

## CLINICAL INVESTIGATIONS

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# Preoperative Dipyridamole Thallium Imaging and Ambulatory Electrocardiographic Monitoring as a Predictor of Perioperative Cardiac Events and Long-term Outcome

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**Background:** Dipyridamole thallium imaging (DTI) and ambulatory electrocardiography (AECG) have been advocated as means to stratify risk before vascular surgery. The purpose of this study was to compare the predictive value of both tests in noncardiac surgery patients for perioperative cardiac morbidity and long-term mortality.

**Methods:** One hundred eighty patients were referred to the nuclear cardiology laboratory for DTI before noncardiac surgery. In patients with normal electrocardiograms and who consented, an ambulatory electrocardiogram was recorded for 24 h. DTI results were classified as negative, positive, or

strongly positive (included in positive). Patients were assessed for a minimum of 12 months, and Kaplan-Meier cardiovascular survival curves were constructed with a log-rank statistic of equality with  $P < 0.05$  significant.

**Results:** One hundred nine patients had both tests and then underwent surgery, sustaining 10 perioperative cardiac events (cardiac death, myocardial infarction, or symptomatic ischemia). The positive predictive values for DTI (18%) and AECG (25%) were similar, as were the likelihood ratios for positive tests (DTI = 2.1, AECG = 3.3). The likelihood ratios of a negative test were also similar (DTI = 0.45, AECG = 0.48). A strongly positive thallium defect had a somewhat greater likelihood ratio (3.5) for in-hospital events and was the only test result associated with a significantly worse long-term cardiac survival.

**Conclusions:** AECG and DTI demonstrated a similar, although lower than initially reported, ability to stratify risk and predict short-term outcome. Only quantitative dipyridamole thallium also had predictive value for long-term prognosis. (Key words: Evaluation: preoperative. Outcome: long-term. Myocardial infarction. Surgery: noncardiac. Testing: ambulatory electrocardiography; dipyridamole thallium imaging.)

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PERIOPERATIVE cardiac complications continue to represent a significant source of morbidity in high-risk patients undergoing noncardiac surgery.<sup>1</sup> Multiple strategies have been proposed to reduce such risk.<sup>1-7</sup> In patients with poor exercise tolerance, such as those with peripheral vascular disease, noninvasive testing strategies have been suggested as a means of identifying patients with occult significant coronary artery disease. One such test, dipyridamole thallium imaging (DTI), has been extensively studied in vascular surgery patients since the initial report almost a decade ago.<sup>8,9</sup> Abnormal patterns on thallium imaging have been shown to be predictive of perioperative morbidity in the vast majority of studies.<sup>9-20</sup> However, the utility of the test has been questioned.<sup>21,22</sup> Eagle *et al.* pointed out that not all patients benefit from DTI, but certain patient groups can be identified in whom diagnostic



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yield is optimal.<sup>23</sup> Additionally, quantitative thallium imaging has been proposed as a means of increasing the diagnostic utility of testing.<sup>13,15</sup>

Holter monitoring or ambulatory electrocardiography (AECG) has been advocated as a less invasive and less costly alternative for risk prediction before noncardiac surgery. The presence of preoperative ST segment changes has been shown to predict cardiac morbidity in both vascular and nonvascular surgery patients.<sup>24,25</sup> However, the utility of this test also has been questioned.<sup>26,27</sup> Additionally, unlike DTI, quantification of the extent of myocardium at risk has not been performed using AECG monitoring.

An optimal preoperative testing strategy should influence perioperative care and management decisions and assess long-term risks and outcomes. Coronary artery disease is the primary cause of long-term morbidity and mortality after vascular surgery.<sup>28</sup> The combined risk of a vascular procedure and that resulting from the presence of significant associated coronary artery disease may be greater than the combined risk of coronary revascularization followed by the scheduled noncardiac surgery. By obtaining a perioperative and long-term risk assessment, the risks and benefits of interventions, such as coronary revascularization, can be better determined.<sup>29</sup>

We hypothesized that both AECG and DTI would predict in-hospital outcome and long-term survival. Additionally, we hypothesized that quantification of the thallium defect and the silent ischemia burden would add prognostic value and increase the positive predictive value of the test. To address this issue, we prospectively performed AECG monitoring for ST segment changes in patients referred for DTI before noncardiac surgery.

## Materials and Methods

All patients referred to the nuclear cardiology laboratory for DTI before noncardiac surgery during the period from March 1990 until February 1992 were considered suitable for study. One hundred eighty patients underwent DTI, 93 males and 87 females. The average patient age was  $69 \pm 9$  yr (range 45–90 yr).

### Perioperative Cardiac Events

A postoperative cardiac event was defined as (1) death from a cardiac cause, (2) myocardial infarction (MI) with either new Q waves on ECG or increased total CK

and an MB isoenzyme fraction  $>5\%$  associated with new persistent ECG changes (significant ST segment change depression or T wave inversion  $>2$  mm in 2 leads of a 12-lead ECG or a new left bundle branch block), and (3) unstable angina/ischemia (defined by new ST segment changes  $>1$  mm depression) or T wave inversion  $>2$  mm) on 2 or more leads of a 12-lead ECG with chest pain, pulmonary edema, or signs of cardiovascular dysfunction).

