Prediction of 8-year cardiovascular outcomes in patients with systemic arterial hypertension: Value of stress ^{99m}Tc-tetrofosmin myocardial perfusion imaging in a high-risk cohort

Marisa C. G. Tjong Joe Wai, BSc,[a] Machiel J. M. Ottenhof, BSc,[a] Hendrik J. Boiten, BSc,[a] Roelf Valkema, MD, PhD,[b] Ron T. van Domburg, PhD,[a] and Arend F. L. Schinkel, MD, PhD[a]

Objective. **Systemic arterial hypertension is a strong and prevalent cardiovascular risk factor. Currently, information on the very long-term prognostic value of single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in patients with systemic arterial hypertension is lacking. The aim of this study was to assess the value of stress ^{99m}Tc-tetrofosmin MPI for the prediction of very long-term outcome in these patients.**

Methods. **The study population consisted of 608 patients with systemic arterial hypertension who underwent exercise or dobutamine stress ^{99m}Tc-tetrofosmin MPI for the assessment of known or suspected coronary artery disease. Follow-up was successful in 600 (99%) patients. The endpoints were all-cause mortality, cardiac death, nonfatal infarction, and coronary revascularization. Kaplan-Meier survival cures were constructed and univariate and multivariate analyses were performed to identify predictors of very long-term outcome.**

Results. **The mean age of the patients was 59 ± 10 years, and 65% of them were male. MPI findings were normal in 301 patients (50%). Myocardial perfusion abnormalities were fixed in 162 (27%) and reversible in 137 (23%) patients. During a median 8.1-year follow-up, 241 (40%) patients died (121 cardiac deaths), 52 (9%) had a nonfatal myocardial infarction, and 128 (21%) underwent coronary revascularization. Survival curves in patients with a low vs a high summed difference score diverged up to 5 years after the test was performed. Multivariate analyses demonstrated that SPECT MPI provided incremental prognostic information up to 5 years after the test.**

Conclusions. **Stress ^{99m}Tc-tetrofosmin MPI provides incremental prognostic information for the prediction of cardiovascular outcome in patients with systemic arterial hypertension. Patients with normal stress MPI have a significantly better prognosis as compared with those with an abnormal study, up to 5 years after the test is performed. (J Nucl Cardiol 2013; 20:1030–40.)**

Key Words: Coronary artery disease • hypertension • myocardial perfusion imaging • prognosis

From the Department of Cardiology, Thoraxcenter,[a] and Department of Nuclear Medicine,[b] Erasmus Medical Center, Rotterdam, The Netherlands

Received for publication Dec 17, 2012; final revision accepted Sep 17, 2013.

Reprint requests: Arend F. L. Schinkel, MD, PhD, Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Room Ba304, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands; *a.schinkel@erasmusmc.nl.*

1071-3581/$34.00

doi:10.1007/s12350-013-9790-3

INTRODUCTION

Systemic arterial hypertension is a strong and highly prevalent risk factor for coronary artery disease (CAD). The lifetime risk of becoming hypertensive (blood pressure > 140/90 mmHg) exceeds 90% in industrialized countries.[1] About 50% of ischemic heart disease is attributable to systemic arterial hypertension.[2] Risk stratification of patients with systemic arterial hypertension is clinically important to determine the

optimal management strategy. The non-invasive evaluation of patients with systemic arterial hypertension can be challenging. Pre-existent left ventricular hypertrophy and repolarization abnormalities may hinder the diagnosis of CAD and prognostic stratification by exercise electrocardiographic testing. Stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is an accurate technique for the diagnosis of CAD.[3] Several studies have demonstrated that stress SPECT MPI also provides clinically useful prognostic information in patients with systemic arterial hypertension.[4,5] These previous studies had a follow-up period of 2-3.1 years. Currently, information on the very long-term prognostic value of stress MPI in patients with systemic arterial hypertension is lacking. The very long-term prognostic value of stress SPECT MPI in these patients may be impaired because of an increased underlying cardiovascular risk and an accelerated natural progression of CAD. The objective of this study was to assess the role of stress SPECT MPI for risk stratification in patients with systemic arterial hypertension and to determine the value of this test for the assessment of very long-term outcome.

METHODS

Patient Selection

The study population consisted of 608 consecutive patients with systemic arterial hypertension who were referred for exercise or dobutamine stress ^{99m}Tc-tetrofosmin SPECT MPI, for the evaluation of suspected or known CAD, between 1995 and 2000. All patients underwent SPECT because of known or suspected CAD. Reasons for referral for SPECT were typical angina in 219 (36%) patients, atypical angina in 122 (20%), and/or non-specific symptoms in 30 (5%). The remaining 237 (39%) patients had no symptoms. Arterial hypertension was defined as repeated blood pressure measurements of 140/90 mmHg and/or intake of antihypertensive medications. The choice of stress test was based on the ability to exercise. Patients with limited exercise capacity were referred for the dobutamine stress test. Clinical history was acquired and cardiac risk factors were assessed before nuclear testing. Diabetes mellitus was defined as a fasting glucose level $\geq$ 7.8 mmol/L or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol $\geq$ 6.4 mmol/L or treatment with lipid-lowering medication.

Stress Test Protocol

Exercise stress was performed in 270 patients using a symptom-limited upright bicycle ergometry test with a stepwise increment of 20 W every minute.[4] Three electrocardiographic leads were continuously monitored. Cuff blood pressure measurements and 12-lead electrocardiography were recorded at rest and every minute during exercise and recovery. Dobutamine stress protocol dobutamine-atropine stress testing was performed in 327 patients, as described previously.[4] Dobutamine was injected intravenously, first at a dose of 10 μg/kg per minute for 3 minutes, increasing by 10 μg/kg per minute every 3 minutes up to a maximum dose of 40 μg/kg per minute. If the test endpoint was not reached at a dobutamine dose of 40 μg/kg per minute, atropine (up to 1 mg) was given intravenously. Blood pressure, heart rate, and electrocardiography were continuously monitored. The test endpoints were achievement of target heart rate (85% of maximum age-predicted heart rate), horizontal or downsloping ST-segment depression 2 mm at an interval of 80 ms after the J-point compared with baseline, ST-segment elevation >1 mm in patients without previous myocardial infarction, severe angina, systolic blood pressure fall >40 mmHg, blood pressure >240/120 mmHg, or significant cardiac arrhythmia. Metoprolol was available to reverse the (side) effects of dobutamine/atropine if these did not revert spontaneously after termination of dobutamine infusion. Computer averaging of the electrocardiographic complexes was performed by the Schiller system Cardiovit CSG/12. Significant ST-segment depression was defined as a >1-mm horizontal or downsloping ST-segment depression occurring at 80 ms after the J-point.

