# Risk stratification of patients after myocardial revascularization by stress Tc-99m tetrofosmin myocardial perfusion tomography

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***Background.*** **The aim of this study was to assess the incremental prognostic value of stress technetium 99m tetrofosmin imaging after myocardial revascularization.**

***Methods and Results.*** **We studied 381 patients (aged 60 ± 10 years, 270 men), 4.5 ± 3.2 years after myocardial revascularization (coronary artery bypass grafting in 201 patients and percutaneous coronary intervention in 180 patients), who underwent exercise or dobutamine stress tetrofosmin single photon emission computed tomography. Events during a mean follow-up period of 3.5 ± 1.4 years were cardiac death in 22 patients, nonfatal myocardial infarction in 11 patients (33 hard cardiac events), and late revascularization in 50 patients. There was no incidence of hard cardiac events in the 100 patients with normal perfusion. Hard cardiac events occurred in 19% of patients with reversible perfusion abnormalities and in 4% of patients without them ($P < .01$). The incidence of hard cardiac events was similar in patients with and without angina before stress testing (17/197 [8.6%] vs 16/184 [8.7%]). In a multivariate analysis model, predictors of cardiac death were stress rate pressure product and abnormal perfusion. Reversible perfusion abnormalities were independently associated with the composite endpoints of cardiac death, nonfatal myocardial infarction, and late revascularization. In an incremental multivariate analysis model, an abnormal scan was additive to clinical data in the prediction of hard cardiac events (model $\chi^2 = 17$ vs 11, $P < .01$).**

***Conclusion.*** **Stress Tc-99m tetrofosmin myocardial perfusion imaging provides independent prognostic information for the prediction of cardiac events after myocardial revascularization. Symptoms are not predictive of outcome, and therefore asymptomatic patients should not be deferred from stress testing. A normal study identifies a very low-risk population in whom no further intervention is required. (J Nucl Cardiol 2003;10:615-22.)**

**Key Words: Prognosis • stress testing • myocardial revascularization • myocardial perfusion imaging • technetium 99m tetrofosmin**

Several studies have shown that coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) result in amelioration of myocardial ischemia and anginal complaints, increase in functional capacity, and improvement of left ventricular function in a certain subset of patients with coronary artery disease.[1-4] However, restenosis, graft occlusion, and progression of native coronary artery disease may jeopardize myocardial perfusion and contribute to increased mortality and morbidity rates after revascularization.[1-3] Myocardial ischemia may occur in these patients without associated symptoms.[5-9] Identification of a noninvasive method that provides accurate risk stratification of these patients may be useful in limiting the use of invasive procedures to the high-risk patients. There is a controversy regarding the indication of stress testing in the asymptomatic population after myocardial revascularization.[9-14] Some studies have demonstrated the prognostic value of stress thallium 201 myocardial perfusion imaging in the prediction of cardiac events after myocardial revascularization.[15-20]

The use of technetium 99m–labeled agents provides the advantages of improved imaging quality, increased consistency of image analysis, and a larger injectable

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This study was supported in part by a publication grant from Amersham Health.

Received for publication April 24, 2003; final revision accepted July 7, 2003.

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1071-3581/2003/$30.00 + 0
doi:10.1016/S1071-3581(03)00651-2

dose because of a shorter half-life compared with Tl-201.[21-24] There are currently scarce data to suggest a role for stress testing with the use of Tc-99m–labeled agents as a prognostic tool in patients with previous myocardial revascularization. The aims of this study were (1) to assess the independent value of stress Tc-99m tetrofosmin myocardial perfusion tomographic imaging for the prediction of cardiac death and late cardiac events in patients with previous CABG or PCI after adjustment for clinical parameters and (2) to study the impact of angina before stress testing on the outcome.