### Dipyridamole Myocardial Perfusion Imaging

DTI was performed according to a previously described standardized protocol (fig. 1).<sup>30</sup> Briefly, dipyridamole was infused intravenously at the rate of 0.56 mg/kg body weight over 4 min. Four minutes after the completion of the infusion, 2.5 mCi of thallium-201 was injected. When feasible, patients performed low-level exercise during and after dipyridamole infusion. This consisted of slow walking on a treadmill at a rate of 1 mile/h. Low-level exercise has been shown to increase the predictive accuracy of the test.<sup>31</sup> The patients underwent planar imaging within 5–10 min after injection of thallium-201. Planar imaging was performed in the left anterior oblique, anterior, and left lateral right decubitus position. Second (rest) imaging was performed 3–4 h after infusion of the dipyridamole.

The gamma camera was equipped with a low-energy all-purpose collimator. The energy window (20%) was peaked over the 80 keV energy peak of thallium-201. Images were recorded in  $128 \times 128$  word mode and stored on computer disk. All images were quantified using previously described software.<sup>32</sup>

In brief, after interpolative background subtraction, circumferential count distribution profiles were generated. Myocardial perfusion defects were quantified relative to a normal data base. The images were interpreted as normal or abnormal and as showing fixed, partially reversible, or completely reversible perfusion defects. A strongly positive DTI was determined quantitatively as (1) a reversible defect in two or more coronary artery territories; (2) a defect integral  $>13$ , with  $>50\%$  reversibility; or (3) any reversibility of defects with lung/heart ratio  $>0.50$  (TIMI-IIIb criteria).<sup>33</sup>

Patients who demonstrated a fixed defect on second imaging underwent a separate rest-reinjection imaging study to assess optimally for reversibility of a defect. Reinjection occurred the morning after the initial injection if a fixed defect was observed. Previous work in our laboratory suggests that approximately 40% of fixed defects demonstrate redistribution on reinjec-



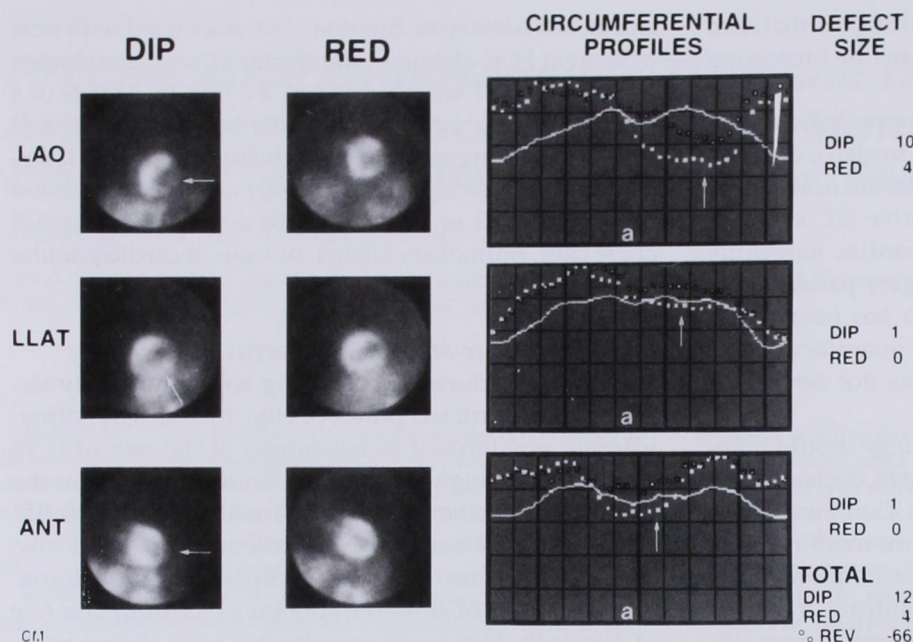


Fig. 1. Thallium-201 dipyridamole stress imaging with quantitative analysis. (Left) Planar images obtained after dipyridamole stress (DIP) and at 2-3-h redistribution imaging (RED). A partially reversible inferolateral myocardial perfusion defect is present (arrows). (Right) Quantification of images using circumferential count profiles. The continuous white line indicates the lower limit of normal thallium-201 distribution. The large white dots indicate the patient's thallium-201 distribution after DIP. The small white dots indicate thallium-201 distribution at RED imaging. Count distribution is displayed counterclockwise starting at 0 h. The apex (a) is at the middle of the graph. Arrows indicating the abnormal area correspond to the arrows placed on the images. Quantitative defect size is indicated for each view. Defect reversibility (%REV) is -66%. LAO = left anterior oblique; LAT = left lateral; ANT = anterior.

tion.<sup>34</sup> For the purposes of analysis, a negative DTI was considered a normal or fixed defect. A positive DTI was considered if there was evidence of myocardial ischemia, as demonstrated by a reversible perfusion defect. A second analysis was performed in which the DTI results were stratified into three categories: normal, fixed only (*i.e.*, scar), and reversible.

