests to predict adverse cardiac outcome (cardiac death or MI) in decreasing order of effectiveness was as follows: DSE, DTS, RNV, and AECG. These results were qualitatively the same for the alternative analysis (Figure 2).

**Table 1.** Study Demographics for Dipyridamole Thallium Scintigraphy (DTS), Radionuclide Ventriculography (RNV), Ambulatory Electrocardiography (AECG), and Dobutamine Stress Echocardiography (DSE) Tests Before Vascular Surgery

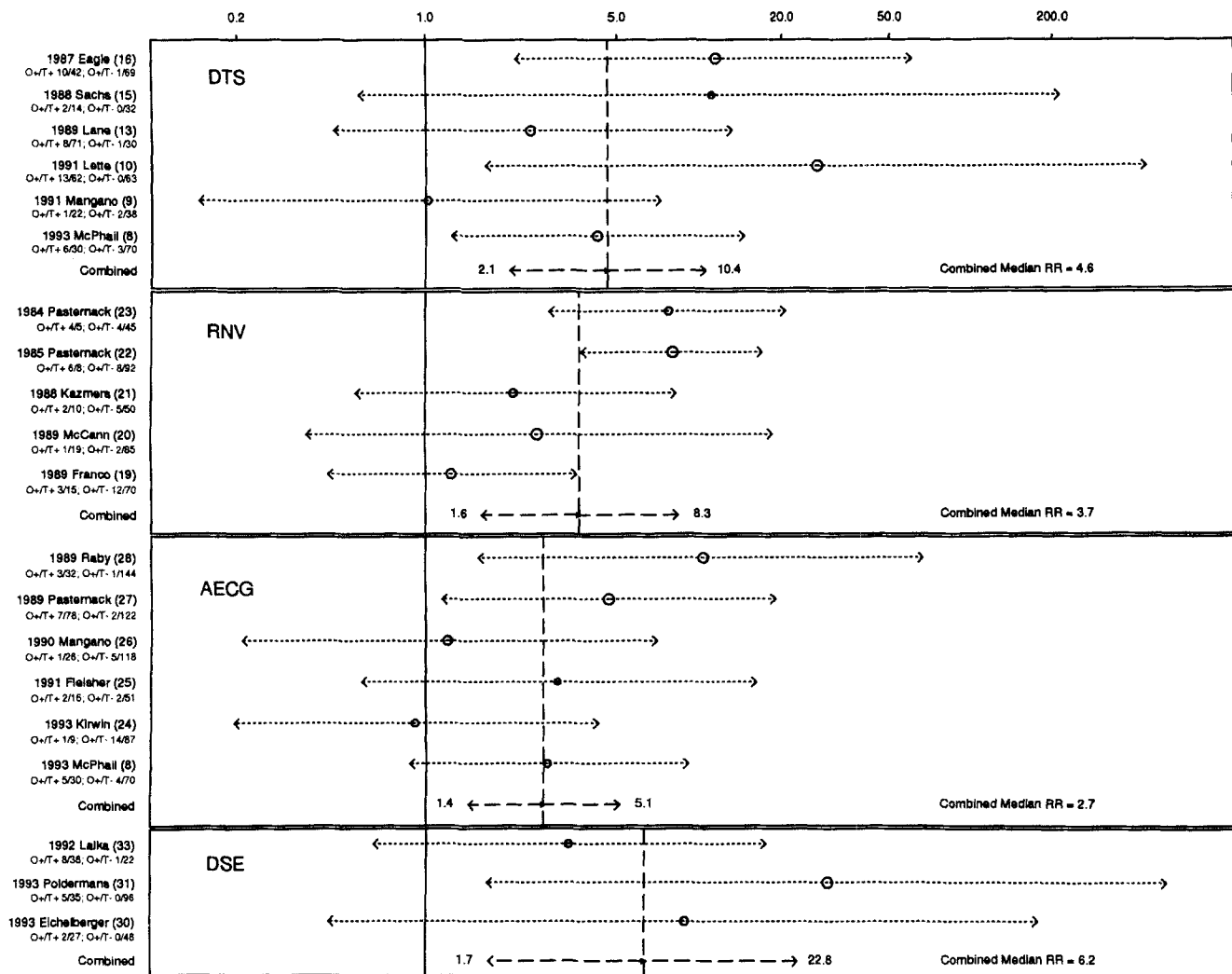
Study (reference)	Consecutive patients selected for study	Physicians blinded to test results	Patients in the study (n)	Surgical procedures (%)			Usefulness of the test as reported by the authors	Other potential risk factors associated with adverse cardiac outcome as reported by the authors	
				Aortic	LEVS	CEA			
<b>DTS studies</b>									
Eagle et al. (16)	No	No	111	80.2	10.8	9	Yes	Pathologic Q waves	
Sachs et al. (15)	?	Yes	46	37	34.7	28.3	Yes		
Lane et al. (13)	No	No	101	8.9	91.1	0	No (not on simple qualitative analysis)		