## METHODS

### Patient Selection

The study population consisted of 388 consecutive patients studied with stress Tc-99m tetrofosmin myocardial perfusion imaging after myocardial revascularization in our laboratory between 1995 and 2000. The choice of stress test was based on the ability to exercise. Follow-up was successful in 381 patients (98%). The data of these patients are reported. All patients gave informed consent before the test. The Hospital Ethics Committee of University Hospital, Rotterdam, Netherlands approved the protocol.

### Stress Test Protocol

Exercise stress testing was performed in 186 patients by use of a symptom-limited upright bicycle ergometry test with a stepwise increment of 20 W every minute. Dobutamine-atropine stress testing was performed in 195 patients as described previously.[25] Dobutamine was injected intravenously, first at a dose of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 minutes and increasing by 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 3 minutes up to a maximum dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If the test endpoint was not reached at a dobutamine dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, atropine (up to 1 mg) was given intravenously.

### Tc-99m Tetrofosmin Single Photon Emission Computed Tomography Imaging

For single photon emission computed tomography (SPECT) imaging, an intravenous dose of 370 MBq Tc-99m tetrofosmin (Myoview; Amersham, Buckinghamshire, United Kingdom) was administered approximately 1 minute before the termination of the dobutamine or exercise test.[25,26] For resting studies, 370 MBq tetrofosmin was injected at least 24 hours after the exercise study. Image acquisition was performed with a triple-head gamma camera system (Prism 3000 XP; Picker, Cleveland, Ohio). For each study, 6 oblique (short-axis) slices from the apex to the base and 3 sagittal (vertical long-axis) slices were defined. Each of the 6 short-axis slices was divided into 8 equal segments. The septal part of the 2 basal slices was excluded from analysis because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. Consequently, a total of 47 segments were identified (3 long axis and 44 short axis).[25,26] The interpretation of the scan was performed by visual analysis. A reversible perfusion defect was defined as a perfusion defect on the exercise images that partially or completely resolved at rest in 2 or more contiguous segments or slices in the 47-segment model. A fixed perfusion defect was defined as a perfusion defect on the exercise images in 2 or more contiguous segments or slices that persists on the resting images in the 47-segment model. The presence of a fixed and/or reversible perfusion defect was considered to indicate an abnormal study. To assess the extent of perfusion abnormalities, the left ventricular myocardium was divided into 6 segments: anterior, inferior, septal anterior, septal posterior, posterolateral, and apical.[26]

### Follow-up

Follow-up data collection was performed by contacting the patient's general practitioner and by review of hospital records. Outcome events were overall death, cardiac death, and nonfatal myocardial infarction. Cardiac death was defined as death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac death. Patients who underwent early myocardial revascularization were censored at the time of revascularization. Hard cardiac events were defined as cardiac death and nonfatal myocardial infarction. All cardiac events were defined as hard cardiac events and late myocardial revascularization (>2 months).

### Statistical Analysis

Continuous data were expressed as mean ± SD. The Student *t* test was used to analyze continuous data. Differences between proportions were compared by use of the $\chi^2$ test. Univariate and multivariate Cox proportional hazard regression models (BMDP Statistical Software Inc, Los Angeles, Calif) were used to identify predictors of late cardiac events. Variables were selected in a stepwise forward-selection manner with entry and retention set at a significance level of .05. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. Variables considered for multivariate analysis were those that were significant in the univariate analysis. The incremental value of myocardial perfusion scintigraphy over the clinical variables in the prediction of events was assessed in 2 models, by adding different scintigraphic data to clinical and stress test parameters. The probability of survival was calculated by use of the Kaplan-Meier method, and survival curves were compared by use of the log-rank test. $P < .05$ was considered statistically significant.