#### Preoperative AECG Monitoring

Study patients were monitored by a calibrated amplitude-modulated ambulatory electrocardiographic monitor (SpaceLabs ambulatory ECG model 90205, Redmond, WA) with modified bipolar leads V3 and V5. These leads were chosen because of their previously reported increased sensitivity for detecting myocardial ischemia.<sup>35</sup> Patients with preexisting left bundle branch block, left ventricular hypertrophy with strain, or baseline ST segment changes caused by digoxin were excluded. The AECG monitors were placed on the patient either at the time of the DTI or on the evening before surgery. All patients were monitored as inpatients. The AECG recordings were analyzed after the surgical procedure to ensure that the results were not available to the clinical caregivers.

Both AECG lead recordings were analyzed for ST segment changes on a SpaceLabs FT2000 computerized analysis system. Twenty-four hour ST-segment and heart rate trends were plotted. A positive AECG, indicative

of myocardial ischemia, was defined as either >1 mm horizontal or downsloping ST segment depression or >2 mm ST segment elevation measured at 60 ms after the J-point and persisting for at least 1 min. All ST changes  $\geq 1$  mm that were observed in the trend plots were printed at 25 mm/s, and the ECG strips were reviewed by two investigators blinded to clinical outcome and DTI results. The number of episodes and duration of ischemia were determined for each patient. Patients who exhibited a normal baseline ECG but who had persistent nonspecific abnormalities on the AECG were excluded.

#### Perioperative Patient Management

The results of the preoperative DTI were available to the responsible physicians, who may have modified perioperative care based on the results. The results of the preoperative Holter monitoring, which is considered a research procedure for this indication in our institution, were not made available to the physicians. All patients were evaluated preoperatively by the anesthesia staff and found to be in their optimal medical condition by both the anesthesia and referring physicians. No signs of uncompensated congestive heart failure were exhibited by any patient before surgery. All patients had a preoperative standard 12-lead electrocardiogram during the 7 days before surgery. Each patient's routine dosage of antianginal medications,  $\beta$



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antagonists, and calcium entry blockers was given on the morning of surgery. The presence of preoperative angina was assessed by review of physician and nursing notes and patient interview on arrival in the operating room. Choice of premedication, intraoperative management, and postoperative monitoring and analgesia were at the discretion of the primary anesthesia and surgical teams. A 12-lead electrocardiogram was obtained on the morning of the first 3 postoperative days or more frequently if clinically indicated. If there were any clinical indications of cardiac morbidity, an additional electrocardiogram was obtained immediately before discharge. Laboratory values including CK-MB levels were obtained according to the policy of the primary physicians; however, virtually all patients had at least two sets during the initial 24 h postoperatively. The practice of obtaining CK-MB isoenzyme measurements was not influenced by the results of the DTI. Interviews of the patients under study were conducted by a member of the research team on the first 3 postoperative days and again on the day of discharge. All ECGs were grouped sequentially and reviewed blindly by a least two members of the investigative team.

#### Long-term Follow-up

An attempt was made to contact all patients a minimum of 12 months after the final enrollment by a member of the investigative team (A.H.N.). The patient or family member was questioned regarding the onset of new chest pain, MI, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), or death. Confirmation of a diagnosis of an MI was attempted by contacting the patient's primary physician. In patients who died, further questioning determined the cause of death. Death from cardiac causes were distinguished from noncardiac causes by review of hospital records or discussion with the patient's primary physician. For patients who could not be contacted, the surgeon was contacted to determine survival status or the date of the last clinic or hospital visit. For the purpose of survival analysis, the primary endpoint was cardiovascular mortality, with a secondary endpoint of cardiovascular morbidity.

#### Statistical Analysis

Differences in patient demographics was determined by Student's *t* test for continuous variables and chi-square or Fisher's exact test for dichotomous data with  $P < 0.05$  as significant (Systat 5.2 for the Macintosh, Systat, Evanston, IL). Preoperative variables studied in-

cluded age, gender, history of coronary artery disease, angina, MI, hypertension, diabetes, recent congestive heart failure, ventricular ectopic activity, and Eagle risk index (age  $> 70$ , diabetes, hypertension, Q waves, ventricular ectopic activity being treated). Surgical variables studied included type of surgery and type of anesthesia. A multivariate model was constructed to determine which variables were independently associated with perioperative morbidity. (JMP 3.0, SAS Institute, Durham, NC). Variables associated with short-term morbidity with a  $P < 0.25$  were placed in a multivariate model. Only those variables that remained predictive with  $P < 0.05$  were considered significant.

Kaplan-Meier survival curves were constructed for both preoperative DTI and AECG monitoring test results. The log-rank statistic of equality with  $P < 0.05$  was used to determine whether a test result was significantly associated with survival. Concordance between tests was determined using a  $\kappa$  statistic.

#### Results

One hundred eighty patients scheduled for surgery underwent DTI. In eight patients, surgery was canceled. In 63 patients, no AECG monitoring was performed. Thus, 109 patients remained who had both DTI and AECG monitoring before scheduled surgery (fig. 2). Eighty-six (79%) patients underwent peripheral vascular surgery; the remaining 23 (21%) underwent nonvascular noncardiac surgery. Of patients undergoing vascular surgery, 31 patients underwent surgery requiring an aortic cross-clamp, 43 patients underwent infrainguinal bypass surgery, 4 underwent mesenteric revascularization, 2 underwent carotid endarterectomy, and 6 underwent amputation. Of those undergoing nonvascular surgery, 10 patients underwent intraabdominal surgery, with the remaining patients undergoing a variety of peripheral procedures.