^{99m}Tc-Tetrofosmin SPECT MPI

An intravenous dose of 370 MBq of ^{99m}Tc-tetrofosmin (Myoview, Amersham, Buckinghamshire, UK) was administered approximately 1 minute before the termination of the stress test. For resting studies, 370 MBq of tetrofosmin was injected at least 24 hours after the exercise study. Image acquisition was performed with a triple-head gamma camera system (Picker Prism 3000 XP; Cleveland, Ohio, USA). The interpretation of the scan was semi-quantitatively performed by visual analysis. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of the patients' clinical data. A reversible perfusion defect was defined as a perfusion defect on the exercise images which partially or completely resolved at rest. A fixed perfusion defect was defined as a perfusion defect on exercise images in two or more contiguous segments or slices, which persists on rest images. An abnormal study was considered in the presence of fixed and/or reversible perfusion defect. The summed stress score (SSS) was calculated by the summation of the scores of the myocardial segments at stress. The SSS was expressed as percent of the total myocardium (% myocardium) by dividing the summed scores by the maximum potential score and multiplying by 100.[6] The SRS is the summed total of each individual segment score obtained during the rest study. The summed difference score (SDS) is the difference between SSS and SRS and indicates the amount of ischemia and the degree of defect reversibility.

Patient Follow-up

Follow-up data were successfully obtained in 600 (99%) patients. Collection of follow-up data was performed by contacting the patient, the patient's general practitioner, civil

Table 1. Patient characteristics and SPECT MPI results

Parameters	Total N = 600	Exercise N = 269	Dobutamine N = 331	*P* value
Age (year)	59 ± 10	57 ± 11	60 ± 10	<.001
Men	389 (65%)	175 (65%)	214 (64%)	.92
Previous myocardial infarction	149 (25%)	61 (23%)	88 (26%)	.27
Previous coronary bypass surgery	93 (16%)	39 (15%)	54 (16%)	.54
Previous percutaneous intervention	117 (20%)	52 (19%)	65 (20%)	.93
Diabetes mellitus	109 (18%)	34 (13%)	75 (23%)	<.05
Hypercholesterolemia	281 (47%)	123 (46%)	158 (47%)	.62
Smoking	120 (20%)	44 (16%)	78 (23%)	<.05
Heart failure	120 (20%)	47 (18%)	73 (22%)	.16
Medication				
Beta-blockers	258 (43%)	121 (45%)	137 (41%)	.38
Diuretics	154 (26%)	48 (18%)	106 (32%)	<.001
ACE-inhibitors	214 (36%)	90 (34%)	124 (38%)	.31
Calcium channel blockers	347 (58%)	147 (55%)	200 (60%)	.15
Nitrate	149 (25%)	63 (23%)	86 (26%)	.47
Digitalis	36 (6%)	12 (5%)	24 (7%)	.15
Resting heart rate	81 ± 18	83 ± 19	79 ± 17	<.05
Stress heart rate	136 ± 20	140 ± 23	133 ± 16	<.001
Resting systolic blood pressure	149 ± 21	147 ± 19	150 ± 23	.07
Stress systolic blood pressure	170 ± 34	185 ± 30	158 ± 31	<.001
Resting diastolic blood pressure	90 ± 13	92 ± 11	88 ± 14	<.001
Stress diastolic blood pressure	88 ± 17	95 ± 14	82 ± 17	<.001
SPECT MPI results				
Normal	301 (50%)	141 (52%)	160 (48%)	.32
Reversible defects	137 (23%)	51 (19%)	86 (26%)	<.05
Fixed defects	162 (27%)	77 (29%)	85 (26%)	.94
Both	93 (16%)	34 (13%)	59 (18%)	.08
SSS	3.52 ± 2.7	3.46 ± 2.79	3.57 ± 2.62	.62
SRS	2.29 ± 2.41	2.35 ± 2.47	2.24 ± 2.36	.62
SDS	1.23 ± 1.23	1.12 ± 1.18	1.33 ± 1.26	.04

registries, and a review of hospital records. Outcome events were overall mortality, cardiac death, nonfatal myocardial infarction, and late (>60 days) coronary revascularization. Overall mortality was ascertained by a review of the civil registry records. A death caused by acute myocardial infarction, significant arrhythmias, or refractory congestive heart failure was defined as cardiac death. Sudden death occurring without another explanation was included as cardiac death. Nonfatal myocardial infarction was defined as new symptoms of ischemia, and/or ECG changes indicative of new ischemia, and/or imaging evidence of myocardial infarction, accompanied by detection of a rise and fall of cardiac biomarkers.[7] Hard cardiac events were defined as the occurrence of cardiac death or nonfatal myocardial infarction. Patients who underwent coronary revascularization (percutaneous coronary intervention or coronary bypass surgery) within 60 days of MPI were excluded from analysis. In these patients, the decision to perform revascularization may be influenced by test results.[8]

Statistical Analysis

Values were expressed as mean value ± standard deviation or number. The Student's *t* test was used to analyze continuous data. Differences between proportions were compared using the Chi-square test. The Diamond and Forrester method was used to calculate the pretest probability of having significant CAD.[9] Univariate and multivariate Cox proportional hazard regression models (SPSS statistical software version 15.0, SPSS, Chicago, IL) were used to identify independent predictors of outcome.[10] Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. The incremental value of SPECT MPI over the clinical variables in the prediction of events was performed according to three models. In Model I, the only SPECT MPI variable entered was the presence of abnormal

