Long-term outcome after cardiac stress imaging

Hendrik Johannes Boiten

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Long-term Outcome after Cardiac Stress Imaging

Lange termijn betekenis van inspanning gerelateerde afbeeldingstechnieken van het hart

Proefschrift

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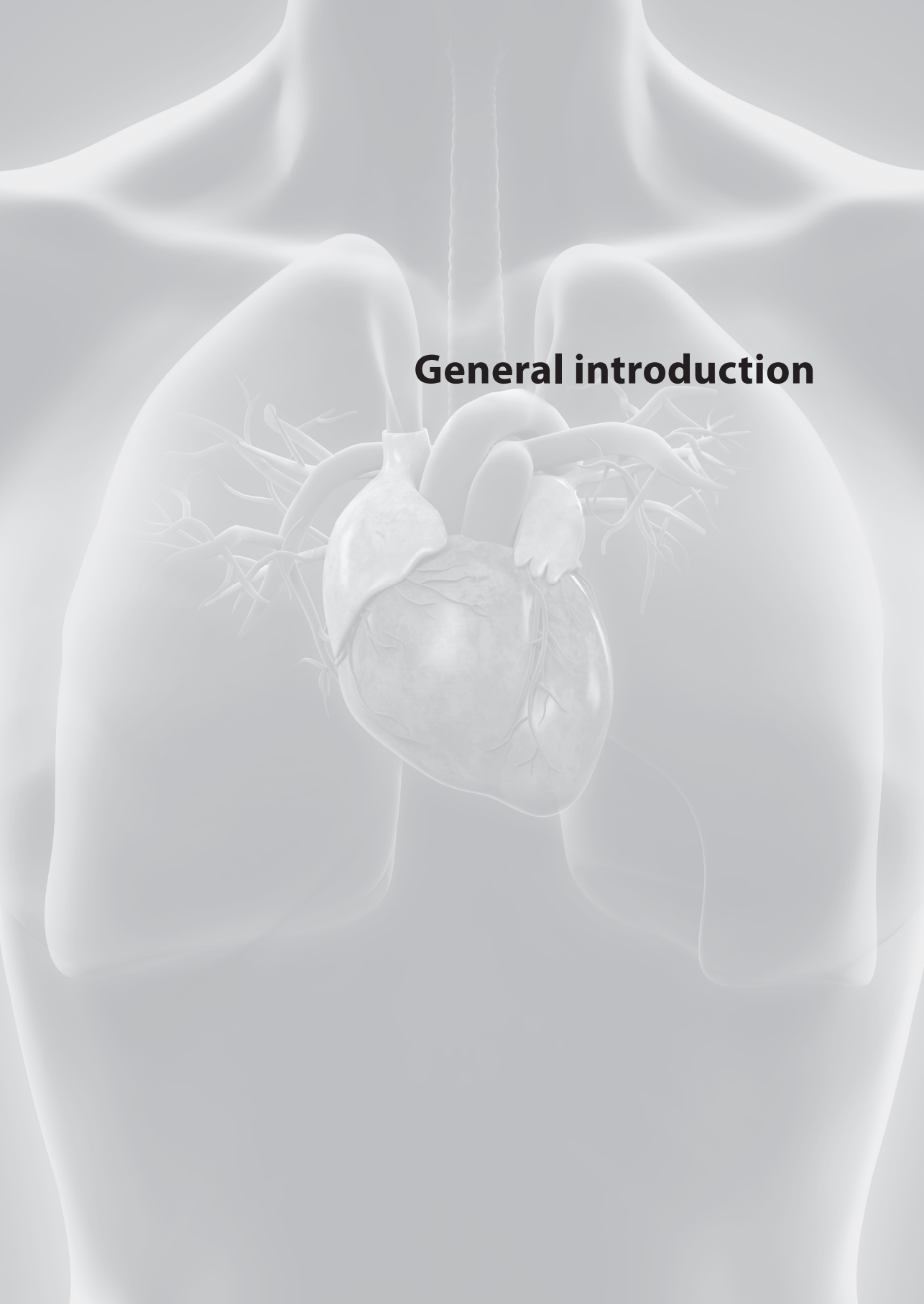
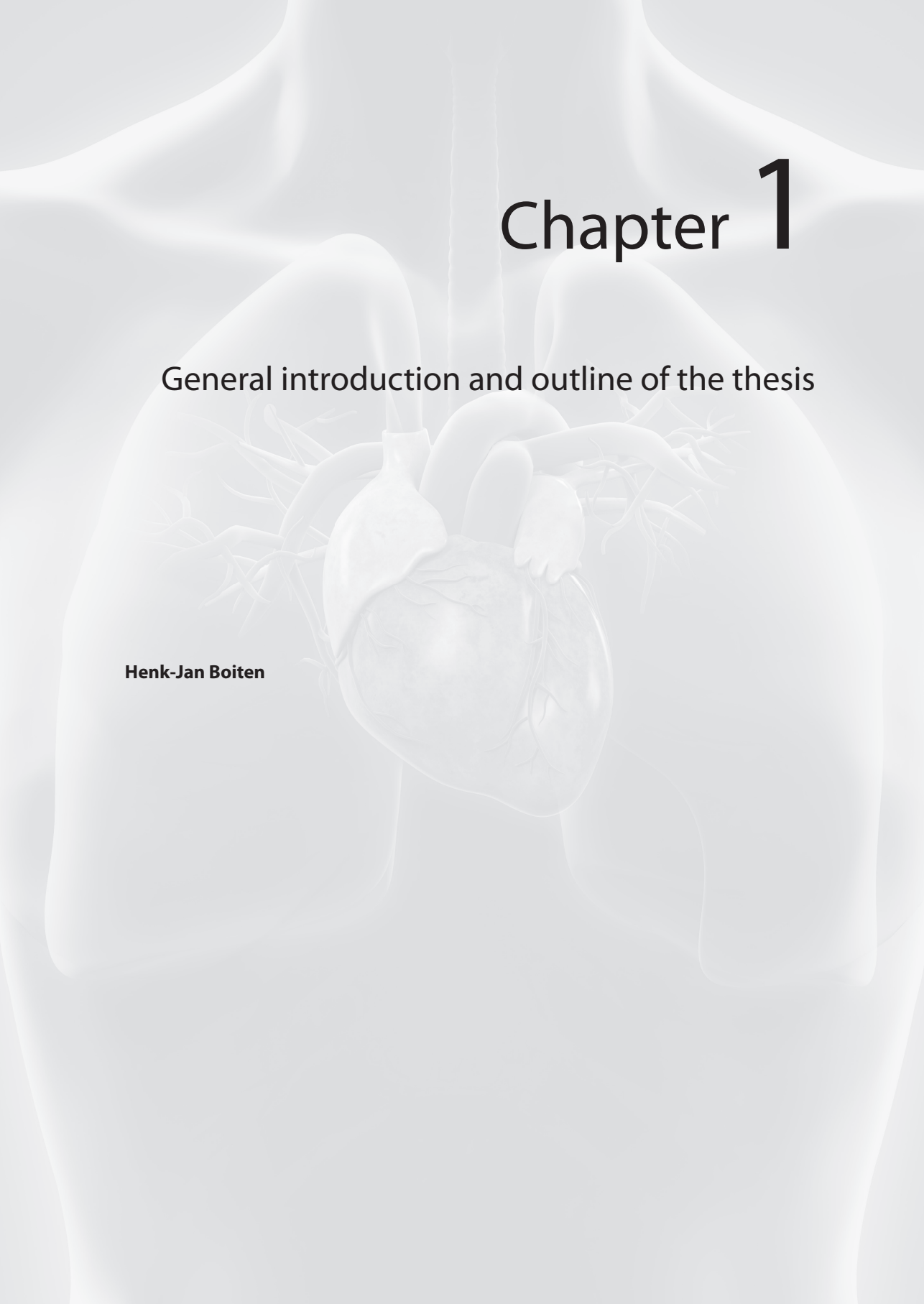


Chapter 1

General introduction and outline of the thesis



Henk-Jan Boiten

Despite major advances in diagnostics and therapy, coronary artery disease (CAD) remains the major cause of mortality worldwide.[1] Due to optimized medical therapy and advanced percutaneous and surgical coronary revascularization procedures, life expectancy of patients with CAD has increased.[2] Coronary heart disease prevalence in the Netherlands in January 2011 was 604.500 habitants (Figure 1). Due to the ageing population, more patients are referred for diagnosis and the assessment of prognosis of CAD. Several invasive and noninvasive modalities are available to detect CAD, including functional imaging (myocardial perfusion imaging [MPI] and stress echocardiography) and anatomical imaging (computed tomography [CT]). The gold standard for detecting significant CAD is invasive coronary angiography. Due to the invasive aspect only patients with a high-pretest likelihood of CAD are referred for this procedure. Noninvasive testing is preferred in patients with a lower pretest likelihood of CAD. Cardiac stress testing is central to the evaluation of patients with known or suspected CAD. The most widely available stress testing modalities combined with imaging are exercise or pharmacologic stress echocardiography and stress radionuclide MPI using single-photon emission computed tomography (SPECT).

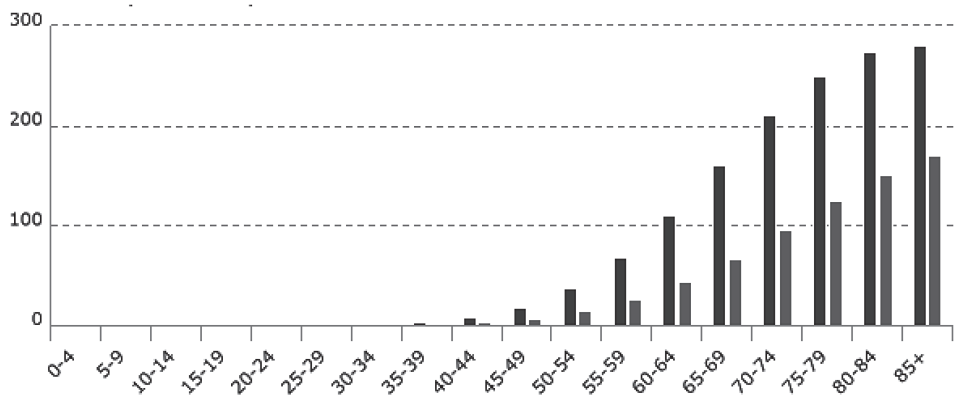


Figure 1. Coronary heart disease prevalence in men (bold) and women (light), per 1000 habitants, in the Netherlands in 2011 according to strata of age (www.volksgezondheidenzorg.info).[3]

From atherosclerosis and myocardial ischemia to imaging

CAD is characterized by atherosclerotic plaques in the coronary arteries. Due to the imbalance between oxygen demand and oxygen supply atherosclerosis can lead to reduced coronary artery blood flow resulting in myocardial ischemia that proceeds from

subclinical to clinical manifestations (Figure 2). After the onset of ischemia there is a temporal sequence of events that occurs, called the 'ischemic cascade'.[4] The earliest abnormality in the ischemic cascade is hypoperfusion, which can be detected by SPECT MPI (Figure 2). This hypoperfusion is then followed by diastolic dysfunction and regional systolic dysfunction. This myocardial dysfunction leads to wall motion abnormalities, which can be evaluated by stress echocardiography. Finally, changes on electrocardiography (ECG) and angina pectoris will occur. Overall, SPECT MPI has a slightly higher sensitivity (84%) as compared to stress echocardiography (80%). Specificity is higher for stress echocardiography (86%) compared to SPECT MPI (77%). These findings are in line with the ischemic cascade (Figure 2), since perfusion abnormalities (detected by SPECT MPI) proceed systolic dysfunction (detected by stress echocardiography).[5]

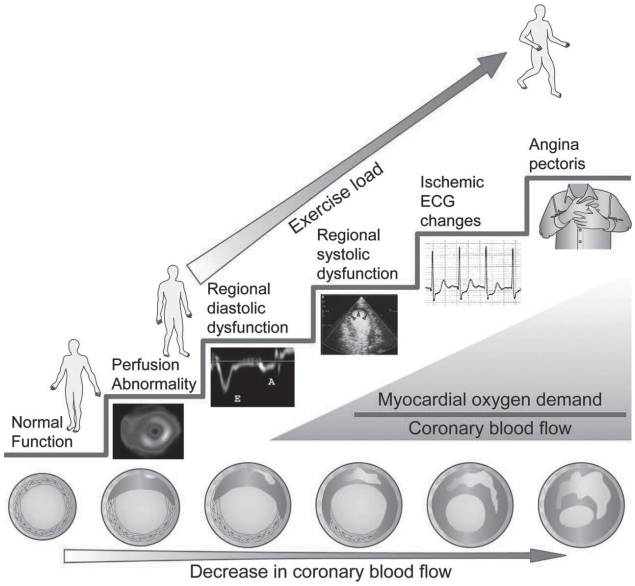


Figure 2. The ischemic cascade. Coronary stenoses will lead to perfusion abnormalities (detected by SPECT), diastolic dysfunction, systolic dysfunction with wall motion abnormalities (detected by echocardiography), ECG changes and angina pectoris (Gaemperli et al.)[6].