#### Canceled or Delayed Noncardiac Surgery

In eight patients, surgery was canceled at least partially because of positive DTI results. An additional eight patients underwent coronary revascularization before noncardiac surgery. Seven of these had strongly positive thallium scans. One patient with an equivocal scan was considered high-risk on clinical grounds (prior MI, chronic renal failure, and mitral regurgitation). All eight of these patients underwent cardiac catheterization. All had significant coronary artery dis-



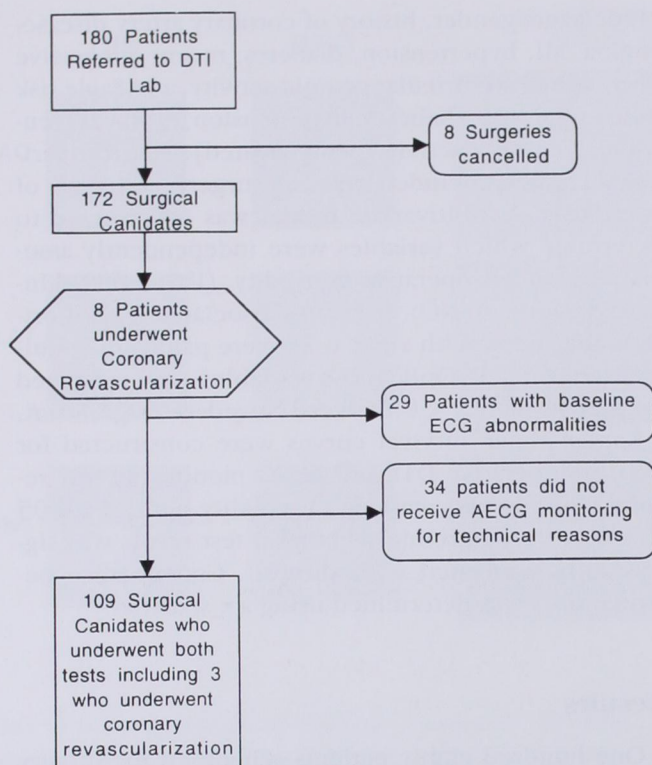


Fig. 2. The fate and monitoring modalities of the 180 patients referred to the dipyridamole thallium imaging laboratory for evaluation before noncardiac surgery.

ease and revascularization (PTCA in five, CABG in three). Of the eight patients, three had AECG monitoring before the coronary revascularization. Only one of the three patients had a positive AECG result. No patient was restudied after the revascularization procedure.

#### AECG Monitoring Not Performed

Sixty-three patients (37%) did not undergo Holter monitoring for technical and logistical reasons. Twenty-nine patients had baseline ECG abnormalities that precluded the electrocardiographic diagnosis of myocardial ischemia, and 2 of 29 patients sustained a perioperative cardiac event. Thirty-four patients either refused monitoring ( $n = 14$ ), had AECG recordings that were uninterpretable ( $n = 7$ ), or were unable to be monitored for logistic reasons ( $n = 13$ ).

#### DTI-AECG Monitoring

One hundred nine patients underwent both tests. Sixty-nine (63%) patients had a negative DTI and 40

(37%) had a positive DTI, of which 11 of these (28%) were high-risk thallium scans. Of the negative DTI, 10 patients demonstrated a fixed defect. Twenty-four (22%) patients had ST segment depression on AECG monitoring. No patient demonstrated significant ST segment elevation or had angina during a period of monitoring. The average duration of monitoring was  $22.8 \pm 10.6$  h (range 18–48 h). The duration of preoperative ST segment monitoring was not significantly different between patients with silent ST segment changes ( $26.4 \pm 12.2$  h) versus those without changes ( $21.8 \pm 10.0$  h). Concordance between the tests was fair ( $\kappa = 0.28$ ; table 1).

#### Short-term Follow-up

Ten of 109 patients (9%) had a perioperative cardiac event: there was 1 cardiac death on postoperative day 5; 4 patients had non-Q wave MI; and 5 patients had unstable angina. Patient demographics in relation to the presence of a perioperative cardiac event are shown in table 2. The incidence of cardiac morbidity by surgical type was as follows: 6% (2 of 31) in patients undergoing aortic surgery, 11% (5 of 43) in patients undergoing infrainguinal bypass surgery, 0% (0 of 2) in patients undergoing carotid surgery, 0% (0 of 4) in patients undergoing mesenteric revascularization, and 4% (1 of 23) in patients undergoing nonvascular surgery. No preoperative clinical variable was significantly predictive of subsequent morbidity in this selected population. Routine surveillance for a perioperative MI was not influenced by the DTI results ( $3.8 \pm 0.16$  ECGs versus  $3.7 \pm 0.19$  ECGs and  $2.5 \pm 0.2$  CK-MB determinations versus  $2.6 \pm 0.25$  CK-MB determinations for a positive and negative DTI result, respectively).