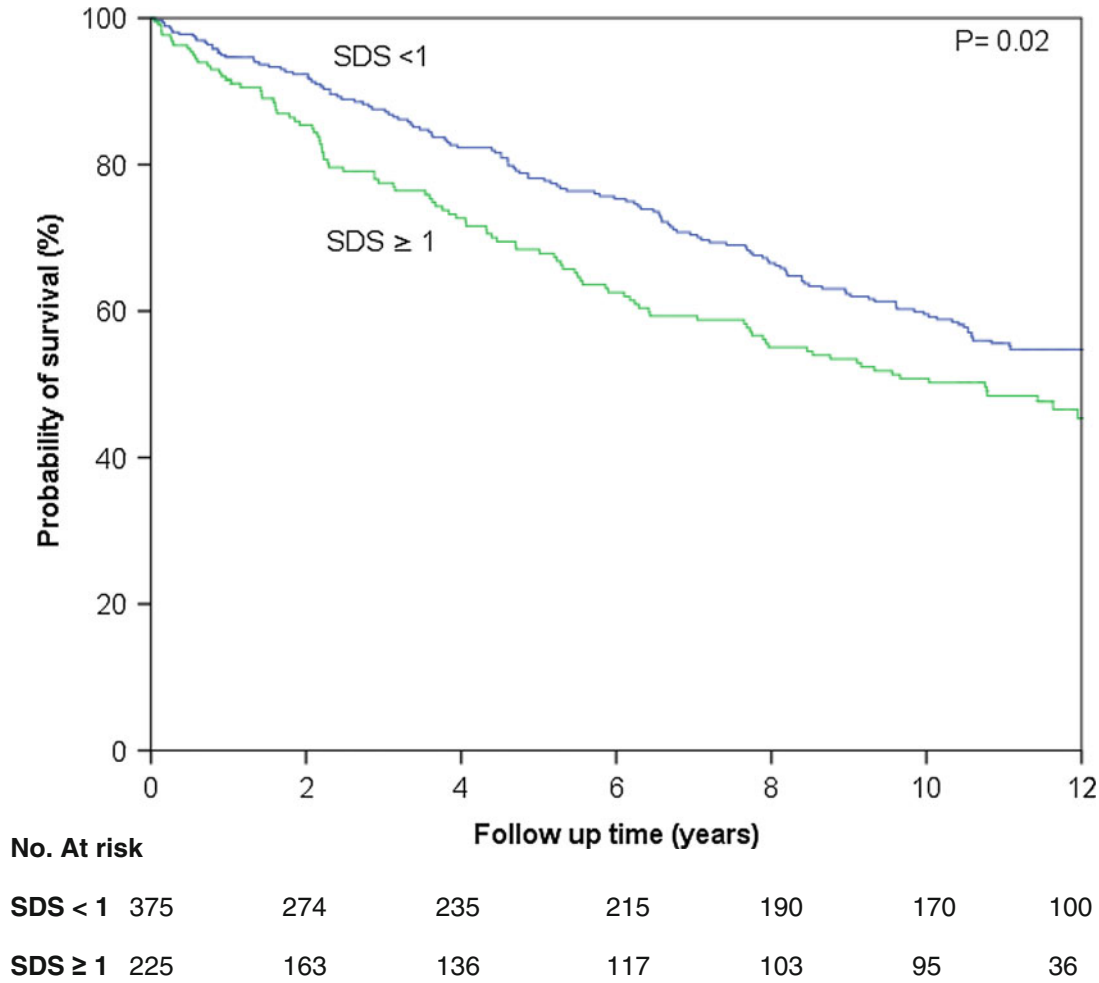


Figure 1. Kaplan-Meier event-free survival for the endpoint of all-cause mortality in patients who underwent stress ^{99m}Tc-tetrofosmin SPECT MPI according to the SDS.

perfusion. In model II, the variable entered was the SDS. To determine the warranty period of SPECT MPI, the multivariate analysis was repeated at 1, 2, 3, and so on years of follow-up. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Receiver operating characteristic (ROC) curves were constructed for each model, and the area under the curve (c-statistic) for each model was assessed. P value $< .05$ was considered statistically significant.

RESULTS

The clinical characteristics of the study population, medication use, and SPECT MPI results are presented in Table 1. The Diamond and Forrester pretest probability of CAD was intermediate in 138 (23%) and high in 163 (27%) patients. Patients in the dobutamine stress MPI group were older, were more likely to have diabetes mellitus, and there were more smokers compared to the exercise group (Table 1). Left ventricular hypertrophy on the ECG was detected in 72 (12%) patients.

Stress Test Results

Patients in the exercise group achieved higher systolic blood pressure, maximal heart rate, and rate-pressure product (Table 1). In the dobutamine group, there more often was a sign of ST-depression than in the exercise group. Diastolic blood pressure decreased significantly with dobutamine stress and showed a modest increase with exercise stress. The target heart rate was achieved in 410 (68%) patients. Patients who were receiving beta-blockers failed more often to reach the target heart rate than patients without beta-blockers [110/256 (43%) vs 74/340 (22%), $P < .05$]. The mean dobutamine dose used was 33 ± 9 μg/kg per minute. Atropine was administered in 129 (39%) patients. Side effects of the dobutamine stress test were short