Cardiac stress testing

Cardiac stress testing is used to provoke ischemic changes that may not be apparent at rest. Symptom-limited treadmill or bicycle exercise is still the preferred method of stress testing, because it can evaluate the reproducibility of the patient's symptoms.[7] During stress testing, blood pressure, heart rate, and electrocardiographic leads are

continuously monitored, which allows the evaluation of exercise capacity and the blood pressure response during exercise, providing additional diagnostic and prognostic information.[8] However, patients are frequently unable to exercise due to a weak general physical condition or the presence of comorbidities such as neuropathy, peripheral vascular disease or chronic obstructive pulmonary disease (COPD). In these patients, exercise-independent pharmacological stress testing represents an alternative. Importantly, the reported sensitivities and specificities of exercise and pharmacological stress testing are similar.[9] Pharmacological stress is of interest because pharmacological stress is used in half of the myocardial perfusion studies performed in the USA.[10]

Table 1. Exercise versus pharmacologic stress testing (Zoghbi et al. [11])

	Exercise stress	**Pharmacologic stress (major agents)**		
		Dipyridamole	**Adenosine**	**Dobutamine**
Mechanism	Physical exercise (bicycle or treadmill)	Inhibits uptake of adenosine	Activation of A2A-receptors	Activation of α-1, ß-1 and ß-2 receptors
Hemodynamic effects	Increase in HR, CO. Vasoconstriction	Coronary vasodilatation	Coronary vasodilatation	Increase in HR, CO and contractility
Contraindications	Myocarditis 2nd or 3rd degree AV block Acute MI	Obstructive lung disease 2nd or 3rd degree AV block Acute MI	Obstructive lung disease 2nd or 3rd degree AV block Acute MI	ACS Severe aortic stenosis Uncontrolled hypertension

HR = heart rate. CO = cardiac output. MI = myocardial infarction. AV = atrio-ventricular. ACS = acute coronary syndrome.

Table 1 shows the comparisons between exercise stress and some frequently used pharmacologic stress agents.[11] Usually, dipyridamole or adenosine is used in case of pharmacologic stress. In patients who have contraindications to these vasodilators dobutamine is recommended.[12] Dobutamine is a synthetic catecholamine with a half-life of 2 minutes. It has alpha-1 (mild), beta-1 (strong) and beta-2 (mild) agonist activity resulting in an increase of myocardial oxygen demand, thereby mimicking the exercise stress by increasing the blood flow.[13] Previous data showed that increased blood flow (hyperemia) induced by dobutamine stress testing is of equal magnitude to hyperemia induced by vasodilator stress agents.[14]

SPECT MPI

MPI using SPECT is useful in identifying regional abnormalities in coronary artery blood flow. It is able to determine the physiological relevance of this blood flow to cardiac function and myocardial viability (myocardium which does not contract at rest but has the potential to recover). Stress MPI is also useful in detecting myocardial perfusion defects which are not detectable in rest. Advantages of SPECT include assessment of myocardial perfusion and regional function at rest and stress and its widely established prognostic information.[15] The use of MPI requires the intravenous injection of a radioactive blood flow marker (tracer) followed by imaging of regional myocardial uptake in contrast to stress echocardiography.[16,17] Free ^{99m}Technetium, due to diffusion in total body water, is not extracted in the myocardium. So, for ^{99m}Technetium to be indicative of coronary blood flow, it must be coupled to a compound that selectively accumulates in the myocardium. ^{99m}Technetium-labeled sestamibi and tetrofosmin are useful radiopharmaceuticals and provide a lower radiation burden than thallium. These tracers are currently the most frequently used radiotracers for assessing myocardial perfusion.[17]

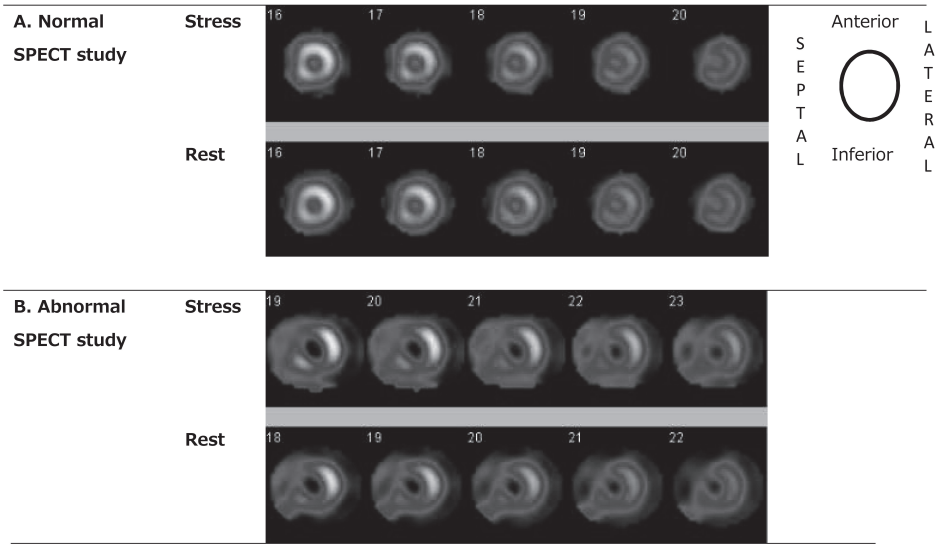


Figure 3. Example of ^{99m}Tc-sestamibi stress-rest SPECT myocardial perfusion imaging.
A. Normal SPECT study. B. Abnormal SPECT study: perfusion defects anterior and septal.

After injection of the radiopharmaceutical, MPI using SPECT is performed. It reveals the distribution of the concerning radioactive tracers, and therefore the relative blood flow

to the different regions of the myocardium. The gamma rays emitted (hence 'emission') by the radiotracers are detected by the gamma camera from the SPECT system. The basis for SPECT imaging is that severe myocardial ischemia or myocardial infarction can destroy cells in a way that they will not take up the radiopharmaceutical (perfusion defect). The presence of a perfusion defect is defined as an abnormal study (Figure 3).

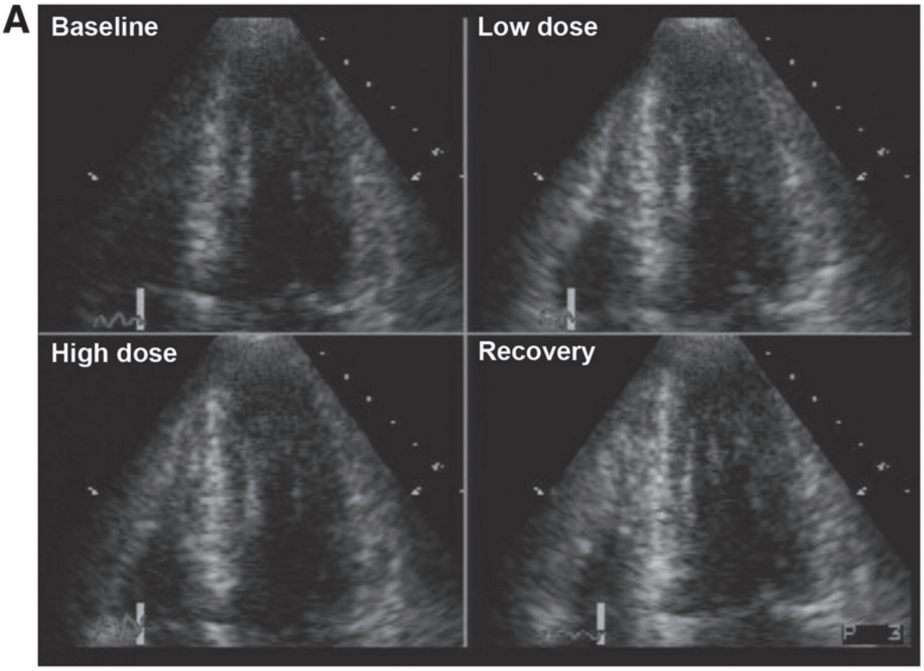


Figure 4A.

Normal dobutamine stress echocardiogram. Normal left ventricle wall motion and thickening at baseline, and further improvement of wall motion and thickening (hyperkinesia) during low- and high-dose dobutamine infusion, and recovery phase.

SPECT MPI interpretation includes the type (reversible, fixed, both), the site, and the extent and severity of the perfusion defect. For the interpretation of a SPECT MPI study a segmental model of the left ventricle is used. Each myocardial segment is assigned a score from 0 to 3 (0 = normal; 1 = slightly reduced; 2 = moderately reduced; and 3 = severely reduced or absent uptake of the radiotracer). Summation of the scores of the myocardial segments generate the summed stress score (SSS) and the summed rest score (SRS). The difference between stress and rest scores is defined as the summed difference score (SDS). This scores provide quantitative information on the extent and severity of a myocardial perfusion defect.

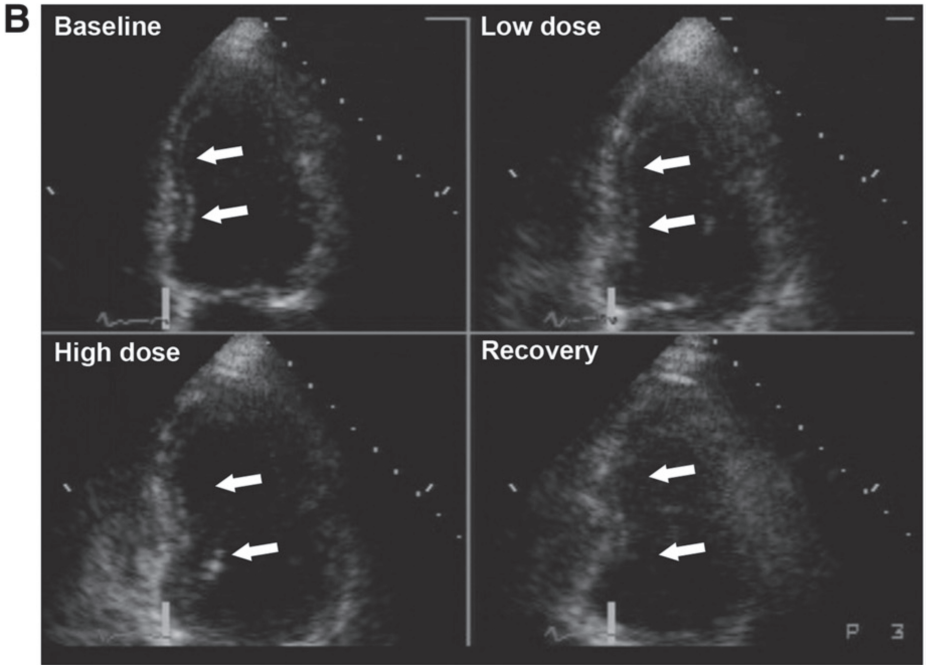


Figure 4B.