## RESULTS

### Clinical Data

The mean age of patients was 60 ± 10 years. There were 270 men (71%). Previous revascularization procedures were CABG in 201 patients and PCI in 180 patients. The mean time between the revascularization

procedures and the stress test was 4.5 ± 3.2 years. Of the patients, 187 (49%) had a history of previous myocardial infarction and 197 (52%) had anginal complaints before stress testing. Risk factors for coronary artery disease were hypertension in 175 patients (46%), diabetes mellitus in 56 (15%), hypercholesterolemia in 216 (57%), and smoking in 96 (25%). Medications at the day of the study included β-blockers in 142 patients (37%), angiotensin-converting enzyme inhibitors in 135 (35%), and calcium channel blockers in 205 (54%). Revascularization was complete in 343 patients (90%). The mean number of coronary arteries treated with PCI was 1.8 ± 0.8. In patients who underwent CABG, 183 (91%) received internal mammary grafts, and the mean number of grafts was 2.7 ± 1.1.

### Stress Data

The mean heart rate increased significantly with exercise (78 ± 15 beats/min vs 129 ± 23 beats/min) as well as with dobutamine (74 ± 13 beats/min vs 128 ± 17 beats/min). Angina occurred in 138 patients (36%), and ST-segment depression occurred in 84 patients (22%). The mean achieved workload with exercise was 141 ± 41 W. The mean dobutamine dose was 36 ± 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Atropine was administered in 101 patients (52%).

### SPECT and Follow-up Results

A normal perfusion scan was detected in 100 patients (26%). Myocardial perfusion abnormalities included fixed defects in 159 patients (42%) and reversible defects in 122 (32%). The prevalence of an abnormal scan was higher in patients who underwent dobutamine testing as compared with patients who underwent exercise stress testing (78% vs 69%, $P < .05$). Perfusion abnormalities were detected in 159 patients (79%) with previous CABG and 122 (68%) with previous PCI ($P < .01$).

During a mean follow-up period of 3.5 ± 1.4 years, 40 patients (10%) died. Of those, 22 (55%) died as a result of cardiac causes. Nonfatal myocardial infarction occurred in 11 patients (3%), and 62 (16%) underwent coronary revascularization, which was early (within 60 days of stress testing) in 12 patients and late (>60 days from the stress test) in 50 patients. The incidence of hard cardiac events was similar in patients with and without angina before stress testing (17/197 [8.6%] vs 16/184 [8.7%]). Clinical and perfusion data of patents with and without hard cardiac events during follow-up are shown in Table 1.

In the 197 patients with angina before stress testing, the annual hard cardiac event rate was 0% in the 67 patients with normal perfusion and 3.6% in the 130 patients with abnormal perfusion. In the 184 patients without angina before stress testing, the annual hard cardiac event rate was 0% in the 33 patients with normal perfusion and 3.4% in the 151 patients with abnormal perfusion.

### Predictive Value of Clinical Data and SPECT Results

An abnormal perfusion scan was detected in all patients with subsequent hard cardiac events. Hard cardiac events occurred in 23 of 122 patients (19%) with reversible perfusion abnormalities and in 10 of 259 patients (4%) without them. Univariate and multivariate predictors of cardiac death, hard cardiac events, and all cardiac events are presented in Table 2. An abnormal perfusion scan was independently associated with an increased risk of cardiac death as well as hard cardiac events. In an incremental multivariate analysis model, an abnormal scan was additive to clinical data in the prediction of hard cardiac events (model $\chi^2 = 17$ vs 11, $P < .01$). Reversible perfusion defects were independently predictive of the composite endpoint of all events. Receiver operating characteristic curves identified 2 ischemic segments (in the 6-segment model) as the best cutoff that separated patients with reversible perfusion abnormalities with regard to risk of cardiac events.

Event-free survival curves (hard cardiac events) in patients with normal scan results as compared with patients with abnormal scan results based on the type of previous intervention are shown in Figure 1. Patients with abnormal scan results and previous CABG showed a trend toward a worse outcome as compared with those with abnormal scan results after PCI, but the difference did reach statistical significance. A history of angina before stress testing did not have an impact on outcome in patients with abnormal scan results (Figure 2 shows patients with previous CABG and Figure 3 shows patients with previous PCI). The incidence of hard cardiac events was higher in patients who underwent dobutamine perfusion scanning as compared with patients who underwent exercise scanning (14% vs 4%).