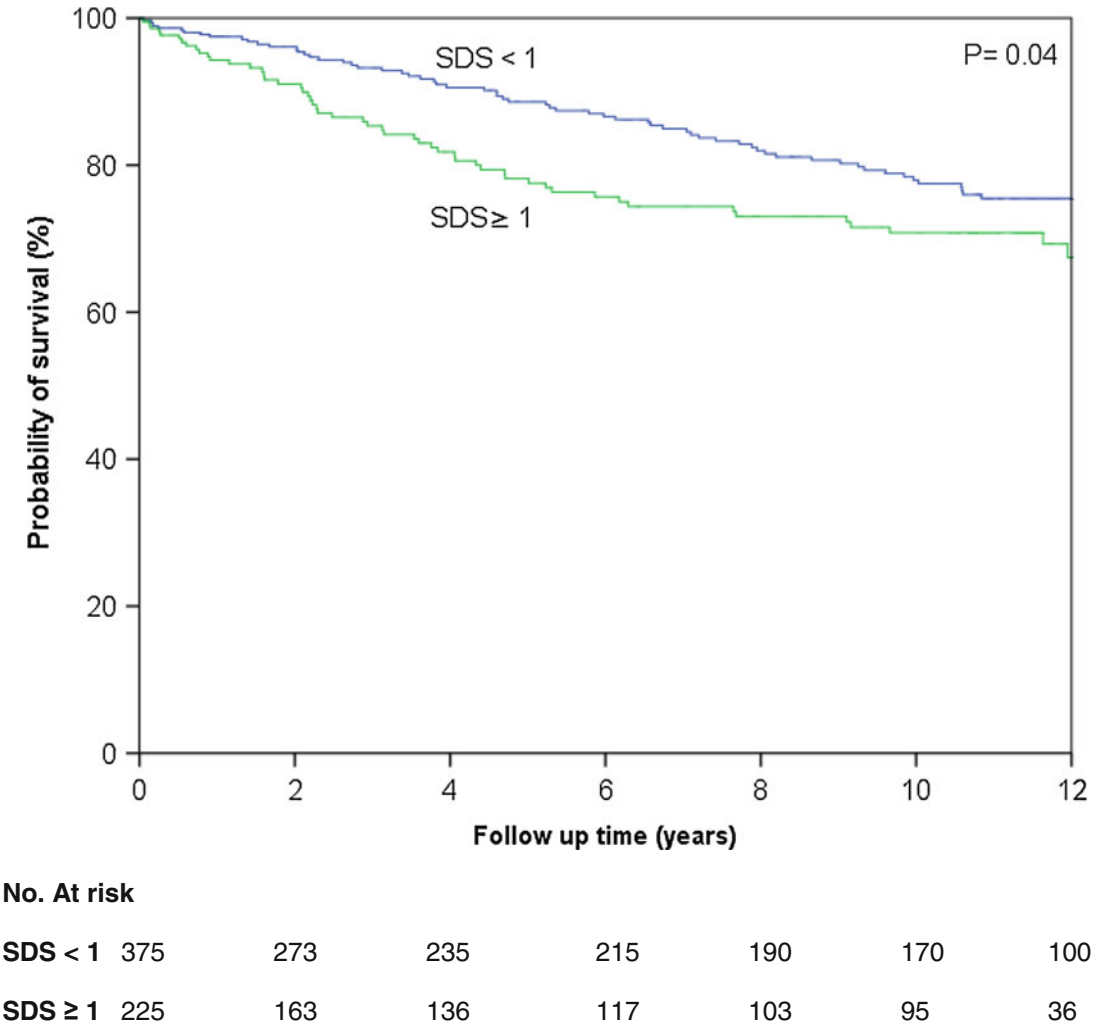


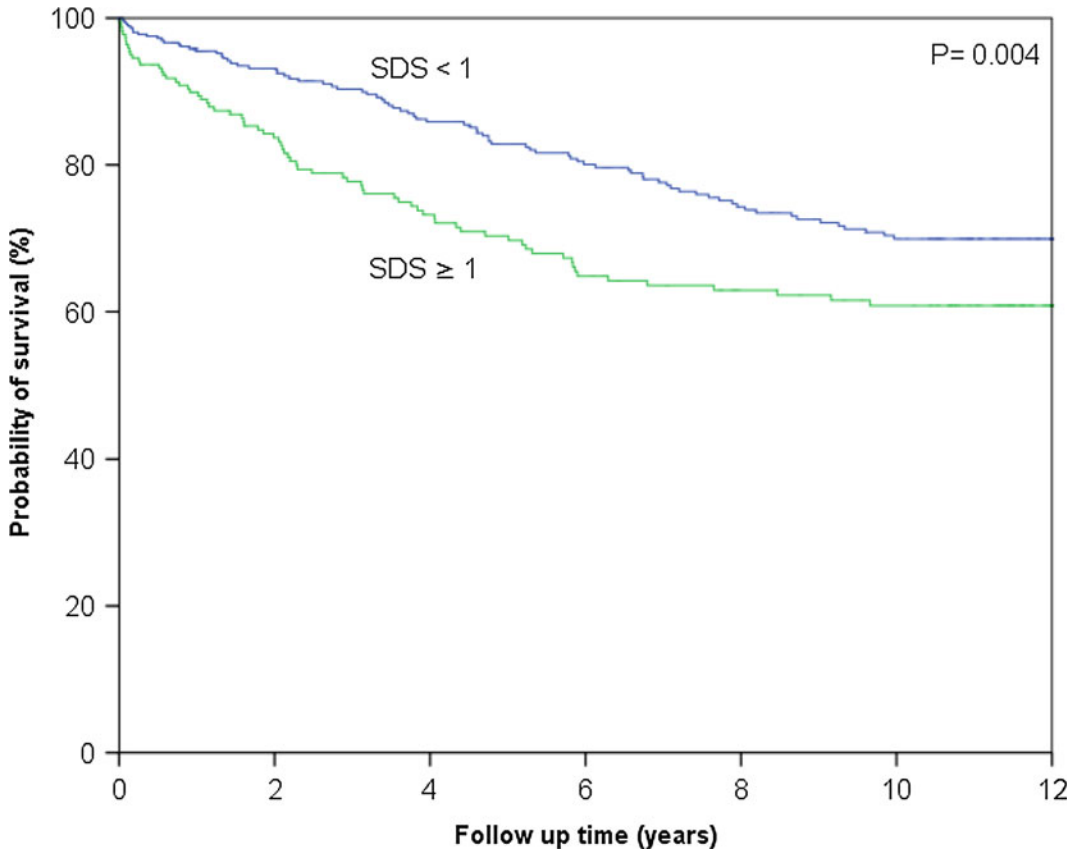
Figure 2. Kaplan-Meier event-free survival for the endpoint of cardiac mortality in patients who underwent stress ^{99m}Tc-tetrofosmin SPECT MPI according to the SDS.

ventricular tachycardia in 7 (1%) patients and transient atrial fibrillation in 8 (1%) patients. No patient experienced a myocardial infarction or ventricular fibrillation. Minor side effects were dizziness in 40 (7%) patients, headache in 18 (3%), and nausea in 12 (2%).