Lette et al. (10)	Yes	No	125	71.2	22.4	6.4	Yes	Redistribution defects in >three segments or in left anterior descending artery distribution, history of angina and high Goldman risk score	
Mangano et al. (9)	Yes	Yes	60	55.3	40	4.7	No		
McPhail et al. (8)	No	Yes	100	91	9	0	Yes		
<b>RNV studies</b>									
Pasternack et al. (23)	Yes	No	50	100	0	0	Yes		
Pasternack et al. (22)	Yes	No	100	0	100	0	Yes		
Kazmers et al. (21)	No	No	60	100	0	0	No		
McCann and Wolfe (20)	No	No	104	100	0	0	No		
Franco et al. (19)	Yes	No	85	0	100	0	No		
<b>AECG studies</b>									
Raby et al. (28)	Yes	Yes	176	32	52	16	Yes	Angina at rest Early postoperative ischemia	
Pasternack et al. (27)	Yes	No	200	33.5	26.5	40	Yes		
Mangano et al. (26)	No	Yes	144 <sup>a</sup>	?	?	?	No		
Fleisher et al. (25)	No	No	67	?	?	0	Yes		
Kirwin et al. (24)	No	No	96	23.9	76.1	0	No		
McPhail et al. (8)	No	Yes	100	91	9	0	Yes		
<b>DSE studies</b>									
Lalka et al. (33)	No	No	60	100	0	0	Yes	Inability to achieve target heart rate (<120/min) and more severely abnormal DSE results	
Poldermans et al. (31)	Yes	Yes	131	71.3	28.7	0	Yes	Age >70 yr	
Eichelberger et al. (30)	Yes	Yes	75	26.7	61.3	12	Yes		