Abnormal dobutamine stress echocardiogram The interventricular septum is hypokinetic at baseline, becomes normokinetic during low-dose dobutamine infusion, and becomes akinetic during high-dose dobutamine infusion and during the recovery phase. This biphasic response during DSE is indicative of significant CAD, probably in the left anterior descending artery.

Echocardiographic imaging

Another frequently used noninvasive stress modality in evaluating patients for known or suspected CAD is stress echocardiography. This cardiac stress method consists of two-dimensional imaging of left ventricular wall motion and thickening using dobutamine as a stressor (dobutamine stress echocardiography [DSE]). Advantages of DSE include its availability, relatively low cost and lack of radiation exposure.[15]

Imaging is acquired at rest and continuously during the stress test and the recovery phase. The Wall Motion Score Index (WMSI) can be determined at rest and peak stress as the sum of the segmental scores of the left ventricular segments divided by the total number of segments. Each segment is scored using a 5-point scale as follows: 1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, and 5 = dyskinesis. Ischemia on echocardiography is defined as new or worsened wall motion abnormalities (WMAs) during stress, which is indicated by an increase of wall motion score. Ischemia

was not considered to be present when akinetic segments at rest became dyskinetic during stress. DSE results are defined as abnormal if there was ischemia during stress or fixed WMAs.

Cardiac imaging in Rotterdam

From approximately January 1990, numerous patients underwent cardiac stress imaging at the Thoraxcenter of the Erasmus Medical Center in Rotterdam (Erasmus MC, formerly known as Dijkzigt Ziekenhuis). SPECT MPI or DSE was performed in patients with known or suspected CAD for evaluating various aspects of ischemic heart disease, including diagnosis, risk assessment and stratification, assessment of myocardial viability and evaluation of left ventricular function. Clinical data (i.e. cardiac risk factors) including age, gender, diabetes mellitus, smoking, hypertension, hypercholesterolemia, heart failure, cardiac history (previous myocardial infarction, previous revascularization) and medication use were collected before the stress test. Then, all obtained data, including stress test results and imaging data, were collected in an electronic registry that accumulated in the course of daily clinical care. Patients were then followed during the subsequent years. Follow-up data were obtained by a questionnaire, reviewing hospital records contacting the patient's general practitioner, and/or review of civil registries. Follow-up events were all-cause mortality, cardiac mortality, non-fatal myocardial infarction and/or coronary revascularization. The cause of death was retrieved at Statistics Netherlands (www.cbs.nl). Prior to contacting the patient, the online municipal civil registry was used to determine the patient's present survival status. The collection of all these data (follow-up included) forms the basis of this thesis.

Previous researchers of the Thoraxcenter[18] reported the outcomes of DSE and/or stress SPECT MPI for short- and medium term follow-up. These reports examine data of various patient cohorts (patients with versus without angina pectoris, after coronary revascularization etc.), multiple clinical scenarios (hypertension, obesity, diabetes mellitus, heart transplant patients, assessment of known or suspected CAD, etc.), and different types of stress (exercise or pharmacologic stress) and different types of tracers (sestamibi or tetrofosmin). From a clinical point of view, these studies provides information in risk stratifying patients and optimal clinical management.

Gaps in knowledge about cardiac stress imaging

SPECT MPI and DSE are safe non-invasive imaging techniques to identify and risk stratify patients with known or suspected CAD. Both techniques have been implemented in in-

ternational guidelines.[1,7,9] Stress testing is still the most common noninvasive technique to assess patients with known or suspected CAD.[19] In the last decades, stress testing has been used for both detecting CAD and providing prognostic information.[20] Stress testing for the assessment of prognosis is recommended in patients with intermediate or high pretest probability of CAD.[7,17] The prognostic value of SPECT MPI and DSE is well established for the short- and medium term follow-up. SPECT parameters and DSE results have incremental prognostic value to clinical and stress test variables in separating low- and high-risk patients according to risk of mortality and future cardiac events. This information is used to guide further evaluation and therapy. However, over time, patients may develop hemodynamically significant CAD that was not present at time of the stress test. Several studies have examined the 'warranty period' of a normal stress test.[21,22] A warranty period is defined as the duration of time whereby the patient's risk alters significantly from that observed during the early portion of follow-up.[23] Several clinical characteristics may affect the risk of cardiac events over time, including the existence of hypertension, a previous myocardial infarction and the presence of diabetes mellitus. Also the inability to perform an exercise test, a history of CAD, gender, and increasing age are significant predictors of adverse outcome. Moreover, in heart transplant recipients progression of cardiac allograft vasculopathy (CAV) may occur.[24] These patients considered at increased risk of cardiac events may have an accelerated progression of CAD. From a clinical point of view, it is important to determine the warranty period; patients with a normal stress test have a favorable prognosis. Hence, with no changes in symptoms these patients could be spared further (invasive) evaluation. However, no data are available regarding the long-term prognostic value of SPECT MPI and DSE. This creates uncertainties in the clinical management of these patients. For clinicians it is important to know for what time-period they can rely on the results of the stress test.

Aim and outline of the thesis

The primary aim of this thesis was to evaluate the long-term outcome of both SPECT MPI and stress echocardiography, either with exercise stress or pharmacologic stress (dobutamine). As radionuclide tracers ^{99m}Tc-tetrofosmin and ^{99m}Tc-sestamibi were used. All-cause mortality, cardiac mortality, nonfatal MI and/or late coronary revascularization were primary endpoints of interest during long-term follow-up. The large electronic registry (the CLINT system, developed and maintained by Dr. Ron T. van Domburg,)[25] that accumulated in the course of daily clinical care during the last decades was the basis of this thesis.

In **Part A** the long-term prognostic value of a normal cardiac stress test is described. Patients with normal SPECT MPI are considered at low risk of cardiac events. The very long-term outcome after normal exercise stress SPECT MPI is described in **Chapter 2**. Exercise electrocardiography (ECG) is useful in evaluating patients with known or suspected CAD, but exercise ECG may be false negative. Therefore, **Chapter 3** focused on the long-term outcome after exercise stress SPECT MPI in patients with known or suspected CAD while exercise ECG testing was normal.

In **Part B** the long-term outcome after cardiac stress testing is studied in several patients groups considered at increased risk of adverse events. The duration of a low risk status after a normal stress test is unclear. Importantly, during a long follow-up period, several competing risks may affect the warranty period. In **Chapter 4**, the long-term prognostic value of exercise SPECT MPI using ^{99m}Tc-tetrofosmin as a tracer is determined in patients with known or suspected CAD. Pharmacologic stress (like dobutamine) is employed in patients unable to perform exercise testing because of disease complications like diabetes mellitus and obesity. Such patients consitute a high-risk group due to the underlying cardiovascular risk profile. Also, the inability to perform an exercise test is a strong predictor of adverse outcome in itself. In **Chapter 5**, the long-term prognostic value of exercise and dobutamine stress SPECT MPI is evaluated in obese patients. Another specific group of high-risk patients are heart transplant recipients. To date, long-term data of SPECT MPI in heart transplant recipients are lacking. Accordingly, in **Chapter 6** the long-term prognostic value of SPECT MPI in this patient group is evaluated. In patients with limited exercise capacity due to disease complications such as stroke, neuropathy, or peripheral vascular disease, dobutamine stress testing represents an achievable alternative to vasodilator stress (like adenosine). The prognostic value of dobutamine stress ^{99m}Tc-sestamibi SPECT in patients with limited exercise capacity is studied in **Chapter 7**. In addition, elderly patients have a high cardiovascular risk status. The long-term value of noninvasive imaging modalities for prognostic stratification is also important in these patients, especially due to the ageing population. As a consequence, in **Chapter 8**, the long-term cardiovascular outcomes of dobutamine stress SPECT MPI is studied in elderly patients (defined as ≥65 years).

The surface ECG is probably the most commonly used test in cardiology, it is simple, low-cost, and widely available. QRS duration as assessed on the surface ECG has prognostic value in several patients groups, for example in patients with heart failure and left ventricular systolic dysfunction.[26,27] In **Chapter 9**, the long-term prognostic value of QRS duration in patients undergoing dobutamine stress SPECT MPI is discussed. Then, the long-term prognostic value of dobutamine stress SPECT MPI (**Chapter 10**) and DSE

(**Chapter 11**) is described in patients with diabetes mellitus unable to perform an exercise test. Currently, it is not known whether the prognostic value of DSE is preserved at long-term outcome in high-risk patients. Accordingly, the long-term outcome of DSE in high-risk patients unable to perform exercise testing, is assessed in **Chapter 12**. In **Chapter 13** the fourteen year outcome after stress SPECT MPI compared to DSE is studied.

In patients presenting with an ACS coronary revascularization reduces the incidence of all-cause mortality and nonfatal MI.[28] Optimal medical therapy, percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) are treatment options in these patients. However, information about the impact of coronary revascularization in patients with stable CAD is controversial. The 'jury is still out' regarding the benefit of revascularization in patients with stable CAD.[29] In **Part C** the impact of early coronary revascularization is studied in patients with myocardial ischemia at DSE and myocardial ischemia at stress SPECT in **Chapter 14** and **15**, respectively.

Finally, in **Part D**, we summarize the main findings and discuss the results described in this thesis in a broader perspective. In addition, future challenges according to SPECT MPI and echocardiography are addressed (**Chapter 16**).