SPECT Results and Outcome

A total of 299 (50%) patients had an abnormal SPECT MPI. Reversible defects were detected in 137 (23%) patients. Fixed defects alone were detected in 162 (27%). Patients who underwent a dobutamine stress test had a higher incidence rate of reversible perfusion abnormalities than patients who performed an exercise stress test. A cutoff value for the SDS was used to distinguish patients with a favorable prognosis and patients with an adverse prognosis: 375 (63%) patients had a SDS < 1 and 225 (37%) patients had a SDS ≥ 1.

Follow-up was successful in 600 patients over a median follow-up period of 8.1 years. During this period, 241 (40%) patients died, of which 121 (50%) patients died because of cardiac causes. There were 52 nonfatal myocardial infarctions. A total of 128 patients underwent coronary revascularization during follow-up. Cumulative survival in the patients with a SDS ≥ 1 was 0.68, 0.51, and 0.45 at the 5-, 10-, and 12-year follow-up, respectively, and 0.78, 0.60, and 0.55 in the patients with a SDS < 1 (Figure 1). The cumulative survival curves showed a lower probability of survival for patients with a SDS ≥ 1 ($P = .02$). During the 12-year follow-up, the annualized all-cause mortality rate was 3.0% in patients with a SDS < 1 and 3.8% in patients with a SDS ≥ 1. The annualized cardiac mortality rate was 1.4% among patients with SDS < 1 and 2.0% among patients with a SDS ≥ 1 (Figure 2). The annualized hard cardiac event rate was 1.8% and 2.7%



No. At risk							
SDS < 1	375	269	228	203	176	157	93
SDS ≥ 1	225	157	127	105	92	85	32

Figure 3. Kaplan-Meier event-free survival for the endpoint of hard cardiac events (cardiac mortality and nonfatal myocardial infarction) in patients who underwent stress ^{99m}Tc-tetrofosmin SPECT MPI according to the SDS.

in patients with SDS $<$ 1 and SDS $\geq$ 1, respectively (Figure 3).

Patients who were able to perform an exercise test had a better prognosis as compared with the patients who underwent a dobutamine stress test in conjunction with SPECT MPI. All-cause mortality was significantly higher in the dobutamine group than in the exercise group (Figure 4). The cardiac mortality rate was higher in the dobutamine group than in the group of patients who underwent the exercise test (Figure 5). There was no difference in the incidence rate of coronary revascularization between the two stress test groups.

Incremental Prognostic Value of SPECT

Multivariate analyses were performed for every year of follow-up after the initial SPECT MPI to determine the warranty period of SPECT MPI. According to the multivariate models, the maximum length of prognostic value of SPECT MPI study was 5 years (Table 2). This is the last moment were the variable abnormal perfusion had significant incremental value for the prediction of all-cause mortality. At a follow-up duration of 5 years, multivariate analysis demonstrated that SPECT MPI parameters failed to predict cardiac mortality (Table 3) and cardiac mortality/nonfatal infarction (Table 4). At a follow-up duration of 5 years, the SPECT results were not predictive of outcome any longer, and age and male gender were the primary determinants of outcome (Tables 2, 3, 4). The ROC curves were constructed for each model. The area under the curve for the model with only clinical variables (0.765) was significantly lower ($P < .001$) than that for model 1 (0.819) and model 2 (0.816). The areas under