Aortic = aortic aneurysm surgery or aortobifemoral graft surgery; LEVS = lower extremity vascular surgery; CEA = carotid endarterectomy.  
<sup>a</sup> Of 474 patients undergoing noncardiac surgery, 144 underwent vascular surgery.

## Discussion

The prevalence of symptomatic and asymptomatic CAD in vascular surgical patients is high (2,39); these patients have a high risk of developing adverse cardiac events in the postoperative period (3,4). The risk of cardiac complications ranges from 5% to 40% (5). Reported incidences include 21% after infrainguinal procedures (40), 15% after aortic procedures (40), and 11.7% after carotid endarterectomy under regional anesthesia with prophylactic nitroglycerin infusion (41). Clinical risk

factors are minimally useful in the prediction of cardiac complications after vascular surgery (2,6). A recent survey to determine the frequency of preoperative tests before vascular surgery in current clinical practice revealed that DTS was the most frequently used test and Holter monitoring (AECG) the least (42). It has not been clear which of the four tests is better for predicting adverse cardiac outcome in terms of "effectiveness." Effectiveness can be attributed to a product or technology when it demonstrates a desired benefit under conditions of actual use (34). In the present context, a

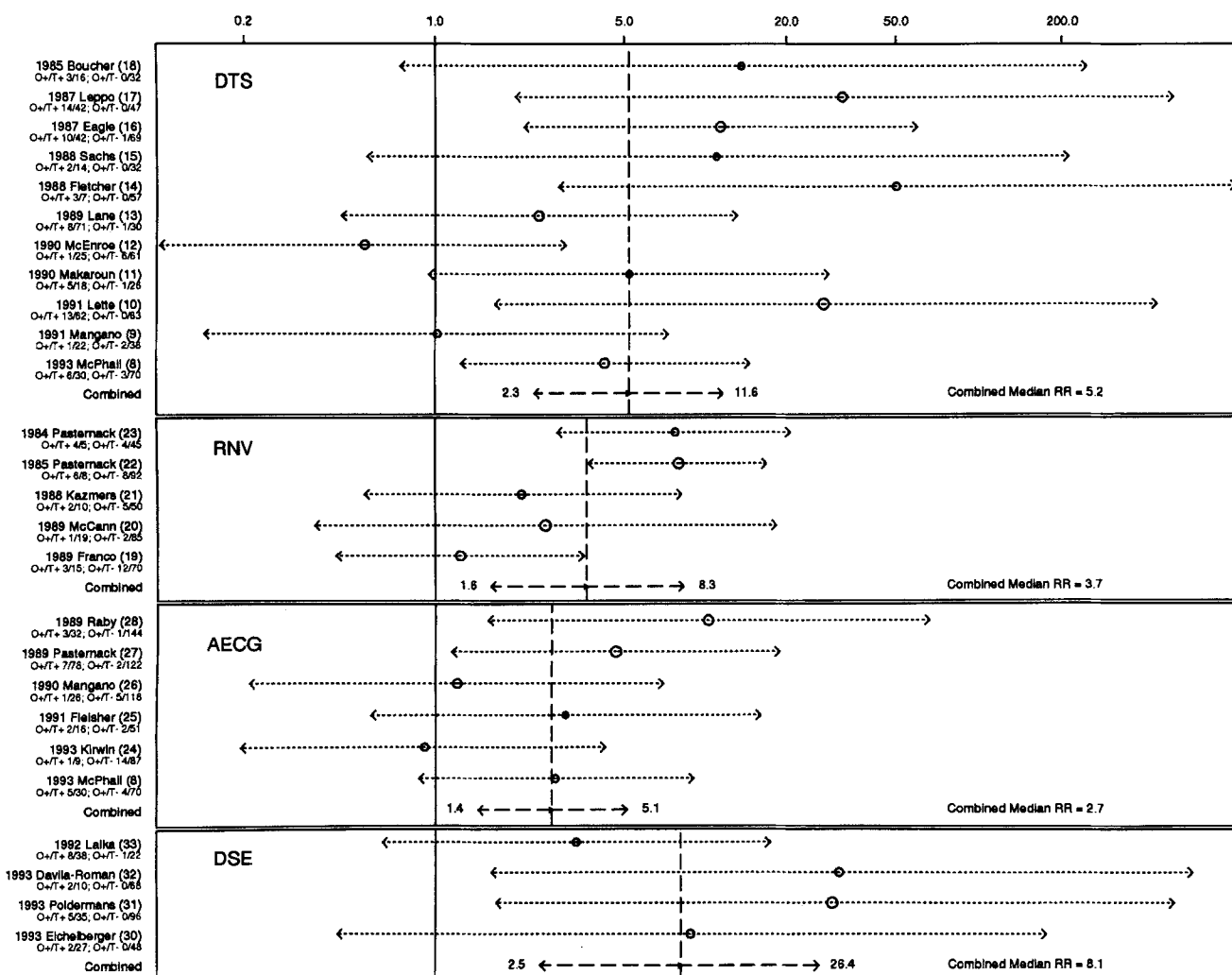


**Figure 1.** Meta-analysis of studies with no myocardial revascularization procedures before vascular surgery. Relative risk (RR) with 95% confidence intervals for adverse cardiac outcome (cardiac death or myocardial infarction) after vascular surgery in studies of four preoperative tests: dipyridamole thallium scan (DTS), ejection fraction estimation by radionuclide ventriculography (RNV), ambulatory electrocardiography (AECG), and dobutamine stress echocardiography (DSE). The center of the circle represents the point estimate of R.R. The area of a circle is proportional to the study sample size for the respective test group. The vertical solid line represents a RR of 1: outcome is similar whether the test is positive or negative. The vertical interrupted line represents the combined median RR for the studies. Final conclusions were based on the data shown in this figure. O+ = outcome positive; O- = outcome negative; T+ = test positive; T- = test negative. Outcome refers to cardiac death or myocardial infarction.