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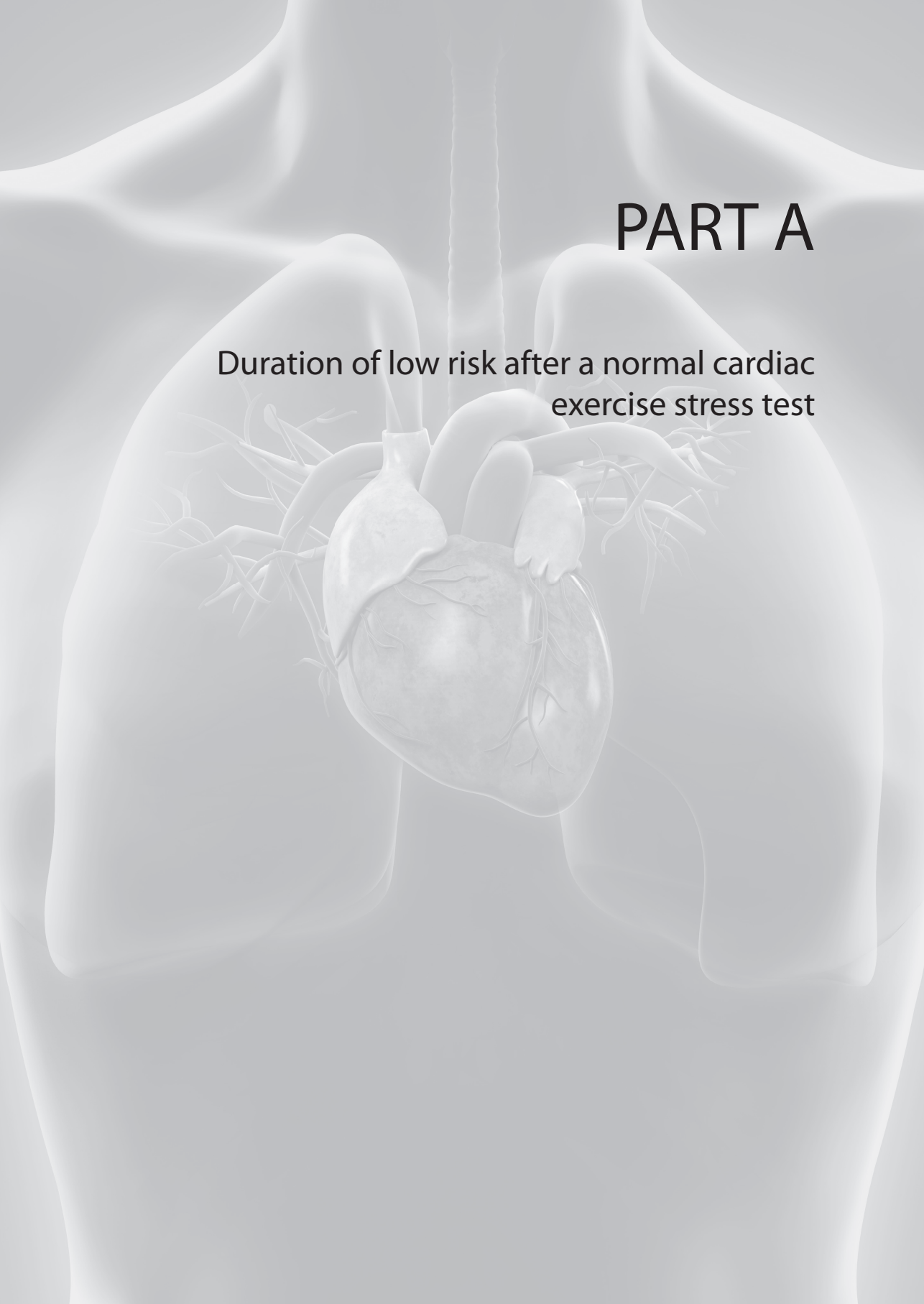
PART A

Duration of low risk after a normal cardiac exercise stress test



Chapter 2

15-year outcome after normal exercise ^{99m}Tc-sestamibi myocardial perfusion imaging: what is the duration of low risk after a normal scan?

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Hendrik J. Boiten
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Journal of Nuclear Cardiology. 2012;19:901–906.

ABSTRACT

Objective. The goal of this study was to evaluate the very long-term outcome after normal exercise ^{99m}Tc-sestamibi myocardial perfusion single-photon emission computed tomography (SPECT). Exercise ^{99m}Tc-sestamibi SPECT is widely used for risk stratification, but data on very long-term outcome after a normal test are scarce.

Methods. A consecutive group of 233 patients (122 men, mean age 54 ± 12 years) with known or suspected coronary artery disease (CAD) underwent exercise ^{99m}Tc-sestamibi SPECT and had normal myocardial perfusion at exercise and at rest. Follow-up endpoints were all-cause mortality, cardiac mortality, nonfatal myocardial infarction, and coronary revascularization. Predictors of outcome were identified by Cox proportional hazard regression models using clinical and exercise testing variables.

Results. During a mean follow-up of 15.5 ± 4.9 years, 41 (18%) patients died, of which 13 were cardiac deaths. A total of 18 (8%) patients had a nonfatal myocardial infarction, and 47 (20%) had coronary revascularization. The annualized event rates for all-cause mortality, cardiac mortality, cardiac mortality/nonfatal infarction, and major adverse cardiac events were, respectively, 1.1%, 0.3%, 0.7%, and 1.8%. Multivariate analysis demonstrated that the variables age, male gender, diabetes, diastolic blood pressure at rest, rate pressure product at rest, peak exercise heart rate, and ST-segment changes were independent predictors of major adverse cardiac events.

Conclusion. Patients with suspected or known CAD and normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT have a favorable 15-year prognosis. Follow-up should be closer in patients with known CAD, and/or having clinical and exercise parameters indicating higher risk status.

Key Words: Coronary disease, prognosis, follow-up studies, radioisotopes.

INTRODUCTION

Exercise ^{99m}Tc-sestamibi myocardial perfusion single-photon emission computed tomography (SPECT) provides clinically useful information for diagnosis and risk stratification of patients with known or suspected coronary artery disease (CAD). Accurate risk stratification of these patients is required to optimize patient management. A recent meta-analysis of the literature demonstrated that normal myocardial perfusion SPECT has a high negative predictive value for cardiac events.[1,2] Patients with normal myocardial perfusion SPECT are considered at low risk of cardiac events, the annualized event rate is generally <1% during the first few years after testing. Accordingly, in these low risk patients, further (invasive) diagnostic and therapeutic strategies and associated medical care costs can be avoided.[1-3]

However, over time, a significant change in risk may occur after a normal myocardial perfusion SPECT. The underlying clinical risk and history of CAD significantly influence the event rate after a normal myocardial perfusion SPECT. Moreover, a temporal component of risk has been identified, which may increase the annualized cardiac event rate to 2%, even in the presence of a normal myocardial perfusion SPECT.[4] These observations have led to the perception that a "warranty period" exists after a normal myocardial perfusion SPECT. In the currently available literature, mean follow-up after myocardial perfusion SPECT was approximately 3 years.[1-3] Data of very long-term outcome after normal myocardial perfusion SPECT are lacking, and consequently, the duration of the low-risk status after a normal test is not clear. This creates uncertainties in patient management recommendations. The goals of the current study were as follows:

1) To assess very long-term outcome after normal myocardial perfusion SPECT.
2) To define a low-risk period after normal myocardial perfusion SPECT.
3) To identify predictors of increased risk.

METHODS

Study Design

The study population consisted of 242 consecutive patients with known or suspected CAD who underwent exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT and had normal myocardial perfusion at exercise and at stress. The majority of the study population has been described in a previous study from our center.[5] The local medical ethics com-

mittee approved the protocol, and all the patients gave informed consent. A structured interview and clinical history were obtained, including assessment of cardiac risk factors, and the symptoms before the exercise test.

Exercise Testing Protocol

All the patients performed a symptom-limited upright bicycle ergometry test with stepwise increment of 20 W every minute. Cuff blood pressure measurement and standard 12-lead surface electrocardiograms were obtained at rest and every minute during exercise, until the end of the recovery phase. The electrocardiograms were digitally stored and analyzed by an experienced observer. Test endpoints included the following: severe angina, decrease in systolic blood pressure fall >40 mm Hg, blood pressure >240/120 mm Hg, or significant cardiac arrhythmia. An ischemic response was defined as ≥1 mm horizontal or downsloping ST-segment depression at 80ms after the J point.

Myocardial Perfusion SPECT

Approximately 1 minute before the termination of the exercise test, an intravenous dose of 370 MBq of ^{99m}Tc-sestamibi was administered as previously described.[5] For resting studies, 370 MBq of the same tracer was administered at least 24 h after the exercise test. Image acquisition was performed using a SPECT camera system (Orbiter camera; Siemens, Iselin, NJ; or Picker Prism 3000XP camera; Picker, Cleveland, OH). Thirty-two projections were obtained, from the left posterior oblique to the right anterior oblique over 180^0. The semiquantitative interpretation of the scan was performed by visual analysis assisted by the circumferential profiles analysis. Stress and rest tomographic views were reviewed side-by-side by two experienced observers who were unaware of the patients' clinical data. In case of disagreement, a majority decision was achieved by a third observer. A normal study was defined as the absence of perfusion abnormalities.

Patient Follow-Up

Follow-up data were collected in the year 2011 and were completed in respect of 233 patients (96%). Outcome data were obtained by evaluation of hospital records, contacting the patient's general practitioner, and/or review of civil registries. The date of the last review or consultation was used to calculate follow-up time. Endpoints were all-cause mortality, cardiac death, nonfatal myocardial infarction, and coronary revascularization.

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.[6] Major adverse cardiac events (MACE) were defined as the occurrence of cardiac death, nonfatal myocardial infarction, or revascularization.

Statistical Analysis

Values were expressed as mean ± SD or number, and compared using the Student's t test or chi-squared test. 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.[7] 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. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. P value <.05 was considered statistically significant.

Table 1. Patient characteristics

Age (years)	54 ± 12
Men	122 (52%)
Height (cm)	170 ± 10
Weight (kg)	74 ± 13
Hypertension	78 (33%)
Smoking	61 (26%)
Hypercholesterolemia	63 (27%)
Diabetes mellitus	16 (7%)
ACE-inhibitor	29 (12%)
Beta-blocker	78 (33%)
Known coronary artery disease	57 (24%)
Prior coronary revascularization	55 (24%)
Prior myocardial infarction	19 (8%)
Typical angina	58 (25%)
Atypical angina	120 (52%)
Nonspecific symptoms	14 (6%)
No symptoms	41 (18%)

RESULTS

Clinical Characteristics

Clinical characteristics of the 233 patients are summarized in Table 1. A total of 222 (95%) patients had an interpretable ECG at baseline. There were no major side effects or complications as result of the test. There was a significant increase in heart rate (78 ± 15 to 147 ± 24 beats/minute, P<.001), and systolic blood pressure (138 ± 22 to 188 ± 25 mm Hg, P<.001) from rest to peak exercise. The mean workload was 143 ± 43 W, corresponding with an exercise duration of 7 minutes. The target heart rate (85% of the maximal predicted heart rate) was reached in 173 patients (74%). Exercise-induced angina occurred in 29 (12%) patients, and 19 (8%) had ST segment depression during the exercise test.

Outcome

Kaplan-Meier survival curves and cumulative event rate are presented in Figures 1, 2, 3, 4, and 5. During a mean follow-up of 15.5 ± 4.9 years, 41 (18%) patients died, of which 13 were cardiac deaths. A total of 18 (8%) patients had a nonfatal myocardial infarction. Coronary revascularization procedures were performed in 47 patients (20%). Seventeen patients (7%) underwent coronary artery bypass surgery, and 30 (13%) underwent percutaneous coronary intervention. The annualized event rates for all-cause mortality, cardiac mortality, cardiac mortality/nonfatal infarction, and major adverse cardiac events were respectively 1.1%, 0.3%, 0.7%, and 1.8%. All-cause mortality was significantly higher in patients with known CAD (Figure 5).

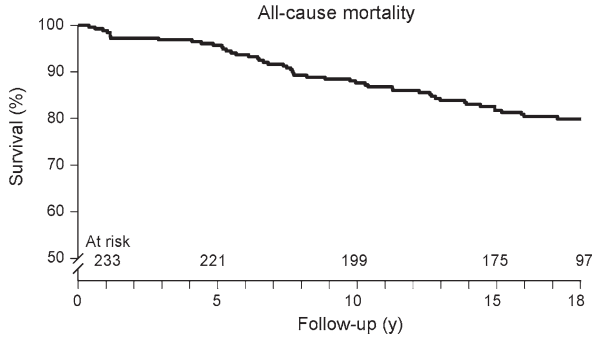

Figure 1. Kaplan-Meier event-free survival for the endpoint of all-cause mortality in patients with normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT.