## DISCUSSION

In this study we assessed the independent prognostic value of stress Tc-99m tetrofosmin myocardial SPECT imaging in the prediction of cardiac death and late cardiac events in 381 patients studied at a mean of 4.5 years after myocardial revascularization. Cardiac events during a median follow-up of 3.5 years were cardiac death in 22 patients, nonfatal myocardial infarction in 11

**Table 1.** Clinical, stress testing, scintigraphic, and outcome data in patients with and without hard cardiac events during follow-up

| Parameter | Hard cardiac events | | *P* value |
|---|---|---|---|
| | Yes (33 patients) | No (348 patients) | |
| Age (y) | 62 ± 10 | 59 ± 10 | <.01 |
| Men | 28 (85%) | 242 (70%) | <.05 |
| Previous myocardial infarction | 18 (55%) | 179 (51%) | NS |
| Previous PCI/CABG | 11/22 | 190/158 | <.05 |
| Angina before stress testing | 17 (52%) | 180 (52%) | NS |
| Diabetes mellitus | 10 (30%) | 46 (13%) | <.05 |
| Stress heart rate (beats/min) | 125 ± 23 | 130 ± 19 | <.05 |
| Stress systolic blood pressure (mm Hg) | 155 ± 32 | 165 ± 31 | <.01 |
| Stress rate pressure product | 191,312 ± 4,811 | 22,840 ± 5,994 | <.01 |
| ST-segment depression | 13 (39%) | 71 (20%) | <.05 |
| Scan results | | | <.001 |
| Normal | 0 (0%) | 100 (29%) | |
| Reversible defects | 23 (70%) | 99 (28%) | |
| Fixed defects | 10 (30%) | 149 (43%) | |

*NS,* Not significant.

patients, and late myocardial revascularization in 50 patients. There was no incidence of cardiac death or myocardial infarction in the 100 patients who had a normal perfusion scan. In a Cox multivariate analysis model, an abnormal perfusion scan was independently associated with the increased risk of cardiac death and hard cardiac events. Reversible perfusion abnormalities were independently associated with the risk of composite endpoints of hard events and late revascularization. In an incremental model, perfusion abnormalities were additive to clinical data in predicting hard cardiac events. The incidence of hard cardiac events was similar in patients with and without angina before stress testing.

The adverse outcome associated with an abnormal scan was similar in patients with and without a history of angina. This finding indicates that one cannot rely on symptoms after revascularization to identify high-risk patients. Diabetes mellitus was an independent predictor of cardiac events, consistent with previous studies that showed an association between diabetes mellitus and increased mortality rate after myocardial revascularization.[27] Our study demonstrated that this association was persistent even after adjustment to other clinical and SPECT data.

### Impact of Type of Stress Test and Previous Revascularization Procedure

An abnormal dobutamine perfusion study was associated with worse outcome as compared with an abnormal exercise perfusion study. This may be explained by the association of an inability to exercise with other comorbid conditions.[28] A history of previous CABG was univariately associated with an increased risk of cardiac events. However, this relationship was not evident in the multivariate analysis model. A normal perfusion study was related to an excellent event-free survival irrespective of the type of stress test or the method of previous revascularization. These findings are in line with those of previous studies that showed an excellent outcome after a normal study in a general patient population with known or suspected coronary artery disease.[29,30] Hachamovitch et al[29] reported that multiple clinical factors added incremental prognostic value in patients with a normal myocardial perfusion imaging study, affecting their risk and its temporal pattern, and may alter the appropriate timing of repeat testing, hence establishing the existence of a "warranty" period for normal studies. In our study the low-risk warranty in patients with a normal study was maintained during the mean of 3.4 years after the test.