test was considered effective if the combined RR and 95% CI was more than one (null hypothesis value). Ideally, to determine the effectiveness of the four non-invasive tests, patients should be recruited to participate in a prospective, multicenter study in which test results would be blinded to physicians, and outcomes could be evaluated. But this approach is logistically difficult to implement, time-consuming, and expensive. In addition, ethical issues could arise because of blinding of test results to physicians. Despite its inherent limitations, meta-analysis may address the question.

Meta-analysis is a systematic approach that combines evidence from several studies to evaluate the effectiveness of therapies or other interventions. The final

product has both quantitative and qualitative elements, as it takes into account the numerical results and sample sizes of individual studies as well as more subjective issues such as quality, extent of bias, and strength of study design. It also allows one to plan new studies (43). Four steps have been proposed to reach a meaningful conclusion from meta-analysis: formulation of a question, selection of trials, use of good methodology to obtain and analyze data, and appropriate interpretation (44). We believe that our analysis fulfills these four criteria. The random-effects model (36) used in our meta-analysis accounts for the heterogeneity between studies by weighting within-study results and incorporating between-study differences in



**Figure 2.** Alternative meta-analysis with inclusion of studies in which less than 20% of patients had myocardial revascularization procedures before vascular surgery. In these studies, patients who underwent revascularization were not considered for analysis. Relative risk (RR) with 95% confidence intervals for adverse cardiac outcome after vascular surgery in studies of four preoperative tests: dipyridamole thallium scan (DTS), ejection fraction estimation by radionuclide ventriculography (RNV), ambulatory electrocardiography (AECG), and dobutamine stress echocardiography (DSE). The center of the circle represents the point estimate of RR. The area of a circle is proportional to the study sample size for the respective test group. The vertical solid line represents a RR of 1: outcome is similar whether the test is positive or negative. The vertical interrupted line represents the combined median RR for the studies. Final conclusions were not based on the data shown in this figure. O+ = outcome positive; O- = outcome negative; T+ = test positive; T- = test negative. Outcome refers to cardiac death or myocardial infarction.

the calculation of the variance, and therefore 95% CIs, for the variable of interest. Data acquisition in our meta-analysis followed accepted guidelines (43,45,46). Care was taken to avoid the bias that can result from multiple publications.

The variable used to combine evidence from different studies in this analysis was RR. For a noninvasive preoperative test, it is equally important to know the probability of cardiac events when the test is positive as well as when it is negative. RR uses both of these probabilities. Another useful variable for interpretation of diagnostic and equivalent tests is likelihood ratio (Appendix A) (5,35). Computational details for estimating 95% CIs for this variable have also been described

(47). The advantage of the likelihood ratio is that it does not depend on the prevalence of a disease. However, given a high prevalence of CAD and cardiac events in patients presenting for vascular surgery, irrespective of the type of procedure, we are justified in using RR in our analysis.

The combined RR (95% CIs) for DTS found by our analysis was 4.6 (2.1-10.4). Since the combined RR and 95% CI is greater than one, this test is effective in predicting the cardiac events after vascular surgery. We considered the presence of a redistribution defect in any one segment as a positive DTS test result. The results from the DTS test are amenable to quantitative analysis. A recent study (10) found that quantitative

analysis stratified cardiac risk better than a simple qualitative result, such as presence or absence of redistribution defect in one segment, although the validity of that hypothesis cannot be supported from our analysis. There was bias for better predictive value of DTS in early studies. This finding is not surprising because of the possibility of *pretest referral bias* (48) in early studies where patients were not recruited consecutively. Improvement in perioperative care over time may also explain the phenomenon of decreasing predictive value.