The positive and negative predictive values, likelihood ratios, sensitivity, and specificity of the two tests for perioperative events were not significantly different (table 3). The positive predictive value of AECG monitoring was 25% and of DTI was 18%. The negative

Table 1. Concordance between Preoperative Tests and Outcome

	No Preoperative Silent Ischemia	Preoperative Silent Ischemia
DTI (–)	60	9
DTI (+)	25	15
$\kappa = 0.28$		



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Table 2. Patient Demographics

	Total Group (n = 109)	No Event (n = 99)	Event (n = 10)
Age		68 ± 9	70 ± 10
Male	54 (50%)	50 (50)	5 (50)
Coronary artery disease	79	71 (72)	8 (80)
Angina	33	30 (30)	3 (30)
Q waves	52	47 (47)	5 (50)
Congestive*	7	6 (6)	1 (10)
Heart failure			
Diabetes	47	43 (43)	4 (40)
Ventricular ectopic activity	3	3 (3)	0 (0)
Risk†			
Low	8	6 (75)	2 (25)
Medium	84	79 (94)	5 (6)
High	17	14 (82)	3 (18)
Anesthesia (general)	78	71 (71)	7 (70)
Postoperative intensive care unit	90	80 (80)	10 (100)

Values in parentheses are percentages.

\* History of compensated congestive heart failure.

† Risk as defined by Eagle *et al.*<sup>23</sup>

predictive value of AECG was 95% and of DTI was 96%. The likelihood ratios of a positive test were similar (DTI = 2.1, AECG = 3.3). The likelihood ratios of a negative test also were similar (DTI = 0.45, AECG = 0.48). No patient with a fixed defect sustained a perioperative cardiac event. If only strongly positive thallium imaging was used as a positive result, the positive predictive value was 40% and negative predictive value 94%. The quantification of preoperative silent ischemia did not add additional prognostic information when evaluated by total duration of ischemia (morbidity =  $0.7 \pm 0.7$  min/h; no morbidity =  $1.6 \pm 0.4$  min/h) or number of episodes (morbidity =  $1.3 \pm 0.8$  episodes/

24 h; no morbidity =  $2.5 \pm 0.5$  episodes/24 h). In the subset of patients with a moderate Eagle risk (one or two risk factors), the positive predictive values were similar (AECG = 19%, DTI = 13%) as were the negative predictive values (AECG = 97%, DTI = 96%). In a multivariate model, preoperative testing remained the only independent predictor of risk in this population.

A similar incidence of cardiac events (16 of 172 patients or 9%) was observed in the total cohort of 172 surgical patients who underwent DTI. No patient who underwent coronary revascularization before noncardiac surgery sustained a perioperative event. When the test was evaluated in the entire surgical cohort and stratified into weakly and strongly positive scans, the likelihood ratio of a negative test was 0.58, a weak positive was 1.0, and a strong positive was 3.5.

#### Long-term Survival

Follow-up was  $16 \pm 9$  months and complete in 108 of 109 (99%) patients. There were 8 (7%) cardiac deaths (1 perioperative and 7 after discharge from the hospital) and 15 cardiac events (8 cardiac deaths, 4 MI, 2 CABG, 1 unstable angina). Kaplan-Meier survival curves for cardiac death after the perioperative period were separately constructed for the 108 patients according to the preoperative test results (figs. 3 and 4). Cardiovascular event-free survival curves were constructed for the 102 patients who were personally contacted, and event status was verified. There was no difference in survival for patients with positive or negative AECG monitoring. Using a simple dichotomous interpretation of DTI, a positive DTI was not a significant predictor of survival. When analyzed separately, fixed defects were not predictive of long-term survival, because all ten patients were alive at follow-up. When DTI results were stratified quantitatively by extent of abnormality, strongly positive thallium imaging was

Table 3. Predictive Value of Preoperative Testing for Perioperative Cardiac Events in the Population That Underwent Both Tests (n = 109) and the Total Population (n = 172)

Test	n	Sensitivity (%)	Specificity (%)	Likelihood Ratio, Positive	Likelihood Ratio, Negative	Positive Predictive Value (%)	Negative Predictive Value (%)
AECG	109	60	81	3.3	0.48	25 (6/24)	95 (81/85)
DTI	109	70	66	2.1	0.45	18 (7/40)	96 (66/69)
DTI, strongly positive	109	40	94	6.7	0.64	40 (4/10)	94 (93/99)
DTI	172	63	65	1.8	0.58	15 (10/65)	94 (101/107)
DTI, strongly positive	172	38	89	3.5	0.70	26 (6/23)	93 (139/149)

Values in parentheses are ratios.