### Previous Studies After CABG

Miller et al[15] studied 411 patients within 2 years after CABG by exercise Tl-201 scintigraphy. The number of abnormal Tl-201 segments was independently associated with the follow-up endpoints. Nallamothu et al[18] studied 255 patients who underwent coronary an-

**Table 2.** Predictors of cardiac events by Cox models

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| **Parameter** | **RR (95% CI)** | ***P* value** | **RR (95% CI)** | ***P* value** |
| *Cardiac death* | | | | |
| Diabetes mellitus | 3 (1.2-6.7) | .01 | | |
| Stress RPP* | 1.3 (1.1-1.6) | .01 | 1.2 (1.1-1.4) | .01 |
| Abnormal scan | 11 (1.5-77) | .001 | 9.8 (2.2-73) | .005 |
| Reversible defects | 2.3 (1.2-5.5) | .01 | | |
| Fixed defects | 3.4 (1.3-11) | .01 | | |
| *Hard cardiac events* | | | | |
| Male gender | 2.1 (1.1-5.6) | .03 | 2.3 (1.1-5.7) | .02 |
| Diabetes mellitus | 2.9 (1.3-6.5) | .005 | 2.6 (1.2-5.5) | .01 |
| Previous CABG | 1.7 (1.1-4.2) | .03 | | |
| Stress RPP* | 1.21 (1.1-1.4) | .02 | 1.21 (1.1-1.4) | .04 |
| Abnormal scan | 5.9 (1.5-16.5) | .0001 | 4.4 (1.5-15) | .001 |
| *All cardiac events* | | | | |
| Male gender | 2.2 (1.1-4) | .004 | 2 (1.1-3.8) | .01 |
| Diabetes mellitus | 2.8 (1.3-4.5) | .001 | 2 (1.1-3.5) | .01 |
| Previous CABG | 1.5 (1.1-4.1) | .02 | | |
| Referral for dobutamine | 1.8 (1.2-6.5) | .01 | | |
| ST depression | 1.9 (1.1-3.1) | .008 | | |
| Abnormal scan | 2 (1.2-3.2) | .001 | | |
| Reversible defects | 3.1 (1.5-4) | .005 | 2.2 (1.3-3.6) | .001 |

*RR,* Risk ratio; *RPP,* rate pressure product.
*Per 1 unit.

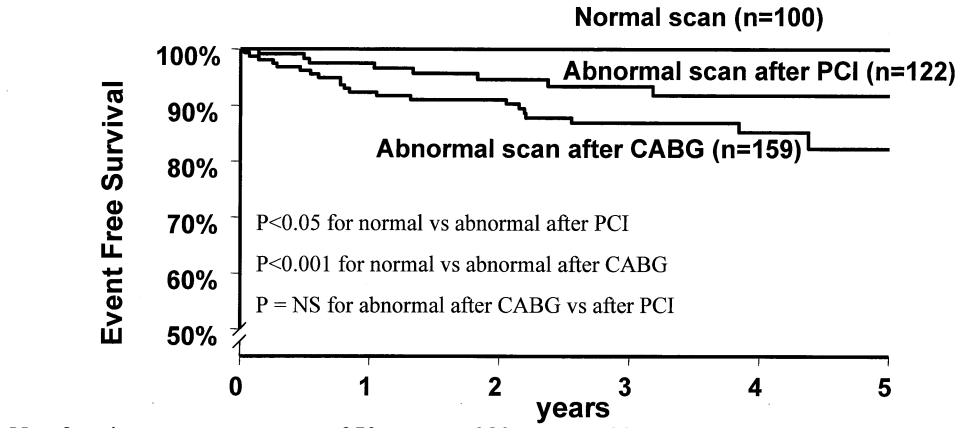
giography and stress Tl-201 at a mean of 5 years after CABG. During a mean follow-up of 41 months, there were 24 cardiac deaths and 10 nonfatal myocardial infarctions. The SPECT variables of multivessel perfusion abnormality, perfusion deficit size, and increased lung thallium uptake were independent predictors of death and total events. Alazraki et al[17] studied 336 patients 1 year after revascularization (CABG or PCI) by stress Tl-201 SPECT. The incidence of composite cardiac events (death, infarction, late myocardial revascularization) was higher in patients with reversible perfusion abnormalities than in those without them (19% vs 6%). Palmas et al[19] studied 294 patients at a minimum of 5 years after CABG with exercise thallium SPECT. There were 20 cardiac deaths and 21 nonfatal myocardial infarctions during a mean follow-up of 31 months. The Tl-201 summed reversibility score and the presence of increased lung uptake of Tl-201 added incremental prognostic information. Zellweger et al[31] studied 1544 patients at a mean of 7.1 years after CABG who underwent dual-isotope SPECT imaging. During follow-up, 53 cardiac deaths occurred. A multivariate analysis identified age, ischemia, and infarct size as independent predictors of cardiac death. The authors concluded that symptomatic patients may benefit from testing at 5 years or less after CABG and all patients may benefit from testing more than 5 years after CABG.