For the RNV test, combined RR (95% CI) was 3.7 (1.6–8.3) when ejection fraction  $\leq 35\%$  was considered a positive result. The point estimate and 95% CI are above 1, indicating that the test is effective. In a study not included in our analysis in which ejection fraction  $< 30\%$  was the end-point for a positive result (49), the authors concluded that RNV is an accurate predictor of cardiac events after aortic surgery. Whether an end-point of  $< 30\%$  improves the predictive value for the RNV test cannot be answered from our analysis because the studies we selected did not report cardiac events separately for patients with an ejection fraction  $< 30\%$ . As with the DTS studies, the trend was for predictive value of the RNV test to decrease in more recent studies.

For AECG monitoring of preoperative ischemia, RR (95% CI) was 2.7 (1.4–5.1) indicating this test is also effective for predicting adverse cardiac outcome. A positive result was an ischemic duration  $> 1$  min, the only uniformity in the reported results of the selected studies. Whether ischemia duration per hour of AECG monitoring or cumulative ischemic time further improves the predictive value for this test cannot be answered from our analysis. The predictive value for this test has also decreased in more recent studies, although the first two studies in this group recruited patients consecutively.

For DSE, RR (95% CI) was 6.2 (1.7–22.8), which suggests that the test may be very effective compared to the other three tests. Unlike the trend in the studies of other tests, predictive value improved in the later studies, although any conclusion about DSE is limited by the few studies reported to date. The last two studies in this group were well designed with respect to recruiting patients consecutively and blinding test results to physicians. Changes in regional wall motion (see Methods for definition) in any one segment on echocardiography during dobutamine infusion were considered a positive test result. The results of this test also are amenable to quantitative analysis. On multiple regression analysis, one study found that more severely abnormal DSE results better stratified cardiac risk (33).

An evaluation of these preoperative tests must also consider the advantages, disadvantages, and

complications of each test (Table 2). The reported percentage of complications obtained from the DTS studies included in our analysis was 8.2% (from a total of 702 patients). The complications were minor and not life-threatening. A recent report of the use of DSE in 1118 patients found that the test could be performed without serious complications from myocardial ischemia (55). The most common arrhythmias, frequent premature ventricular complexes (15%) and premature atrial complexes (8%), were well tolerated and rarely required treatment. There were no serious complications due to myocardial ischemia, and noncardiac side effects were minor. Because of concerns of cost and safety associated with preoperative testing, some have suggested selective use of testing based on clinical evaluations (5,58–60). However, two recent studies (2,10) did not support this approach.

The limitations of this study reflect the limitations of meta-analysis in general (46,61,62). Meta-analysis is essentially observational, and represents a retrospective look at data already accumulated. Differences among outcomes that may occur between studies may represent an essential source of bias in a meta-analysis of this kind. Since meta-analysis reflects studies that span time, differences in concurrent anesthetic and surgical management may affect overall outcome of the analysis. In addition, at a particular given time, outcomes could be a function of institutional morbidity rates. Multiple publication and publication bias can present problems in the interpretation of meta-analysis. In the present analysis, care was taken to avoid the bias resulting from multiple publications. Publication bias refers to the tendency whereby research with statistically significant results is more likely to be submitted and published than work with null or nonsignificant results (63).

Heterogeneity of study design presents another problem for meta-analysis. Two aspects of study design have a great impact on the predictive value of a given test in an individual study and therefore the yield of this meta-analysis. They are patient selection and blinding of test results. A test may have been performed in consecutive patients presenting for vascular surgery or in selected patients chosen according to clinical criteria. The predictive value of a given test is likely to be higher when selected patients are tested than when consecutive patients are tested. Selection bias occurs because sicker patients (patients with high prior probability for coronary artery disease and therefore adverse cardiac outcome after surgery) among the patients presenting for vascular surgery are more likely to get the test. The predictive value of a given test is likely to be lower in unblinded studies. Unblinding of test results may alter the surgical and perioperative anesthesia care and therefore outcome. In unblinded studies, patients with positive test results may undergo