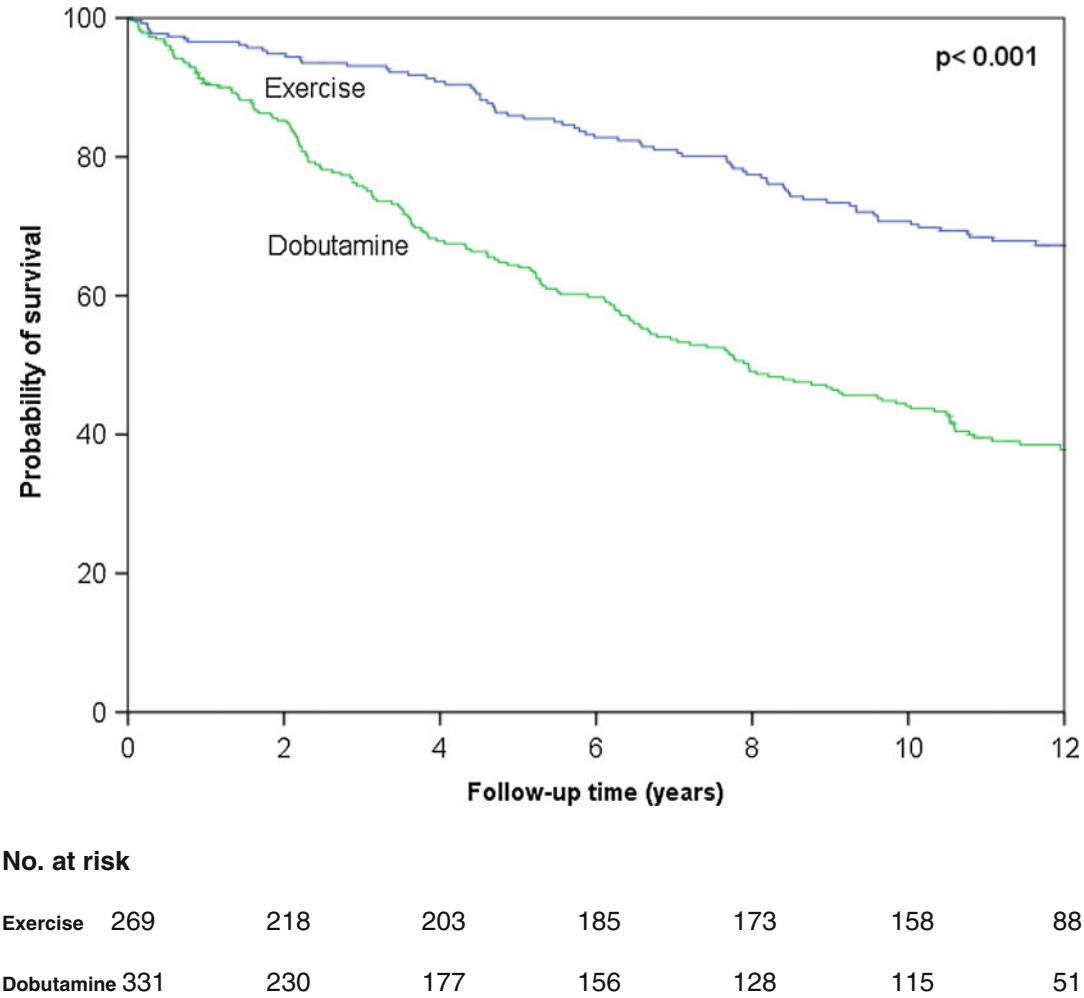


Figure 4. Kaplan-Meier event-free survival for the endpoint of all-cause mortality in patients who performed an exercise test or underwent dobutamine stress testing in conjunction with ^{99m}Tc-tetrofosmin SPECT MPI.

the ROC curve for model 1 and model 2 were not statistically different. The cumulative survival curves (Figures 1, 2, 3) also demonstrate that at 5 years after SPECT MPI, patients with a normal study had a better long-term prognosis than patients with an abnormal SPECT MPI. After that period, the survival curves did not diverge any longer indicating that there was no significant difference in outcome for normal or abnormal SPECT MPI after 5 years of follow-up. There was no interaction between type of stress test (i.e., exercise or pharmacological stress test) and results.

DISCUSSION

The present study shows that stress ^{99m}Tc-tetrofosmin SPECT MPI provides valuable information for prognostic stratification of patients with systemic arterial hypertension and known or suspected CAD, up to 5 years after initial testing. After that period, the risk of adverse outcome increased equally in both patients with a normal and abnormal SPECT MPI study. According to this finding, doctors can rely on the results of the SPECT MPI up to 5 years after the initial study is performed. A few studies have demonstrated the incremental prognostic value of SPECT MPI over clinical variables in the prediction of mortality and cardiac events in patients with systemic arterial hypertension.[4,5] No previous reports have addressed the warranty period of SPECT MPI in these patients.

Previously, Elhendy et al[4] reported the 3.1 ± 1.3-year follow-up of this study population who underwent exercise or dobutamine stress ^{99m}Tc-tetrofosmin MPI in our center. During the follow-up, 109 (18%) patients died, of which 42 (39%) died because of cardiac causes. Independent predictors of cardiac mortality were age, history of myocardial infarction, stress rate-pressure