### Previous Studies After PCI

Cottin et al[20] studied 152 patients 5 months after coronary stenting with stress Tl-201 imaging. The relative risk of major cardiac events for patients with significant ischemia was 10.5 compared with nonischemic patients. Ho et al[16] studied 211 patients who underwent exercise Tl-201 1 to 3 years after PCI. Two thirds of the patients were symptomatic. The summed stress score exhibited a significant univariate association ($P = .047$) with the endpoint of cardiac death or myocardial infarction.

### Impact of Symptoms

Current American Heart Association guidelines recommend radionuclide studies only in symptomatic patients.[11] In our study symptoms were not predictive of outcome. Lauer et al[12] studied 873 symptom-free patients with previous CABG with the use of exercise




| | | | | | |
|---|---|---|---|---|---|
| **Nr of patients** | **350** | **283** | **205** | **115** | **55** |
| **Normal scan** | **91** | **74** | **53** | **30** | **14** |
| **Abnormal after PCI** | **112** | **91** | **66** | **37** | **18** |
| **Abnormal after CABG** | **147** | **118** | **86** | **48** | **23** |

**Figure 1.** Kaplan-Meier survival curves (endpoint of cardiac death and nonfatal myocardial infarction) in patients with normal and abnormal stress Tc-99m tetrofosmin SPECT results based on type of previous revascularization.

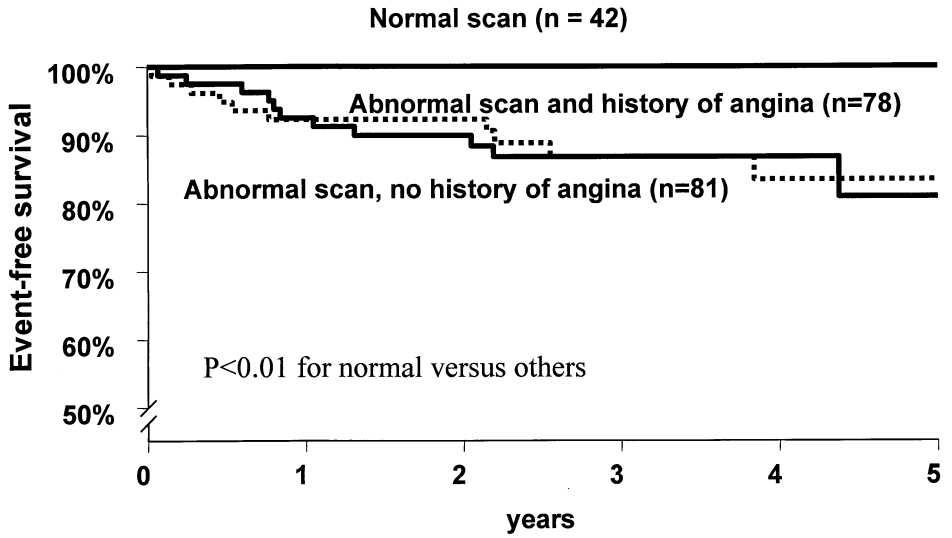



**Figure 2.** Kaplan-Meier survival curves in patients with previous CABG (endpoint of cardiac death and nonfatal myocardial infarction) with normal and abnormal stress Tc-99m tetrofosmin SPECT results based on previous history of angina.