**Table 2.** Advantages and Disadvantages of Preoperative Noninvasive Tests Before Vascular Surgery

Test	Advantages	Disadvantages
DTS	Sensitivity for detection of CAD ranges from 60% to 90% and specificity from 80% to 100% (50)	Requires overnight fasting  Contraindicated in patients with unstable angina, recent myocardial infarction, bronchial asthma, and chronic obstructive pulmonary disease Requires delayed imaging at 3-4 h and maybe even at 18-24 h (51) Reported failure to detect severe CAD and therefore to predict the cardiac events after vascular surgery (52,53)
RNV AECG	Noninvasive estimation of left ventricular function Simple to use	Exposure to radioactive material Nonspecific changes in ST segment can occur due to changes in body position or drugs (54) Baseline abnormalities (strain pattern, digoxin effect, bundle-branch pattern, pacemaker) may prohibit use of ST segment changes as a marker for myocardial ischemia
DSE	Relatively safe without serious complications due to myocardial ischemia (55) Takes less than 1 h and can be done in an outpatient setting Sensitive (78%) and specific (93%) for detecting CAD (56) Sensitivity enhanced by addition of atropine during dobutamine infusion (57) Detects ischemia due to dynamic factors (stress) which can occur in the perioperative period	Possibility of life-threatening complications such as ventricular fibrillation (31)

CAD = coronary artery disease; DTS = dipyridamole thallium scanning; RNV = radionuclide ventriculography for ejection fraction; AECG = ambulatory electrocardiography; DSE = dobutamine stress echocardiography.  
Numbers in parentheses are reference numbers.

conservative operations or receive better care such as increased use of hemodynamic monitoring, increased use of nitroglycerin, or longer stay in the intensive care unit. Such care may decrease the rate of adverse cardiac outcome after surgery. Studies in which patients are recruited consecutively and physicians are blinded to test results are likely to provide a relatively unbiased predictive accuracy for a given test.

Our conclusions about the effectiveness of DSE may be criticized for various reasons. Our analysis was limited to only three studies. One might argue that the predictive value of DSE may decrease as more studies are conducted. We believe a reduction in predictive value may not occur. The earliest study (33) was less well designed than the two more recent DSE studies (30,31) with respect to patient recruitment and blinding of test results. The two later studies revealed a better predictive value than the first study. In addition, a recent study (29) found DSE to be highly valuable in risk stratification before aortic surgery. In that recent study, risk stratification with DSE allowed surgery to be

performed in 74 of 81 patients with no operative deaths and a 4.1% rate of perioperative MI.

We grouped fixed defects and absence of redistribution defects as negative results for DTS. However, fixed defects may show redistribution on delayed imaging performed at 18-24 h (51), suggesting that fixed defects might be considered positive DTS test results. Unfortunately, in most studies, cardiac events were not reported separately for patients with fixed defects. The timing of delayed DTS imaging was reported in five studies in which repeat scanning was performed at 3-4 h. The duration of preoperative monitoring of silent ischemia for AECG differed between studies and ranged from 12 to 48 h. Sites of electrode lead placement and duration of ischemia required to define a positive test result also differed slightly between studies. In one study duration was 40 s (27); in the rest, 1 min. AECG monitoring for detection of myocardial ischemia may be limited, as nonspecific ST-segment changes may occur perioperatively due to changes in body temperature, serum electrolytes, ventilation,

body position, or drugs administered (54). These changes frequently occur in the preoperative setting and may limit the interpretation of AECG.

According to Thompson and Pocock (64) "meta-analysis is not an exact statistical science that provides definitive simple answers to complex clinical problems. It is more appropriately viewed as a valuable objective descriptive technique, which often furnishes clear qualitative conclusions about broad treatment policies, but whose quantitative results have to be interpreted cautiously." Potential problems and biases can affect the outcome of a meta-analysis, and therefore the quantitative information provided by it. Although meta-analysis gives us quantitative information about the variable of interest (RR for a particular test, in the present context), conclusions are best interpreted only in qualitative terms. Results of this analysis will not allow us to conclude that DSE is 2.3 times as effective as AECG in predicting adverse cardiac outcome after vascular surgery. Still, the greater objectivity of this approach is a clear advantage over the more subjective narrative review (65).