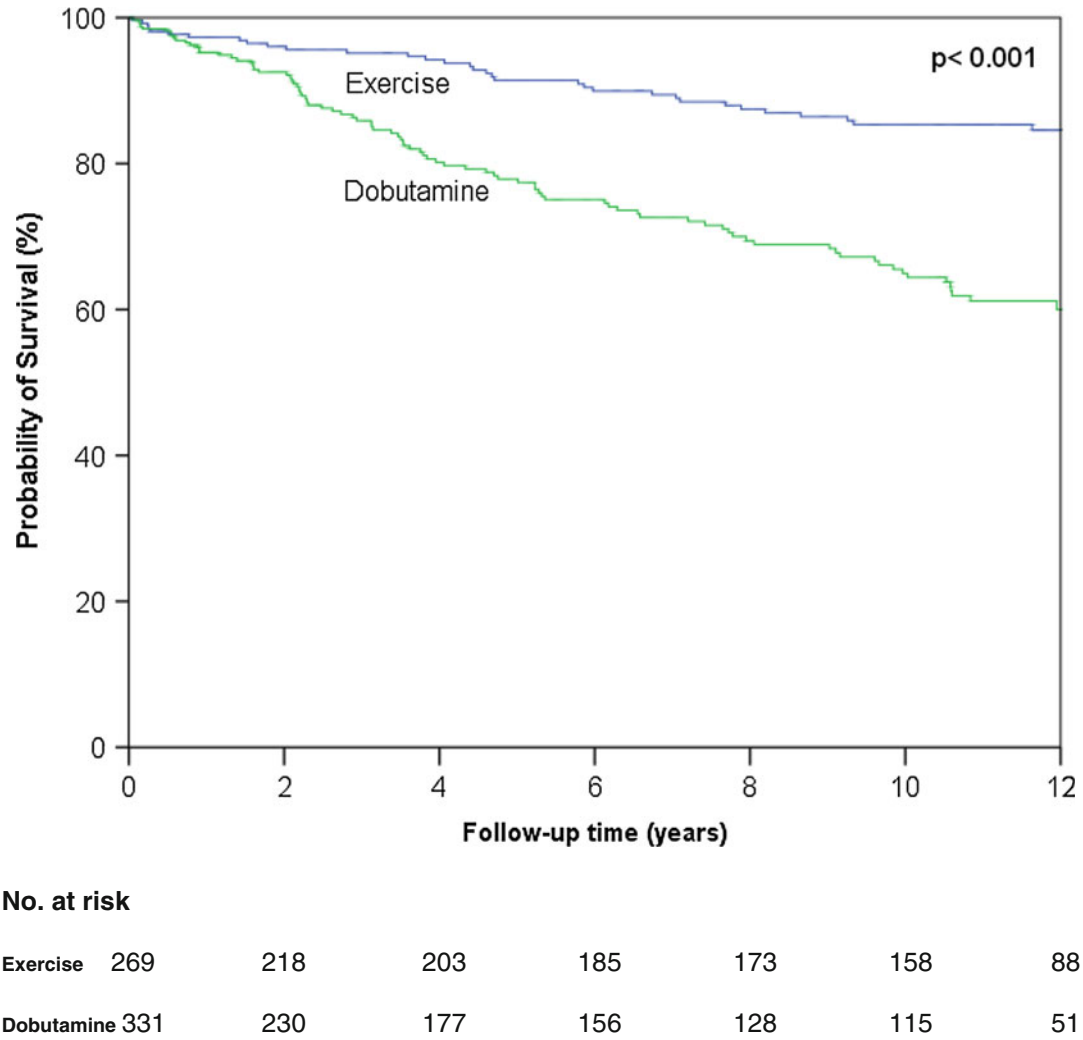


Fig. 5. Kaplan-Meier event-free survival for the endpoint of cardiac mortality in patients who performed an exercise test or underwent dobutamine stress testing in conjunction with ^{99m}Tc-tetrofosmin SPECT MPI.

product, and abnormal perfusion at SPECT MPI. Both fixed and reversible abnormalities were predictive of mortality. SPECT MPI provided prognostic information incremental to clinical data for the prediction of cardiac mortality. Bigi et al[5] studied 415 hypertensive patients who underwent rest and stress (exercise in 278 and dipyridamole in 137) gated ^{99m}Tc-sestamibi SPECT MPI. Follow-up endpoints were death and acute coronary syndrome. During a median follow-up of 24 months, 12 cardiac deaths and 32 acute coronary syndrome cases occurred. The multivariate analysis demonstrated that age, SSS, and peak end-systolic volume were predictors of outcome. The combined assessment of left ventricular perfusion and dimensions significantly improved risk stratification in hypertensive patients. The present study confirms and extends the information from these previous studies. This is the first study that has examined the long-term predictive value of ^{99m}Tc-tetrofosmin SPECT MPI in patients with systemic arterial hypertension. The median follow-up duration in this study was 8.1 years, as compared to 2-3.1 years in the previous studies. Hachamovitch et al[11] demonstrated that a warranty period after SPECT MPI exists. This warranty period is influenced by a temporal component of risk, which may increase the annualized cardiac event rate to 2%, even in the presence of a normal study. The current long-term follow-up revealed that a warranty period of SPECT MPI exists in patients with systemic arterial hypertension. The prognostic value of SPECT MPI was maintained up to 5 years after the date of the initial test. After that 5-year period,

Table 2. Multivariate predictors of all-cause mortality at 5-year follow-up

	Clinical variables	Model I	Model II
Age	1.05 (1.03–1.07)	1.05 (1.03–1.07)	1.05 (1.03–1.07)
Male gender	2.48 (1.64–3.73)	2.13 (1.37–3.31)	2.37 (1.51–3.73)
Previous revascularization	0.65 (0.44–0.97)	0.57 (0.37–3.31)	0.61 (0.39–0.94)
Diabetes mellitus	1.77 (1.21–2.60)	1.34 (0.89–2.00)	1.33 (0.88–2.00)
Smoking	1.75 (1.21–2.53)	1.74 (1.18–2.56)	1.56 (1.04–2.33)
Heart failure	2.54 (1.77–3.66)	1.93 (1.31–2.88)	1.86 (1.23–2.82)
SPECT MPI			
Abnormal perfusion		1.55 (1.05–2.29)	
SDS			1.10 (0.97–1.25)
Chi-square		136	129
P value		.03	.15

Values are expressed as Cox proportional hazard ratio (95% confidence interval). In model I, the only SPECT MPI variable entered was the presence of abnormal perfusion. In model II, the variable entered was the SDS.

Table 3. Multivariate predictors of cardiac mortality at 5-year follow-up

	Clinical variables	Model I	Model II
Age	1.03 (1.01–1.06)	1.03 (1.01–1.06)	1.03 (1.01–1.06)
Male gender	2.65 (1.49–4.73)	2.35 (1.29–4.28)	2.67 (0.92–2.68)
Heart failure	1.78 (1.07–2.95)	1.65 (0.95–2.67)	1.57 (0.95–2.77)
Previous PCI	0.47 (0.22–0.99)	0.44 (0.21–0.94)	0.52 (0.24–1.11)
SPECT MPI			
Abnormal perfusion		1.34 (0.82–2.32)	
SDS			1.90 (0.93–1.25)
Chi-square		75	72
P value		.07	.27

Values are expressed as Cox proportional hazard ratio (95% confidence interval). In model I, the only SPECT MPI variable entered was the presence of abnormal perfusion. In model II, the variable entered was the SDS.

Table 4. Multivariate predictors of cardiac death or nonfatal myocardial infarction at 5-year follow-up

	Clinical variables	Model I	Model II
Age	1.02 (1.01–1.04)	1.02 (1.01–1.04)	1.02 (1.01–1.04)
Male gender	3.05 (2.03–4.57)	2.90 (1.90–4.41)	3.00 (1.97–4.58)
Diabetes mellitus	1.67 (1.13–2.47)	1.67 (1.13–2.47)	1.67 (1.13–2.49)
Heart failure	2.04 (1.42–2.94)	2.01 (1.40–2.90)	1.97 (1.35–2.87)
SPECT MPI			
Abnormal perfusion		1.04 (0.74–1.45)	
SDS			1.03 (0.91–1.18)
Chi-square		96	91
P value		.26	.62

Values are expressed as Cox proportional hazard ratio (95% confidence interval). In model I, the only SPECT MPI variable entered was the presence of abnormal perfusion. In model II, the variable entered was the SDS.

the information obtained from SPECT MPI failed to reliably predict the risk of outcome. Explanations for the loss of prognostic information provided by SPECT MPI after these 5 years are likely the increasing patient age and natural progression of CAD. The event rate in patients with a normal myocardial SPECT study was relatively high. This may be caused by several factors. First, the pretest probability of CAD of the study population was relatively high. Second, the follow-up was successful in a high proportion of the study population. Third, the follow-up duration was substantially longer than in previous studies. The current findings may have consequences for the clinical management of patients with systemic arterial hypertension. More frequent monitoring of patients with systemic arterial hypertension after the 5-year period may be justified. Repeated testing after that period may be considered depending on the patient's symptoms and clinical status. Clearly, the appropriateness criteria for cardiac radionuclide imaging should be used to determine whether repeated SPECT MPI is indicated.[12]

New Knowledge Gained

Stress ^{99m}Tc-tetrofosmin MPI provides prognostic information for the prediction of outcome in patients with systemic arterial hypertension up to 5 years after the test is performed. After that 5 year period the information derived from SPECT MPI fails to reliably predict outcome in this high-risk patient group.