Tl-201 SPECT. During a mean follow-up of 3 years, there were 57 deaths and 72 patients had major events. Tl-201 perfusion defects were predictive of death and major events after adjustment for clinical variables. Acampa et al[32] studied 206 patients with exercise Tc-99m sestamibi SPECT between 12 and 18 months after PCI. During a mean follow-up of 37 months, 24 patients had events. The occurrence of cardiac events was higher in the presence of ischemia at SPECT in symptomatic and symptom-free patients.

## Study Limitations

Referral for stress testing in this study was made according to physician discretion and not per study protocol. Referral bias may have existed by selecting a

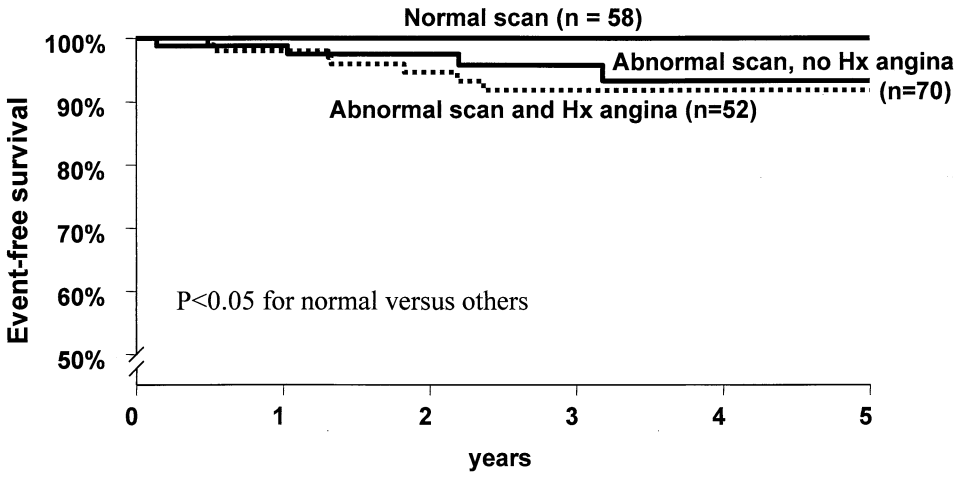



**Figure 3.** Kaplan-Meier survival curves in patients with previous PCI (endpoint of cardiac death and nonfatal myocardial infarction) in patients with normal and abnormal stress Tc-99m tetrofosmin SPECT results based on previous history (*Hx*) of angina.

higher-risk population for stress testing. Therefore it cannot be concluded from this study that SPECT imaging should be routinely performed in all patients after so many years after revascularization. It is possible that the results may have differed if patients without clinical indications for stress testing were included. We used a 47-segment model and not the 17-segment model recommended for image analysis. However, there are no data to suggest that our model is less effective than the 17-segment model in evaluation of coronary artery disease. Finally, the study included patients who underwent two different methods of revascularization with possible differences in clinical approaches to monitoring each group. The study, however, showed an excellent outcome in patients with normal perfusion and an increased risk in patients with perfusion abnormalities regardless of type of revascularization.

## Summary and Conclusion

Stress Tc-99m tetrofosmin myocardial perfusion SPECT imaging provides independent prognostic information for the prediction of cardiac death and major cardiac events after adjustment for clinical data in patients with previous myocardial revascularization. The incidence of cardiac events is similar in patients with and without angina. Therefore the absence of symptoms in these patients should not be interpreted as an indicator of a low-risk status. Stress myocardial perfusion imaging could effectively stratify these patients with regard to their risk of future events, irrespective of symptoms. A normal study identifies a very low-risk population in whom no further testing is required.

## Acknowledgment

*The authors have indicated they have no financial conflicts of interest.*

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