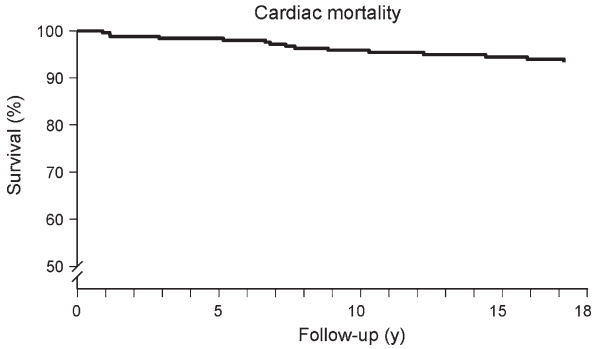

Figure 2. Kaplan-Meier event-free survival for the endpoint of cardiac mortality in patients with normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT.

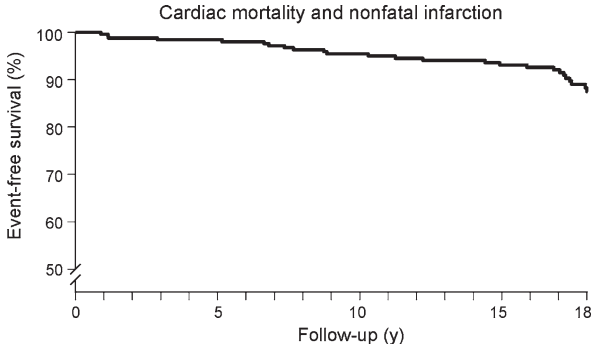

Figure 3. Kaplan-Meier event-free survival for the endpoint of cardiac mortality and nonfatal myocardial infarction in patients with normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT.

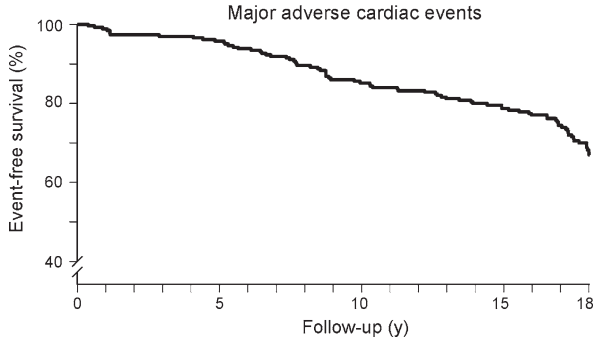

Figure 4. Kaplan-Meier event-free survival for the endpoint of major adverse cardiac events in patients with normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT.

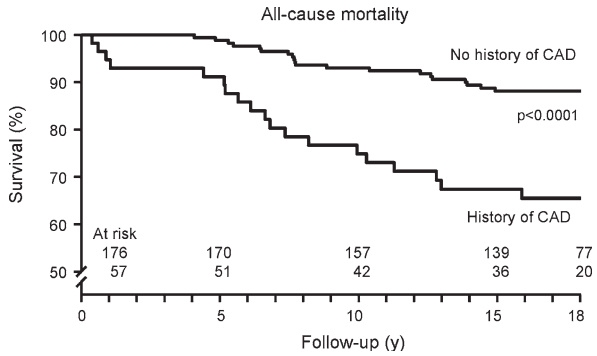

Figure 5. Kaplan-Meier event-free survival for the endpoint of all-cause mortality in patients with normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT, with or without a history of CAD.

Table 2. Univariate predictors of outcome

	All-cause mortality	Cardiac mortality	Cardiac mortality/ nonfatal infarction	Major adverse cardiac events
Clinical features				
Age >70 years	7.46 (2.84–19.51)	2.52 (0.51–12.56)	1.39 (0.38–5.10)	3.59 (1.37–9.38)
Male gender	1.53 (0.77–3.05)	2.53 (0.65–9.78)	1.96 (0.84–4.57)	2.44 (1.41–4.24)
Hypertension	0.79 (0.38–1.65)	0.43 (0.09–2.03)	1.43 (0.63–3.24)	1.43 (0.82–2.49)
Smoking	0.76 (0.34–1.69)	1.06 (0.27–4.13)	0.78 (0.30–2.05)	0.65 (0.34–1.21)
Hypercholesterolemia	0.60 (0.26–1.39)	0.26 (0.03–2.06)	1.16 (0.48–2.79)	1.19 (0.66–2.15)
Diabetes mellitus	3.12 (1.07–9.14)	1.38 (0.17–11.52)	2.81 (0.84–9.44)	2.35 (0.84–6.57)
ACE–inhibitor	1.97 (0.81–4.84)	0.69 (0.09–5.62)	0.53 (0.12–2.37)	1.25 (0.57–2.76)
Beta-blocker	0.91 (0.44–1.87)	1.70 (0.50–5.76)	2.39 (1.06–5.38)	1.62 (0.93–2.83)
Prior myocardial infarction	1.77 (0.60–5.21)	1.13 (0.14–9.37)	2.21 (0.68–7.24)	2.57 (0.99–6.66)
Stress test results				
Heart rate at rest	0.99 (0.89–1.18)	0.92 (0.61–1.40)	0.84 (0.64–1.11)	0.91 (0.79–1.04)
Peak exercise heart rate	0.80 (0.71–0.90)	0.60 (0.46–0.86)	0.72 (0.60–0.86)	0.82 (0.75–0.90)
Diastolic blood pressure rest	0.75 (0.58–0.97)	0.55 (0.31–0.98)	0.70 (0.46–1.05)	0.77 (0.63–0.95)
Rate pressure product at rest	1.03 (0.93–1.14)	0.96 (0.75–1.22)	0.94 (0.80–1.10)	0.97 (0.90–1.05)
Typical angina	0.72 (0.24–2.20)	0.69 (0.09–5.62)	1.26 (0.40–3.94)	2.02 (0.92–4.43)
ST segment changes	0.53 (0.12–2.38)	0.00 (0.00–4.18)	0.89 (0.19–4.08)	1.28 (0.49–3.31)

Values are expressed as Cox proportional hazard ratio and 95% confidence interval

Risk Stratification

Univariate analysis demonstrated that age, diabetes mellitus, diastolic blood pressure at rest, and heart rate during exercise was predictors of all-cause mortality (Table 2). Diastolic blood pressures at rest and peak exercise heart rate were predictors of cardiac mortality. Beta-blocker use, and peak exercise heart rate were predictors of cardiac mor-

tality/nonfatal infarction. Age, male gender, diastolic blood pressure at rest and peak exercise heart rate were predictors of major adverse cardiac events. Multivariate models demonstrated that age, male gender, diabetes, heart rate at rest and peak exercise heart rate were independent predictors of all-cause mortality (Table 3). Heart rate at rest and peak exercise heart rate were predictors of cardiac mortality (Table 4). Male gender, diabetes, and peak exercise heart rate were predictors of cardiac mortality/nonfatal infarction (Table 5). Age, male gender, diabetes, diastolic blood pressure at rest, rate pressure product at rest, peak exercise heart rate, and ST segment changes were independent predictors of major adverse cardiac events (Table 6).

Table 3. Multivariate predictors of all-cause mortality

	HR (95% CI)	*P* value
Age*	1.06 (1.04–1.09)	<.001
Male gender	2.70 (1.45–5.03)	.002
Diabetes	3.06 (1.22–7.65)	.02
Heart rate at rest	1.30 (1.07–1.58)	.01
Peak exercise heart rate	0.80 (0.69–0.92)	.03

Values are expressed as Cox proportional hazard ratio and 95% confidence interval.

* Per 1 unit increment.

Table 4. Multivariate predictors of cardiac mortality

	HR (95% CI)	*P* value
Heart rate at rest	1.73 (1.02–2.94)	.04
Peak exercise heart rate	0.50 (0.35–0.69)	<.001

Values are expressed as Cox proportional hazard ratio and 95% confidence interval.

DISCUSSION

In this study, very long-term outcome after normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT was assessed in respect of 233 patients with known or suspected CAD. The 15.5 ± 4.9-year follow-up demonstrated that the overall outcome of these patients was favorable. Annualized event rates were relatively low during the entire follow-up period. Particularly, in the first 5 years after normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT, annualized event rates were very low. Predictors of increased risk were identified by multivariate analyses of clinical and exercise test data. Clinical predictors

of adverse outcome were age, male gender, and diabetes. Exercise testing variables associated with an increased risk were heart rate at rest, peak exercise heart rate, diastolic blood pressure at rest, rate pressure product at rest, and ST segment changes.

Currently, there are no studies providing very long term outcome data, and consequently the duration of the low-risk status after a normal test is not clear.[1-4] Several previous studies have reported on the medium-term prognosis after a normal myocardial perfusion SPECT. In these previous studies, the number of included patients ranged from 88 to 273, and mean follow-up ranged from 10 months to 7.4 years.[1-3] In the available literature, mean follow-up after myocardial perfusion SPECT was approximately 3 years.[1-3] The previous studies have demonstrated that the medium-term prognosis of patients with suspected or known CAD and normal myocardial perfusion SPECT is favorable. Moreover, several large observational series have studied medium-term prognosis in patients with normal or low-risk thallium-201, ^{99m}Tc-sestamibi, and ^{99m}Tc-tetrofosmin. Meta-analyses of these series revealed that the annualized cardiac mortality rate was approximately 0.5%.[1,2] The Dutch Heart Foundation data[8] indicate that all-cause mortality in men aged 55-64 years, during the period 1986-1998 was (min-max) 2808-3175, and cardiac mortality was 206-422/100.000. In women age 55-64 years, in the period 1985-1996, all-cause mortality was (min-max) 476-771, and cardiac mortality was 64.9-106/100.000. Hence, the event rates in the general population appear to be lower than in the study population. The study patients were referred to exercise myocardial perfusion SPECT by their treating physicians, and the risk profile of the patients was different from that of the general population. In the present study with 15-year follow-up annualized cardiac mortality rate was 0.3% using exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT.

The present study demonstrates that patients with a normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT have a favorable prognosis even at 15-year follow-up. In these patients a watchful waiting approach to care is justified, and additional diagnostic strategies including invasive coronary angiography can be avoided. Previous studies have shown that this type of management strategy may be both clinically effective and cost-effective.[9,10] Clearly, clinical judgment remains important in deciding patient management decisions, also in patients with a normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT. The duration of the low-risk status depends on several factors that influence the natural progression of (subclinical) CAD. The present study demonstrates that several clinical and exercise test parameters can be used to identify patients at increased risk for adverse outcome. Prognosis was worse in patients with a history of CAD. Additionally multivariate analysis demonstrated that several clinical and exercise

testing parameters influence very long-term outcome. Therefore, follow-up should be closer in patients with known CAD, and/or clinical and exercise parameters indicating higher risk status. Repeated testing should be considered in patients with a change in symptoms or worsening clinical status.

Table 5. Multivariate predictors of cardiac mortality/nonfatal myocardial infarction

	HR (95% CI)	*P* value
Male gender	2.61 (1.11–6.14)	<.03
Diabetes	6.93 (2.18–22.04)	<.01
Peak exercise heart rate	0.70 (0.58–0.84)	<.001

Values are expressed as Cox proportional hazard ratio and 95% confidence interval.

Table 6. Multivariate predictors of major adverse cardiac events

	HR (95% CI)	*P* value
Age*	1.03 (1.01-1.06)	<.01
Male gender	2.82 (1.75-4.53)	<.001
Diabetes	3.95 (1.88-8.30)	<.001
Diastolic blood pressure at rest	0.79 (0.64-0.97)	<.03
Rate-pressure product at rest	1.14 (1.04-1.25)	<.01
Peak exercise heart rate	0.80 (0.71-0.89)	<.001
ST segment changes	2.94 (1.44-5.99)	<.01

Values are expressed as Cox proportional hazard ratio and 95% confidence interval.
* Per 1 unit increment.