STUDY LIMITATIONS

This study has some limitations. Long-lasting systemic arterial hypertension may cause left ventricular hypertrophy. Lu et al[13] demonstrated that patients with left ventricular hypertrophy may show false-positive SPECT MPI results. Schulman et al[14] showed that hypertension affects the results of thallium-201 exercise stress testing in patients with low, but not in those with a mid to high, likelihood of CAD. Conversely, Grogan et al[15] demonstrated that in patients with low likelihood of CAD, the prevalence and extent of exercise perfusion abnormalities were similar in patients with and without hypertension. Data on left ventricular hypertrophy were not available in all patients; therefore, we could not test whether left ventricular hypertrophy influenced the prediction of the outcome. Data on renal function were not available in all patients; therefore, we were not able to evaluate renal function as a predictor of outcome. In the present study, patients underwent exercise stress or dobutamine stress ^{99m}Tc-tetrofosmin. It is not clear whether the current results apply also to patients undergoing vasodilator stress MPI. At the time of this study, gated SPECT was not routinely performed in our laboratory; therefore, ejection fraction was not available in all patients. Transient ischemic dilation was not evaluated in the present study. Attenuation correction was also not routinely used. Attenuation correction could have improved the quality of the prediction model.[16,17] In this study, coronary angiography was not routinely performed in these patients; therefore, false-positive and false-negative SPECT MPI may have been included in the analysis.

CONCLUSIONS

Stress ^{99m}Tc-tetrofosmin SPECT MPI provides incremental prognostic information for the prediction of cardiovascular outcome in patients with systemic arterial hypertension. The SDS offers incremental information for the prediction of long-term outcome. Patients with normal stress MPI have a significantly better prognosis as compared with those with an abnormal study, up to 5 years after the test is performed.

Disclosures

None.

References

1. Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet 2007;370:591-603.
2. Lawes CM, Vander Hoorn S, Rodgers A, International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. Lancet 2008;371:1513-8.
3. Gargiulo P, Petretta M, Bruzzese D, Cuocolo A, Prastaro M, D'Amore C, et al. Myocardial perfusion scintigraphy and echocardiography for detecting coronary artery disease in hypertensive patients: A meta-analysis. Eur J Nucl Med Mol Imaging 2011; 38:2040-9.
4. Elhendy A, Schinkel AF, Van Domburg RT, Bax JJ, Poldermans D. Prediction of cardiac death in hypertensive patients with suspected or known coronary artery disease by stress technetium-99m tetrofosmin myocardial perfusion imaging. J Hypertens 2003;21: 1945-51.
5. Bigi R, Bestetti A, Strinchini A, Conte A, Gregori D, Brusoni B, et al. Combined assessment of left ventricular perfusion and function by gated single-photon emission computed tomography for the risk stratification of high-risk hypertensive patients. J Hypertens 2006;24:767-73.
6. Boiten HJ, van der Sijde JN, Ruitinga PR, Valkema R, Geleijnse ML, Sijbrands EJ, et al. Long-term prognostic value of exercise technetium-99m tetrofosmin myocardial perfusion single-photon emission computed tomography. J Nucl Cardiol 2012;19:907-13.
7. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173-95.
8. Hachamovitch R, Berman DS, Kiat H, Cohen I, Cabico JA, Friedman J, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: Incremental

prognostic value and use in risk stratification. Circulation 1996; 93:905-14.
9. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300:1350-8.
10. Cox DR. Regression models and life-tables. J R Stat Soc B 1972; 34:187-202.
11. Hachamovitch R, Hayes S, Friedman JD, Cohen I, Shaw LJ, Germano G, et al. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: What is the warranty period of a normal scan? J Am Coll Cardiol 2003;41: 1329-40.
12. Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pellikka PA, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/ SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. Circulation 2009;119:e561-87.
13. Lu C, Lu F, Fragasso G, Dabrowski P, Di Bello V, Chierchia SL, et al. Comparison of exercise electrocardiography, technetium-99m sestamibi single photon emission computed tomography, and dobutamine and dipyridamole echocardiography for detection of coronary artery disease in hypertensive women. Am J Cardiol 2010;105:1254-60.
14. Schulman DS, Francis CK, Black HR, Wackers FJ. Thallium-201 stress imaging in hypertensive patients. Hypertension 1987;10:16-21.
15. Grogan M, Christian TF, Miller TD, Bailey KR, Gibbons RJ. The effect of systemic hypertension on exercise tomographic thallium-201 imaging in the absence of electrocardiographic left ventricular hypertrophy. Am Heart J 1993;126:327-32.
16. Baghdasarian SB, Noble GL, Ahlberg AW, Katten D, Heller GV. Risk stratification with attenuation corrected stress Tc-99m sestamibi SPECT myocardial perfusion imaging in the absence of ECG-gating due to arrhythmias. J Nucl Cardiol 2009;16:533-9.
17. Pazhenkottil AP, Ghadri JR, Nkoulou RN, Wolfrum M, Buechel RR, Küest SM, et al. Improved outcome prediction by SPECT myocardial perfusion imaging after CT attenuation correction. J Nucl Med 2011;52:196-200.