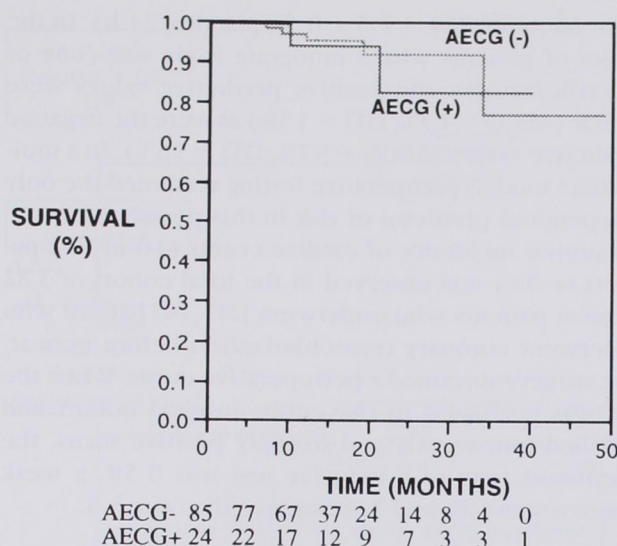


Fig. 3. Long-term survival (cardiac mortality) in 108 patients (99% follow-up) who underwent both tests. The numbers of patients in each group at 5-month intervals are listed below the figure. Preoperative ambulatory electrocardiography monitoring did not differentiate the group with worse long-term survival.  $P = NS$ .

associated with significantly worse cardiac survival and cardiac event-free survival ( $P < 0.01$ ). Negative and weakly positive DTI were associated with a similar survival. When the total group of 172 patients was evaluated, similar findings regarding the predictive value of strongly positive scans were observed (fig. 5). Only one of the eight patients who underwent coronary revascularization before noncardiac surgery (plus had a strongly positive DTI and was in the AECG exclusion group) sustained an event during follow-up, a cardiac death at 13 months in a patient who had a right coronary artery PTCA. Disease in the left anterior descending artery was noted at the time of angiography, but a PTCA of that artery was not attempted.

## Discussion

This study shows that, in patients who had both DTI and AECG monitoring, both tests stratified short-term outcome (perioperative events) on the basis of the test, although their positive predictive values and likelihood ratios were low (18% and 25%, respectively, and 2.1 and 3.3, respectively). Neither simple analysis of DTI nor AECG was predictive of long-term prognosis. However, in our total population of noncardiac surgery patients, quantification of DTI and identification of a

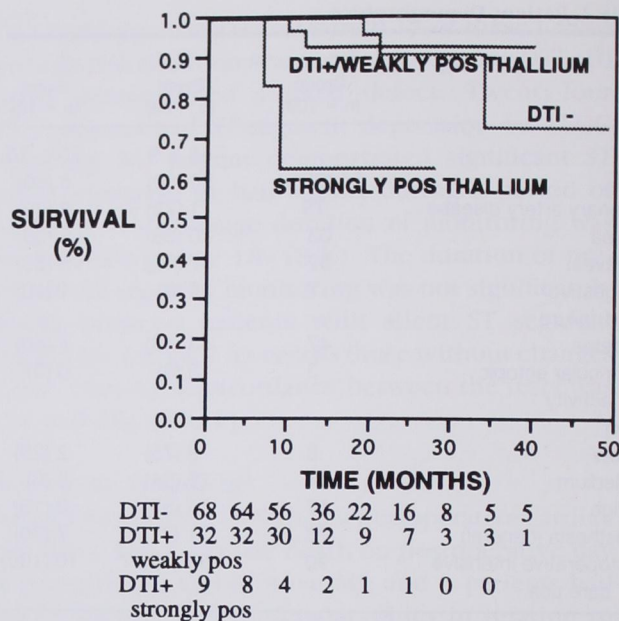


Fig. 4. Long-term survival (cardiac mortality) in 108 patients (99% follow-up) who underwent both tests. The numbers of patients in each group at 5-month intervals are listed below the figure. A strongly positive (pos) thallium scan differentiated the group with worse long-term survival.  $P < 0.01$ .

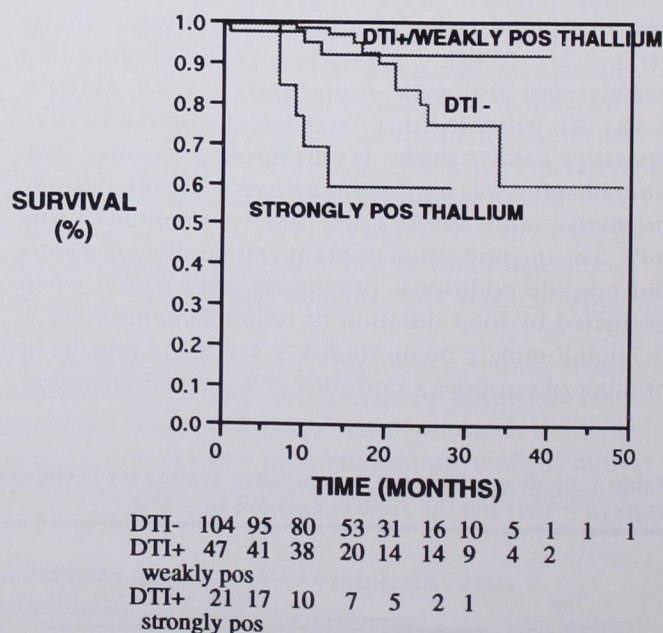


Fig. 5. Long-term cardiovascular event-free survival (morbidity and mortality) for the total population of patients who were referred to dipyridamole thallium imaging and underwent surgery (follow-up,  $n = 160$ ). The numbers of patients in each group at 5-month intervals are listed below the figure. A strongly positive (pos) thallium scan was associated with a significantly worse outcome.  $P < 0.01$ .