Our analysis allows the following conclusions. With the exception of DSE, each of the tests demonstrated a bias for better predictive value in earlier studies. All of the tests (DTS, RNV, AECG, and DSE) are "effective" (the 95% CIs for RR are >1.0) in predicting cardiac death or MI after vascular surgery. Although DSE appears to be the best among these four tests and AECG to have the least predictive value, this conclusion is limited because the 95% CIs for RR overlap. Future studies may be directed toward DSE as this test shows great promise for the prediction of adverse cardiac events after vascular surgery.

## Appendix A

Possible variables that can be estimated for screening or diagnostic tests summarized in two-by-two tables (35) are presented.

## Appendix B: Meta-Analytic CI for RR

We want to combine information about the RR of a test from various studies. Let  $j$  index the studies, where  $j$  runs from 1 to  $J$ , the total number of studies. An estimate of RR based only on the  $j$ th study is  $(E_j/PosT_j)/(NegT_j/G_j)$ , where  $PosT_j = E_j + F_j$ ,  $NegT_j = G_j + H_j$ , and  $E_j, F_j, G_j, H_j$  are the cell counts in the usual two-by-two table (test result along the rows and outcome along the columns). To get a 95% CI for RR based only on the  $j$ th study, we first find a 95% CI for the log RR and then apply the exponential function to the interval. We assume that the variation within a study is known exactly. This is not unreasonable when the sample size for the study is large. An approximate 95% CI, assuming

	Outcome/disease		Total
	Positive	Negative	
Test positive	a	b	a + b
Test negative	c	d	c + d
Total	a + c	b + d	a + b + c + d
Positive predictive value (PPV)	a/(a + b)		
Negative predictive value (NPV)	d/(c + d)		
Relative risk	[a/(a + b)] ÷ [c/(c + d)] or (PPV) ÷ (1 - NPV)		
Sensitivity or true positive (TP)	a/(a + c)		
Specificity or true negative (TN)	d/(b + d)		
Odds ratio	(a/b) ÷ (c/d)		
Likelihood ratio for positive test	[a/(a + c)] ÷ [b/(b + d)] or (TP) ÷ (1 - TN)		
Likelihood ratio for negative test	[c/(a + c)] ÷ [d/(b + d)] or (1 - TP) ÷ (TN)		

a normal distribution, for the log RR based only on the  $j$ th study is:

$$\hat{d}_j \pm 1.96 \sqrt{\sigma_j^2}$$

where  $\hat{d}_j = \log(E_j/PosT_j)(NegT_j/G_j)$ , the estimated log RR, and  $\sigma_j^2 \equiv V((\hat{d}_j) = (1/E_j) - (1/PosT_j) + (1/G_j) - (1/NegT_j))$ . We analyze the log RR instead of the RR because the normal approximation usually works much better for the log RR.

### Hierarchic Model

A two-stage hierarchic model was used to combine information about the RR of a test from various studies. The quantity combined was not the RR but rather the log of the RR. Taking the logarithm of RR made the hierarchic model more appropriate, particularly for the first-stage model. The model assumes that the studies are exchangeable; i.e., we are assuming *a priori* that the studies are equivalent in regard to their outcomes.

#### First-Stage Model

$$\hat{d}_j | D_j = d_j \sim N(D_j, \sigma_j^2) \quad j = 1, \dots, J$$

where  $\hat{d}_j$  is an estimator of  $d_j$ . We treat  $d_j$  as a realization of the random variable  $D_j$ ; i.e., we treat log RR as a random variable, and the true log RR for a study as a realization of the random variable  $D_j$ . In the second stage of the hierarchy  $D_j$  is assumed to have a normal distribution, i.e., we assume that the study effects have a normal distribution (study effect is the log RR of a study).