Study limitations

This study has some limitations. The study population and the number of adverse events were relatively small. Information on changes in medical therapy during follow-up was not available. During the period when the SPECT studies were performed, electrocardiogram gated acquisition was not routinely performed in our laboratory. Gated SPECT provides information on regional and global left ventricular function, which is an important predictor of long-term prognosis. Future studies are needed to clarify the value of gated SPECT for the assessment of very long-term prognosis in patients with normal myocardial perfusion. Finally, in the present study attenuation correction was not applied. Recent data indicate that attenuation correction may further improve diagnostic accuracy of myocardial perfusion SPECT.[11,12]

CONCLUSION

Patients with suspected or known CAD and normal exercise ^{99m}Tc-sestamibi myocardial perfusion SPECT have a favorable 15-year prognosis. Prognosis is particularly favorable during the initial 5 years after testing. Follow-up should be closer after this initial 5-year period and in patients with known CAD, and/or having clinical and exercise parameters indicating higher risk status.

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Chapter 3

Prediction of 9-year cardiovascular outcomes by myocardial perfusion imaging in patients with normal exercise electrocardiographic testing

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ABSTRACT

Aims. Exercise myocardial perfusion imaging (MPI) is widely used, but the long-term prognostic value of this test in patients with normal exercise electrocardiographic testing is not defined.

Methods and results. A consecutive group of 650 patients (428 men, mean age: 56±11 years) with known or suspected coronary artery disease underwent exercise electrocardiographic testing and MPI. Follow-up endpoints were mortality and major adverse cardiac events (MACE). Predictors of outcome were identified by multivariate logistic regression analysis using clinical, exercise electrocardiographic testing and single-photon emission computed tomography (SPECT) variables. A total of 324 (50%) patients had an abnormal SPECT, and 131 (20%) had completely or partially reversible perfusion defects. During a mean follow-up of 9.0±2.0 years, 107 (23%) patients died, 69 (11%) had a non-fatal myocardial infarction, 90 (14%) underwent coronary artery bypass surgery, and 142 (22%) percutaneous coronary intervention. Multivariate analysis demonstrated that the summed rest score was an independent predictor of mortality [hazard ratio (HR): 1.15, 95% confidence interval (CI): (1.08–1.22), P<0.001]. The summed stress score was an independent predictor of MACE [HR: 1.09, 95% CI: (1.04–1.13), P<0.001]. The addition of SPECT variables to clinical and exercise electrocardiographic testing data provided incremental prognostic information for the prediction of mortality and MACE (both P<0.001).

Conclusion. Approximately 20% of patients with known or suspected coronary artery disease and normal exercise electrocardiographic testing have completely or partially reversible myocardial perfusion defects. MPI provides additional information for the prediction of 9-year cardiovascular outcomes in these patients.

INTRODUCTION

Both exercise electrocardiography and exercise myocardial perfusion imaging (MPI) have proved to be clinically useful non-invasive tests for the evaluation of patients with known or suspected coronary artery disease.[1,2] Exercise MPI with single-photon emission computed tomography (SPECT) is a well-validated modality to detect coronary artery disease and provides clinically useful prognostic information.[3-5] Due to basic differences between the two tests, exercise MPI is a more sensitive test for the detection of myocardial ischaemia as compared with exercise electrocardiographic testing.[6] In this context, the impact of MPI on the prediction of long-term outcome in patients with normal exercise electrocardiographic testing has not been evaluated. The aim of this study was to assess the use of exercise MPI for the prediction of long-term cardiovascular outcomes in patients with known or suspected coronary artery disease and normal exercise electrocardiographic testing.

METHODS

Patients

The study population consisted of 650 consecutive patients (428 men, mean age: 56±11 years) referred for exercise myocardial perfusion SPECT for the evaluation of known or suspected coronary artery disease, who demonstrated normal exercise electrocardiographic testing. All patients were referred by their treating physician to exercise stress myocardial perfusion SPECT. The indication for this test was typical angina in 184 (28%) patients, typical angina in 220 (34%), non-specific symptoms in 51 (8%), and risk stratification in 195 (30%). Patients with uninterpretable exercise electrographic testing due to the following resting ECG abnormalities were not included: pre-excitation (Wolff–Parkinson–White) syndrome, electronically paced ventricular rhythm, complete left bundle-branch block, or any intraventicular conduction defect with a QRS duration >120 ms, left ventricular hypertrophy. The local hospital ethics committee approved the study protocol and all patients gave informed consent. A structured interview and clinical history were obtained including the assessment of cardiac risk factors and symptoms.

Exercise protocol

All patients performed a symptom-limited upright bicycle ergometry test with stepwise increment of 20W every minute. Cuff blood pressure measurement and standard 12-lead surface electrocardiograms were obtained at rest and every minute during exercise, until the end of the recovery phase. The electrocardiograms were digitally stored and analysed by an experienced observer. Normal exercise electrocardiographic testing was defined according to the practice guidelines for exercise testing.[1,2] Test endpoints included the following: severe angina, decrease in systolic blood pressure fall >40 mmHg, blood pressure >240/120 mmHg, or significant cardiac arrhythmia. An ischaemic response was defined as ≥1 mm horizontal or downsloping ST-segment depression at 80ms after the J point.

MPI protocol

Approximately 1 min before the termination of the exercise test, an intravenous dose of 370 MBq of technetium-^{99m} (^{99m}Tc)-tetrofosmin (in 477 patients) or ^{99m}Tc-sestamibi (in 173 patients) was administered as previously described.[7] For resting studies, 370 MBq of the same tracer was administered at least 24 h after the exercise test. Image acquisition was performed using a SPECT camera system (Orbiter camera; Siemens, Iselin, NJ, USA; or Picker Prism 3000 × P camera;Picker, Cleveland, OH, USA). Thirty-two projections were obtained over a 180° arc, from left posterior oblique to right anterior oblique, with an acquisition time of 45s per projection. Data were collected in a 64 × 64 matrix (word mode), and images were reconstructed using a filtered back projection algorithm and a ramp reconstruction filter. Transaxial tomograms were reconstructed using the SPETS software package (Nuclear Diagnostics AB, Hägersten, Sweden). From the three-dimensional data, oblique (short axis) and sagittal (vertical long axis), perpendicular and parallel to the long axis, respectively, were reconstructed. The interpretation of the scan was semi-quantitatively performed by visual analysis assisted by circumferential profile analysis. Profile curves of 2.5 standard deviation (SDs) below normal perfusion were considered abnormal. Each of the left ventricular segments was scored using a four-point scoring system (0=normal, 1=slightly reduced, 2=moderately reduced, and 3=severely reduced, or absent uptake). Stress and rest tomographic views were reviewed side-by-side by two experienced observers who were unaware of the patients' clinical data. In the case of disagreement, a majority decision was achieved by a third observer. An abnormal study was considered in the presence of a fixed and/or reversible perfu-

sion defect. The perfusion defect scores were derived by the summation of the score of the six myocardial segments at rest [summed rest score (SRS) and at stress (summed stress score (SSS)]. The difference was expressed as the summed difference score (SDS). These indices were expressed as the percent of the total myocardium (% myocardium) as described previously.[8]

Outcomes evaluation

Outcome data were obtained by review of hospital records and/or contacting the patient's general practitioner. The date of the last review or consultation was used to calculate the follow-up time. In patients who suffered from multiple events during the follow-up, the first event was used to calculate the event-free survival. Endpoints were mortality and major adverse cardiac events (MACE; i.e. death, non-fatal myocardial infarction and coronary revascularization). Nonfatal myocardial infarction was defined as new symptoms of ischaemia, and/or ECG changes indicative of new ischaemia, and/or imaging evidence of myocardial infarction, accompanied by the detection of a rise and fall of cardiac biomarkers.[9]

Statistical analysis

Values were expressed as the mean value ± SD or number, and compared using Student's t-test or X^2 test. Univariate and multivariate Cox proportional hazard regression models (SPSS statistical software version 15.0, SPSS, Chicago, IL, USA) were used to identify the independent predictors of late cardiac events.[10] All clinical features, stress test variables, and SPECT variables were analysed to identify the independent predictors of adverse events. For the multivariate analysis, variables were selected in a stepwise forward selection manner with the entry and retention set at a significance level of 0.05. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). The probability of survival was calculated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. P-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Baseline data of the 650 patients are summarized in Table 1. There were no major side effects or complications as the result of the tests. The haemodynamic changes during exercise electrocardiography are summarized in Table 2. The mean exercise time was 7.2±2.1 min, the mean maximum workload was 144±42W. SPECT demonstrated normal myocardial perfusion in 326 (50%) patients. Completely reversible perfusion defects were detected in 52 (8%) patients, 79 (12%) had partially reversible perfusion defects, and 193 (30%) had fixed perfusion defects. The median SSS (expressed as % of myocardium) was 16.7±15.3, the median SRS was 8.3±13.9, and the median SDS was 2.8±7.0.

Table 1. Clinical characteristics

Age (years)	**56±11**
Men	428 (66%)
Length (cm)	172±9
Weight (kg)	77±14
Hypertension	284 (44%)
Smoking	165 (25%)
Hypercholesterolemia	256 (39%)
Diabetes mellitus	56 (9%)
Chronic obstructive pulmonary disease	36 (6%)
Angiotensin-converting enzyme inhibitor	144 (22%)
Beta blockers	250 (38%)
Calcium channel blockers	277 (43%)
Diuretics	89 (14%)
Nitrates	164 (25%)
Prior coronary revascularization	195 (30%)
Prior percutaneous coronary intervention	83 (13%)
Prior coronary artery bypass surgery	141 (22%)
Prior myocardial infarction	172 (26%)
Typical angina	184 (28%)
Atypical angina	220 (34%)
Non-specific symptoms	51 (8%)

Table 2. Exercise testing data

	Rest	Peak	*P*-value
Heart rate (bpm)	80 ± 18	140 ± 24	<0.001
Systolic blood pressure (mmHg)	137 ± 20	181 ± 30	<0.001
Diastolic blood pressure (mmHg)	87 ± 11	92 ± 14	<0.005
Rate – pressure product (x10^3 mmHg bpm)	11.0 ± 3.2	25.9 ± 8.2	<0.001

Outcomes

During a mean follow-up of 9.2±2.0 years, 107 (16%) patients died. Mortality was significantly higher in patients with an abnormal SPECT study than that in patients with normal SPECT results (Figure 1). A total of 69 (11%) patients had a non-fatal myocardial infarction, 90 (14%) underwent coronary artery bypass surgery, and 142 (22%) underwent percutaneous coronary intervention. Patients with an abnormal SPECT study had a significantly increased MACE rate as compared with patients with normal SPECT results (Figure 2).

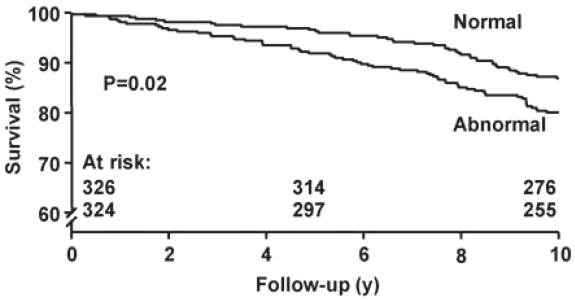

Figure 1. Mortality curves in patients with normal versus abnormal myocardial perfusion SPECT.

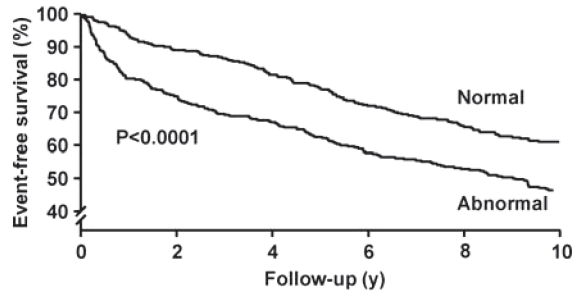

Figure 2. Major adverse cardiac events in patients with normal versus abnormal myocardial perfusion SPECT.