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**Table 4. Sensitivity, Specificity, and Likelihood Ratios of Dipyridamole Thallium Imaging for Perioperative Cardiac Morbidity in Several Representative Series**

Study	n	Sensitivity (%)	Specificity (%)	Likelihood Ratio, Positive	Likelihood Ratio, Negative	P
Boucher <i>et al.</i>	48	100	80	5	0	0.0001
Cutler and Leppo	101	100	69	3.2	0	0.001
Leppo	89	93	62	2.4	0.11	0.008
Eagle <i>et al.</i>	200	83	66	2.4	0.40	0.0002
Mangano <i>et al.</i>	60	46	66	1.4	0.81	0.43
Baron <i>et al.</i>	457	36	65	1.0	1.0	0.90
Current study						
All positives	172	63	65	1.8	0.58	0.05
Strongly positive		38	89	3.5	0.70	0.01

Values in parentheses are percentages.

strongly positive thallium group had the highest positive predictive value (26%) and likelihood ratio (3.5) for perioperative morbidity and delineated the group with a significantly reduced long-term cardiac survival and event-free survival.

The predictive value of dipyridamole thallium imaging has been questioned. In earlier studies, redistribution of perfusion defects on dipyridamole thallium imaging was predictive of perioperative cardiac morbidity in 30–50% of patients.<sup>8,9,36,37</sup> More recent studies have demonstrated a much lower positive predictive value when defining a positive DTI as the presence of any reversibility. Mangano *et al.* studied 60 consecutive patients undergoing vascular surgery and reported a positive predictive value of 27% for adverse cardiac events.<sup>22</sup> That study was unique in that the results of the DTI were not revealed to the clinical caregivers. In addition, the authors used multiple ischemic measures and adverse outcome assessment, although an accompanying editorial questioned the clinical importance of many of these outcomes.<sup>38</sup> Baron *et al.* studied the largest consecutive population (457) of patients undergoing abdominal aortic surgery and also were unable to demonstrate an association between thallium redistribution and perioperative cardiac morbidity.<sup>21</sup> They reported a positive predictive value of 19%. The current study confirms the lower positive predictive value of DTI in an era of reduced morbidity, particularly when the test is known to the clinical caregivers and may be used *a priori* to modify care. We assume that such perioperative interventions lead to reduced morbidity and therefore result in a lower positive predictive value.

Several authors have reported morbidity in patients with fixed defects.<sup>17,39</sup> Reinjection of thallium suggests that some of these areas of fixed defects may represent severe ischemia and be at the highest risk for myocardial necrosis during the stress of surgery.<sup>40–42</sup> We observed no morbidity in our patients with fixed defects using reinjection imaging protocols.

In determining the efficacy of a diagnostic test, the prevalence of disease and incidence of important outcomes affects the post-test predictive value. Likelihood ratios provide a better estimate of the test's ability to discriminate between outcomes and is less influenced by the prevalence of disease in the study population. A likelihood ratio of a positive test of 1.0 means no discrimination and a ratio greater than 10 is, in general, high. Table 4 outlines the value of DTI in the current and selected previous studies. The simple dichotomous interpretation of the test demonstrated no discriminatory ability in the studies of Mangano *et al.* and Baron *et al.* and low discriminatory ability in the current study.<sup>21,22</sup> In contrast, the current study demonstrates an intermediate likelihood ratio for a strongly positive scan, similar to that reported in the original studies. Using a decision analytic model, perioperative morbidity for major vascular surgery has been shown to vary greatly between institutions, and the potential benefit of preoperative testing and coronary revascularization depends on the local morbidity and mortality of the vascular surgery and coronary interventions.<sup>29</sup> Therefore, our results demonstrating an intermediate likelihood ratio for perioperative morbidity support the contention that DTI cannot determine the decision regarding coronary interventions and risk for patients



with low pretest probabilities but may be useful in patients at moderate to high risk in whom the test would raise the probability above the treatment threshold for coronary interventions.<sup>43</sup>

Although redistribution had predictive value, a "strongly positive thallium scan" identified the group at greatest risk. In the cohort of 172 surgical patients, a weakly positive scan did not modify the pretest probability of disease (likelihood ratio of 1.0), whereas a strongly positive scan had an intermediate likelihood (3.5). This confirms the work of Lette *et al.* and Lane *et al.*, demonstrating the value of quantitative thallium imaging for preoperative risk stratification.<sup>13,15</sup> We chose to use the criteria from the TIMI-IIIb trial for the definition of a strongly positive thallium scan.<sup>33</sup> Stratifying the test in this manner provides better discrimination between high-risk patients and others than do the simple dichotomous definitions originally proposed and used in the studies that question the test's utility.<sup>21,22</sup> Because coronary interventions were performed in 7 of 24 patients with strongly positive DTI, the current study may underestimate the value of the test.