Second-Stage Model

$$E(D_j | \mu, \Delta^2) \equiv \mu$$

$$V(D_j | \mu, \Delta^2) \equiv \Delta^2$$

$$D_j | \mu, \Delta^2 \sim N(\mu, \Delta^2)$$

Conditional Mean Estimator

We want to obtain an unbiased estimator of  $\mu$ . A simple estimator exists if we assume that  $\Delta^2$  is known, i.e., if we assume that the between-study variance is known. An unbiased estimator of  $\mu$ , the overall mean of log RR, conditional on  $\Delta^2$  is:

$$\hat{\mu} \equiv \frac{\sum_{j=1}^J w_j^* \hat{d}_j}{\sum_{j=1}^J w_j^*}$$

The variance of  $\hat{\mu}$  conditional on  $\Delta^2$  is:

$$V(\hat{\mu}) = \frac{\Delta^2}{\sum_{j=1}^J w_j^*}$$

where  $w_j^* = (\Delta^2 / \Delta^2 + \sigma_j^2)$ . From the normal-normal model assumed in the Hierarchic Model section,  $\hat{\mu}$  has a normal distribution with mean  $\mu$  and variance given above. We can use this fact to form a conditional CI for  $\mu$ .

Conditional CI

The mean estimator given in the Conditional Mean Estimator section is conditional on  $\Delta^2$ . The idea of empirical Bayes is to estimate  $\Delta^2$  and then act as if we knew the true  $\Delta^2$ . The uncertainty in the estimator of  $\Delta^2$  is not taken into account in the conditional CI. To estimate  $\Delta^2$  we used the method-of-moments estimator given in DerSimonian and Laird (36).

Estimator of  $\Delta^2$ :

$$w_j = \frac{1}{\sigma_j^2}$$

$$\hat{Q}_w = \sum_{j=1}^J w_j (\hat{d}_j - \bar{\hat{d}})^2$$

$$\bar{\hat{d}} = \frac{\sum_{j=1}^J w_j \hat{d}_j}{\sum_{j=1}^J w_j}$$

$$\hat{\Delta}_1^2 = \max$$

$$\left\{ 0, \left\{ \hat{Q}_w - (J - 1) \right\} / \left[ \sum_{j=1}^J w_j - \left( \frac{\sum_{j=1}^J w_j^2}{\sum_{j=1}^J w_j} \right) \right] \right\}$$

Once we have an estimate of  $\Delta^2$ , we substitute the variance estimate into the equations in the Conditional Mean Estimator section to get an estimate of  $\mu$  and the variance of the mean estimator. Using the fact that  $\hat{\mu}$  has a normal distribution, a conditional 95% CI (empirical Bayes interval) for the mean of the log RR,  $\mu$ , is:

$$(\hat{\mu} - 1.96 \sqrt{V(\hat{\mu})}, \hat{\mu} + 1.96 \sqrt{V(\hat{\mu})}).$$

The CI above is for the overall mean of the log RRs,  $\mu$ . Since we are assuming that the study effects have a symmetric distribution, namely a normal distribution, the overall median and the overall mean of the log RRs are the same. Hence, a CI and estimate for the overall mean is also a CI and estimate for the overall median. If we wish to get a CI and point estimate for the overall median of the RRs, we can simply take the exponential of the estimate and CI given above for the log RRs. We cannot take the exponential of the interval and point estimate for  $\mu$  to get an interval for the overall mean of the RRs. However, the distribution of the RRs under the model in the Hierarchic Model section is assumed to be skewed (a lognormal distribution), making the median a more sensible measure of center than the mean. The median is always the value such that 50% of the values lie above and 50% lie below, regardless of the scale. It is the typical value.

The empirical Bayes confidence interval given above will have approximately the correct coverage probability when the information on  $\Delta^2$  is large (typically when the number of studies is large), i.e., when the estimate of  $\Delta^2$  is close to the true  $\Delta^2$ . When the information on  $\Delta^2$  is small, the actual coverage probability is usually less than the nominal coverage probability (e.g., the actual coverage might be 85% instead of the nominal 95%).

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