Univariate analysis

Clinical, exercise testing, and SPECT variables associated with mortality and MACE are summarized in Table 3. Univariate predictors of mortality were age >70 years, prior myocardial infarction, peak rate-pressure product (RPP), abnormal SPECT scan, SRS, and SSS. Univariate predictors of MACE were age >70 years, male gender, hypercholesterolaemia, use of beta blockers, use of calcium channel blockers, prior coronary revascularization, prior myocardial infarction, peak RPP, typical angina, abnormal SPECT scan, SRS, and SSS.

Table 3. Univariate predictors of mortality and major cardiac events

	Mortality		Major adverse cardiac events	
	HR (95 CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Clinical features				
Age >70 years	3.84 (2.19-6.74)	<0.001	2.66 (1.54–4.58)	0.0003
Male gender	1.48 (0.94-2.35)	0.09	1.95 (1.39–2.74)	<0.0001
Hypertension	1.16 (0.76-1.76)	0.49	1.03 (0.75–1.41)	0.86
Smoking	1.54 (0.99-2.42)	0.06	1.08 (0.75–1.53)	0.69
Hypercholesterolaemia	1.31 (0.86–1.99)	0.21	1.49 (1.08–2.04)	0.01
Diabetes mellitus	1.27 (0.63–2.54)	0.50	1.26 (0.73–2.19)	0.40
Beta blockers	1.25 (0.82–1.91)	0.29	1.64 (1.19–2.26)	0.002
Calcium channel blockers	1.28 (0.84–1.94)	0.25	1.40 (1.02–1.92)	0.04
Prior coronary revascularization	0.94 (0.60–1.49)	0.80	2.47 (1.76–3.49)	<0.0001
Prior myocardial infarction	1.86 (1.20–2.88)	0.005	2.17 (1.52–3.10)	<0.0001
Stress test results				
Peak RPP	0.88 (0.82–0.95)	<0.001	0.91 (0.86–0.96)	<0.001
Typical angina	0.89 (0.47–1.67)	0.72	2.20 (1.62–2.99)	<0.001
SPECT scan parameters				
Abnormal scan	1.72 (1.12–2.63)	0.01	2.08 (1.51–2.85)	<0.0001
SRS[a]	1.19 (1.12–1.26)	<0.001	1.09 (1.04–1.14)	<0.001
SSS[a]	1.16 (1.10–1.23)	<0.001	1.12 (1.08–1.17)	<0.001
SDS[a]	0.97 (0.83–1.14)	0.70	1.24 (1.14–1.34)	<0.001

[a]per 5.6% of the total myocardium increment. Values are expressed as the Cox proportional HR and 95% CI.

Multivariate analysis

Multivariate analysis demonstrated that SPECT variables provided incremental prognostic information over clinical data and exercise electrocardiographic test variables for the prediction of mortality and MACE. Exercise electrocardiographic variables provided no incremental information over clinical data for the prediction of outcome. The SRS was an independent predictor of mortality, and provided incremental prognostic information over clinical data and exercise electrocardiographic test variables (P<0.001, Table 4). The SSS was an independent predictor of MACE (P<0.001, Table 5).

Table 4. Multivariate predictors of mortality

	HR (95% CI)	P-value
Age[a]	1.05 (1.03–1.07)	<0.001
Smoking	1.94 (1.26–2.97)	<0.002
SRS[b]	1.15 (1.08–1.22)	<0.001

[a] per 1 unit increment

[b] per 5.6% of the total myocardium increment. Values are expressed as the Cox proportional HR and 95% CI.

Table 5. Multivariate predictors of major adverse cardiac events

	HR (95% CI)	P-value
Age[a]	1.03 (1.02–1.04)	<0.001
Male gender	1.47 (1.12-1.93)	0.006
Prior myocardial infarction	1.53 (1.19–1.96)	<0.001
SSS[b]	1.09 (1.04–1.13)	<0.001

[a] per 1 unit increment

[b] per 5.6% of the total myocardium increment. Values are expressed as the Cox proportional HR and 95% CI.

DISCUSSION

This study assessed the use of exercise MPI for the prediction of outcome in patients with known or suspected coronary artery disease and no electrocardiographic abnormalities during exercise electrocardiographic testing. Approximately 50% of patients with normal exercise electrocardiographic testing had an abnormal myocardial perfusion study, and 20% had completely or partially reversible perfusion defects. Exercise myocardial perfusion SPECT provided significant prognostic information for the prediction of outcome in these patients. Patients with an abnormal SPECT study had a sig-

nificantly increased mortality rate and had significantly more MACE as compared with patients with a normal SPECT.

Despite of its recognized limitations, exercise electrocardiographic testing is frequently used for prognostic stratification of patient with known or suspected coronary artery disease. Current clinical practice guidelines recommend exercise electrocardiographic testing for the initial evaluation and risk stratification of these patients.[1–3] The present results demonstrate that even in patients without electrocardiographic abnormalities during electrocardiographic testing, superior risk stratification can be obtained using myocardial perfusion SPECT. The discrepancy between exercise electrocardiographic testing and SPECT results is probably related to basic differences between these two tests. Angina and electrocardiographic changes (detected by exercise electrocardiographic testing) occur late in the ischaemic cascade, whereas perfusion abnormalities (detected by SPECT) are an early ischaemic phenomenon.[6] These differences result in a higher sensitivity of myocardial perfusion SPECT for the detection of myocardial ischaemia leading to better risk stratification.

In the present study, patients were referred to exercise SPECT for the evaluation of known or suspected coronary artery disease by their treating physicians. Clearly, clinical judgement and application of the appropriateness criteria should be used to select the optimal test for a particular patient.[11] Risk stratification using myocardial perfusion SPECT has disadvantages as radiation exposure to the patient and higher costs. Radiation exposure is an increasingly relevant topic as myocardial perfusion SPECT studies are an important source of medical radiation exposure and patients frequently have multiple procedures performed over time. New cadmium zinc telluride SPECT camera technology may substantially reduce radiation exposure while maintaining image quality.[12] Moreover, an individualized imaging protocol may further reduce study time and radiation exposure. The current study demonstrated that 50% of the patients had normal stress myocardial perfusion images. In these patients resting images are not necessary and a further reduction in the radiation dose can be achieved by using a stress-only imaging protocol.[13] Cost is another factor limiting routine risk stratification using myocardial perfusion SPECT as compared with exercise electrocardiographic testing. Further studies are needed to evaluate whether the initial lower cost of exercise electrocardiographic testing results in lower overall cost of clinical care. The suboptimal accuracy of exercise electrocardiographic testing may result in potential misdiagnosis of obstructive coronary artery disease, which may hinder appropriate patient care. Additionally, myocardial perfusion SPECT has a high negative predicting value, which may avoid the use of unnecessary (invasive) diagnostic procedures.

This study has limitations. First, in this study myocardial perfusion SPECT was performed for risk stratification of patients with known or suspected coronary artery disease. Myocardial perfusion SPECT has a good sensitivity and specificity for the evaluation of coronary artery disease. Still, coronary angiography is considered the reference methods for the assessment of coronary artery disease, and coronary angiography was not routinely performed in these patients. Second, no attenuation correction was used during exercise myocardial perfusion SPECT. Application of attenuation correction may have improved the accuracy of the SPECT studies. Recent data indicate that attenuation correction may further improve risk stratification.[14,15]

In conclusion, ~20% of patients with known or suspected coronary artery disease and normal exercise electrocardiographic testing have completely or partially reversible myocardial perfusion defects. MPI provides additional information for the prediction of 9-year cardiovascular outcomes in these patients.

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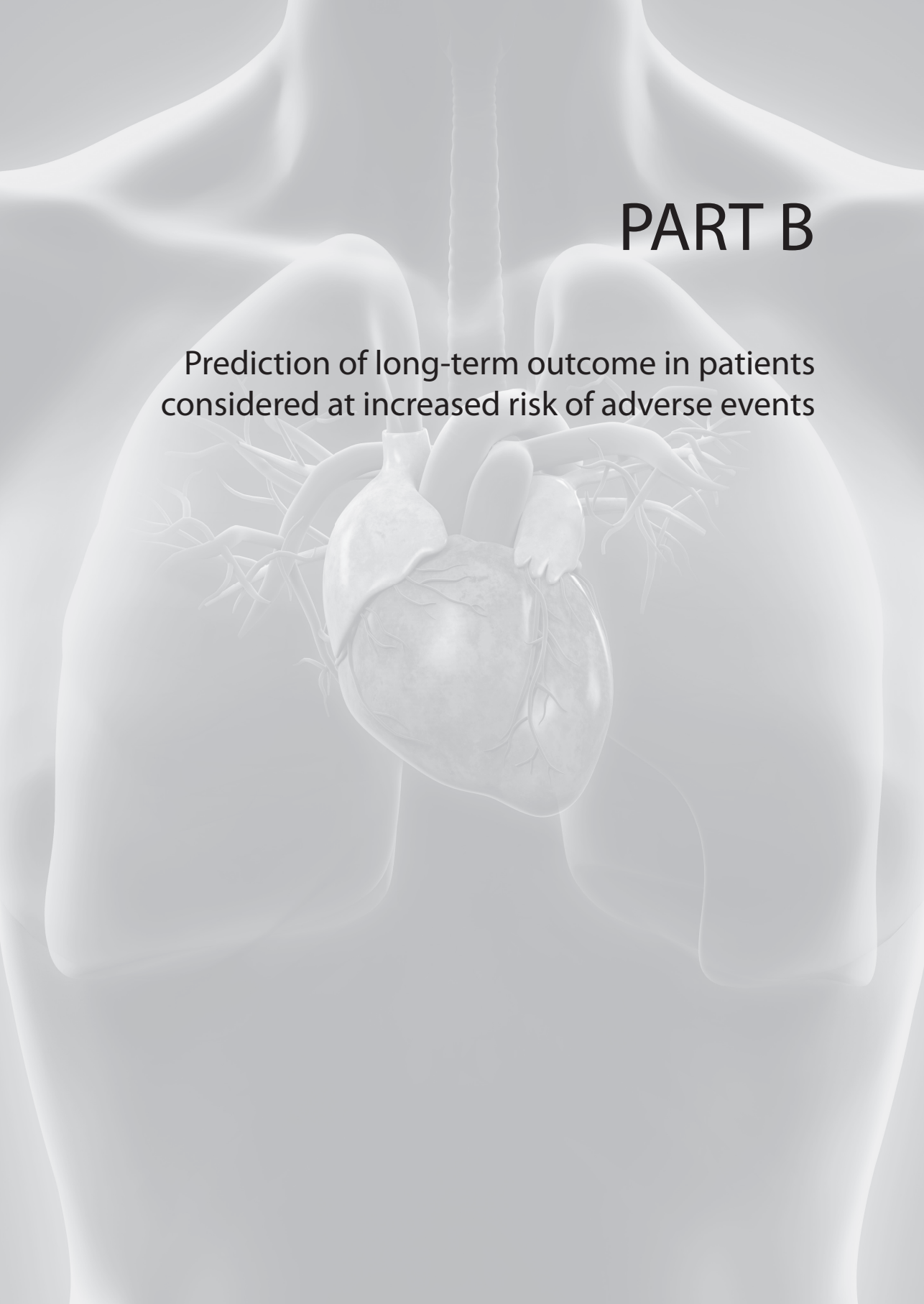
PART B

Prediction of long-term outcome in patients considered at increased risk of adverse events



Chapter 4

Long-term prognostic value of exercise technetium-99m tetrofosmin myocardial perfusion single-photon emission computed tomography

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ABSTRACT

Background. Exercise ^{99m}Tc-tetrofosmin single-photon emission computed tomography (SPECT) is a useful tool for short- and medium-term risk stratifications. Currently, the long-term prognostic application of this technique has not been evaluated.