Preoperative ambulatory electrocardiographic monitoring for silent myocardial ischemia has been shown to be predictive of cardiac morbidity by several investigators, but it was not found to be predictive in two other groups.<sup>24-27,44,45</sup> A relatively important limitation of this potentially cost-effective method is the number of patients in whom the AECG could not be evaluated because of baseline electrocardiographic changes, both in the current and previously reported studies.<sup>25</sup> Additionally, AECG monitoring has been reported as a dichotomous result. Attempting to further stratify patients by the number or duration of episodes did not improve the predictive value of AECG in the current study. This further questions the value of this preoperative testing modality in determining which patients should undergo further diagnostic testing and possible coronary revascularization.

In patients who had both tests, dipyridamole thallium imaging and preoperative silent ischemia monitoring by AECG have similar positive and negative predictive values and likelihood ratios. This is in agreement with the findings of McPhail *et al.*<sup>45</sup> However, there was not great concordance between the two tests, with only 50% of the patients who sustained perioperative morbidity having positive results on both tests.

With regard to long-term survival, the two tests had different predictive values. A positive AECG in the current study was not significantly associated with a poorer

long-term survival, in contrast to the findings of Raby *et al.* and Pasternack *et al.*<sup>44,46</sup> Redistribution on DTI was not associated with a significantly worse survival. However, a strongly positive pattern on DTI was associated with a significantly worse long-term survival. The long-term predictive value of redistribution on DTI is similar to Younis *et al.* and Lette *et al.* but differs from Hendel *et al.*, who reported the worse survival in patients who demonstrated fixed defects.<sup>15,20,47</sup> This difference may reflect a classification scheme in which Hendel *et al.* classified patients with redistribution and a fixed defect into the fixed defect group and the fact that some of the fixed defects in the study by Hendel *et al.* represented severe ischemia as opposed to scar, a technical issue that was addressed in the current study by the use of a reinjection or delayed imaging protocol. This work confirms the long-term predictive value of quantitative dipyridamole thallium imaging in the nonsurgical population, in whom a greater number of redistribution defects was associated with a worse long-term survival.<sup>48</sup> Our results did not demonstrate decreased long-term survival in patients with weakly positive DTI. The reason for this low risk is unclear, although it may reflect more intense medical treatment after the vascular surgery procedure.

There are several potential limitations to our current study. First, our study is limited by the inherent selection bias of studying patients who are referred for dipyridamole thallium imaging for clinical management decisions. Therefore, our patients do not represent a consecutive series of patients undergoing vascular surgery but rather a consecutive series of patients in whom the clinical caregivers suspect the test will provide beneficial information. This population most accurately reflects the patients in whom testing is routinely performed and Bayesian analysis suggests that the test would have the greatest diagnostic accuracy. Therefore, our results are most applicable to a similar population and may not be generalizable to all vascular surgery populations. Second, the results of DTI imaging were made available to the clinical caregivers and used to make decisions regarding coronary revascularization and cancellation of the surgical procedure because of high cardiac risk, as described above. If coronary revascularization and cancellation improves results, this bias could result in a lower positive predictive value and likelihood ratio. If patients with normal DTI images were treated as being at lower risk, and less intense perioperative surveillance leads to increased morbidity, then false-negative results on testing would lead to a



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lower negative predictive value and higher likelihood ratio of a negative test. Further research is required to determine whether interventions based on testing, as in the current study, result in changes in outcome. Third, AECG monitoring was performed subsequent to the dipyridamole thallium test. Only the results of the dipyridamole thallium imaging were available to the clinician and used to make perioperative care decisions. This can have a substantial impact on subsequent analysis concerning the utility of a diagnostic test to predict outcomes. In particular, 7 of 24 patients with a strongly positive DTI underwent coronary revascularization procedures and only 3 had preoperative AECG monitoring. Therefore, the value of AECG to identify patients who might benefit from coronary revascularization is unknown. The duration of AECG monitoring also varied slightly, although the average length of monitoring was 22.8 h. Our patients with preoperative ST segment changes had a longer monitoring time, although the difference was small (5.4 h) and not significant. However, monitoring for 48 h may increase the sensitivity and specificity of the test, as has been suggested in the ambulatory population.<sup>49</sup> Our surveillance method for detecting a perioperative MI depended in part on clinical symptoms and 12-lead ECGs, which were routinely performed only on the first 3 postoperative days. Such a strategy has been proposed as achieving the highest sensitivity and specificity by Charlson *et al.*<sup>50</sup> Although it is possible that asymptomatic elevations of CK-MB might have gone undetected, the clinical relevance of small enzyme leaks has been questioned. Yeager *et al.* demonstrated no difference in long-term outcome in patients who had "enzyme-only" perioperative MIs compared with matched control patients who did not sustain a perioperative MI.<sup>51</sup> In contrast, patients who demonstrated symptomatic perioperative MIs had a significantly worse long-term prognosis. Finally, our identification of MIs during long-term follow-up required symptoms that resulted in hospitalization. Although accurate diagnosis was based on hospital or physician records, silent MIs would not be identified. Hence, it is possible that the incidence of long-term events are underestimated.

In conclusion, AECG and DTI demonstrated a similar, although lower than initially reported, ability to stratify risk and predict short-term outcome. Quantitative DTI also had predictive value for long-term prognosis.

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