Methods and Results. Exercise ^{99m}Tc-tetrofosmin was performed in 655 consecutive patients. Ten patients who underwent revascularization <60 days after nuclear testing were excluded from the analysis. The present data are based on 638 patients with complete follow-up. An abnormal SPECT study was defined as the presence of fixed and/or reversible perfusion defects. End points were cardiac death, nonfatal infarction, and late coronary revascularization. A total of 344 (54%) patients had an abnormal SPECT study. Perfusion defects included fixed defects alone in 186 patients (29%) and reversible defects in 158 (25%) patients. During a mean follow-up of 11±3.3 years, 174 (27%) patients died (all-cause mortality). Nonfatal myocardial infarction occurred in 76 (12%) patients, and late coronary revascularization was performed in 194 (30%) patients. Univariable and multivariable Cox proportional hazard regression analyses showed that exercise ^{99m}Tc-tetrofosmin SPECT provided prognostic information incremental to clinical data and exercise test data. Patients with a normal SPECT had a relatively favorable long-term prognosis, in contrast to patients with an abnormal study who had a significantly increased risk of cardiac events. The SPECT parameters abnormal scan, reversible defect, and summed rest score were strong predictors of long-term outcome.

Conclusion. Exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT has an incremental long-term prognostic value over clinical and stress test parameters for the prediction of major adverse cardiac events.

INTRODUCTION

Technetium-99m (^{99m}Tc)-labeled agents are currently the most frequently used radionuclide tracers for the assessment of myocardial perfusion. Historically, ^{99m}Tc-labeled agents were developed to overcome some limitations of thallium.[1,2] These agents have a higher photon energy and shorter physical half-life, resulting in improved images quality and longer myocardial retention as compared to thallium.[3] Multiple studies have demonstrated the value of ^{99m}Tc-labeled tracers in conjunction with single-photon emission computed tomography (SPECT) for the diagnosis of coronary artery disease, and the estimation of medium-term prognosis.[3-10] Several studies have demonstrated effective risk stratification with ^{99m}Tc-tetrofosmin myocardial perfusion SPECT. Long-term outcome data after exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT are currently not available. Therefore, the aim of this study was to evaluate the long-term prognostic value of exercise ^{99m}Tc-tetrofosmin SPECT for the prediction of major adverse cardiac events in patients with known or suspected coronary artery disease.

METHODS

Study Design

The study population consisted of 655 consecutive patients, who underwent exercise ^{99m}Tc-tetrofosmin SPECT imaging for the evaluation of known or suspected coronary artery disease. The current report details the results of a repeat follow-up from a prior study from our center.[6] The reason to perform this repeat follow-up study was to assess the very long-term prognostic value of exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT. Diamond and Forrester clinical score was used to stratify patients with suspected coronary artery disease into groups with low, intermediate, or high probability of coronary artery disease. All patients gave informed consent before the test. The protocol was approved by the Hospital Ethics Committee. Ten patients who underwent revascularization <60 days after nuclear testing were excluded from the analysis. This exclusion was based on the previously published data indicating that referral to coronary revascularization in the first 60 days after nuclear testing tends to be based on the results of the scan and that referral to revascularization >60 days after nuclear testing tends to be based on the worsening of the patient's clinical status.[11] In December 2010, follow-up was performed. The present data are based on 638 patients with complete follow-up.

Clinical Data

A structured interview and clinical history were obtained, and cardiac risk factors were assessed before nuclear testing. A blood pressure ≥140/90 mm Hg, or treatment with antihypertensive medication was considered as hypertension. A fasting glucose level ≥7.8 mmol/L or the need for insulin or oral hypoglycemic agents was considered as diabetes mellitus. A total cholesterol ≥6.4 mmol/L, or treatment with lipid-lowering medication was considered as hypercholesterolemia.

Exercise Testing

All patients fulfilled a symptom-limited upright bicycle ergometry test with a stepwise increment of 20 W every minute and with three electrocardiographic leads continuously monitored. Cuff blood pressure measurements and twelve-lead electrocardiograms were recorded at rest and every minute during exercise and recovery. The Schiller system Cardiovit CSG/12 (Schiller Inc., Baar, Switzerland) was used for computer averaging of the electrocardiographic complexes.Significant ST-segment depression was defined as a >1-mm horizontal or downsloping ST-segment depression occurring at 80 ms after the J point.[6] The target heart rate was defined as 85% of the maximum heart rate predicted for age and gender.

^{99m}Tc-Tetrofosmin SPECT Imaging

An intravenous dose of 370 MBq of ^{99m}Tc-tetrofosmin (Myoview, Amersham, Buckinghamshire, United Kingdom) was injected approximately 1 minute before the cessation of exercise. In rest studies, 370 MBq of tetrofosmin was administered at least 24 hours after the exercise study. Myocardial images were acquired with a triple-head gammacamera system (Picker Prism 3000 XP, Cleveland, Ohio, USA). For each study, six oblique (short axis) slices from the apex to the base and three sagittal (vertical long axis) slices were defined. Each of the six short-axis slices was divided into eight equal segments. Owing to corresponding of the septal part of the two basal slices to the fibrous portion of the interventricular septum and normally exhibits reduced uptake, this region was excluded from analysis. As a consequence, 47 segments were indentified (3 long axis and 44 short axis). The interpretation of the scan was semiquantitatively performed by visual analysis and aided by circumferential profiles analysis. Exercise and rest tomographic views were reviewed side by side by an experienced observer who was blind to the patients' clinical information. A reversible perfusion defect was defined as a per-

fusion defect on the exercise images that partially or completely resolved at rest in ≥2 contiguous segments or slices. 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. The presence of a fixed and/or reversible perfusion defect was considered as an abnormal study. Each myocardial segment was assigned a score from 0 to 3 (0 = normal; 1 = slightly reduced; 2 = moderately reduced; and 3 = severely reduced or absent uptake). Summed stress score (SSS) and summed rest score (SRS) were calculated by the summation of the scores of the myocardial segments at stress and at rest, respectively. The difference between stress and rest scores, summed difference score (SDS), was considered representative of the extent and severity of myocardial ischemia. Standard 17-segment-based scores were calculated and converted into percent of the total myocardium (% myocardium) by dividing the summed scores by the maximum potential score, and multiplying by 100.[12]

Follow-Up

Collection of follow-up data was performed by contacting the patient, the patient's general practitioner, civil registries, and review of hospital records. Outcome events were overall mortality, cardiac death, nonfatal myocardial infarction, and late (>60 days) coronary revascularization. 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 described by cardiac biomarker levels and ECG-changes. Major adverse cardiac events were the combined endpoint of cardiac death, nonfatal myocardial infarction, or coronary revascularization.

Statistical Analysis

Continuous variables were expressed as the mean ± SD and analyzed using the Student's t test. The chi-squared test was used to compare categorical variables. Univariable and multivariable Cox proportional hazard regression models were performed to determine those variables which were independent predictors of late cardiac events. Variables were selected in a stepwise forward selection manner with entry and retention set of a significance level of 0.05. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval. The assumption of the proportional hazards was evaluated by performing the log-minus-log survival plot. The assumption was

met. Interaction terms were used to investigate collinearity; no interactions were found. The incremental value of myocardial perfusion SPECT over the clinical variables in the prediction of major adverse cardiac events was evaluated using a multivariate analysis including one pre-imaging model and three post-imaging models. Survival curves were generated using the Kaplan-Meier method to assess the probability of survival and were compared using the log-rank test. P <.05 was considered statistically significant.

RESULTS

Clinical Characteristics and Exercise Test Results

The characteristics of the 638 patients are presented in Table 1. Diamond and Forrester pre-test probability of coronary artery disease was low in 51 (8%), intermediate in 364 (57%) and high in 223 (35%) patients. During the exercise test, typical angina was observed in 106 patients, and 124 patients showed significant ST-segment depression. Side effects were short ventricular tachycardia (<10 complexes) in, seven patients (1%), and atrial fibrillation in 8 (1%) patients. Minor side effects included dizziness in 40 (6%) patients, headache in 18 (3%) patients, and nausea in 12 (2%). Patients experienced no myocardial infarction or ventricular fibrillation.

Table 1. Baseline characteristics.

n=638	Number (%)
Age (years)	56 ± 11
Women	210 (33)
Congestive heart failure	70 (11)
Diabetes mellitus	58 (9)
Hypercholesterolemia	268 (42)
Hypertension	275 (43)
Previous myocardial infarction	171 (27)
Previous coronary artery bypass graft	91 (14)
Previous percutaneous coronary intervention	124 (19)
Known coronary artery disease	294 (46)
Smoking	153 (24)
Beta blockers	261 (41)
Calcium antagonists	269 (42)

SPECT results and prognosis

A total of 344 (54%) patients had an abnormal SPECT study. Perfusion defects included fixed defects alone in 186 patients (29%) and reversible defects in 158 (25%) patients. Of these reversible defects, 56 were completely reversible and 102 were partially reversible.

The means (SD) of the SPECT parameters SSS, SRS, and SDS were 3.68 (2.86), 2.43 (2.55), and 1.25 (1.30), respectively. During a mean follow-up of 11±3.3 years, 174 (27%) patients died (all-cause mortality). Nonfatal myocardial infarction occurred in 76 (12%) patients, and late coronary revascularization was performed in 194 (30%) patients. The Kaplan-Meier survival curves are presented in Figures 1, 2, 3, 4, and 5. The survival curves show that a normal ^{99m}Tc-tetrofosmin myocardial perfusion SPECT was associated with relatively low risk for major adverse cardiac events. Conversely, patients with an abnormal study had a significantly increased risk of major adverse cardiac events. Figure 5 demonstrates survival curves for allcause mortality and nonfatal myocardial infarction according to strata of coronary revascularization.

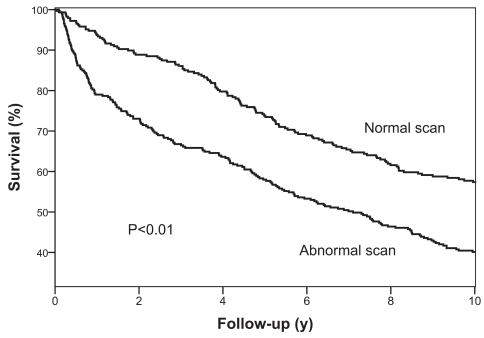

Figure 1. Kaplan Meier survival curves for major adverse cardiac events (cardiac death, nonfatal infarction, and coronary revascularization). Event-free survival was significantly different in patients with a normal and patients with abnormal exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT. y = years.

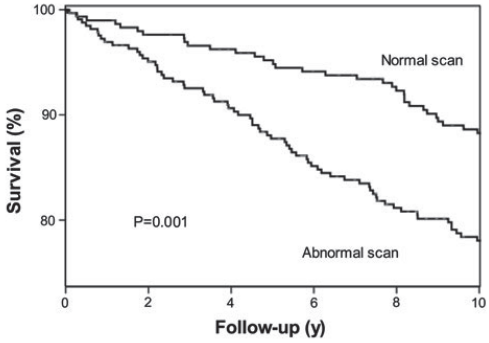

Figure 2. Kaplan Meier survival curves for all-cause mortality. Event-free survival was significantly different in patients with a normal and patients with abnormal exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT. y = years.

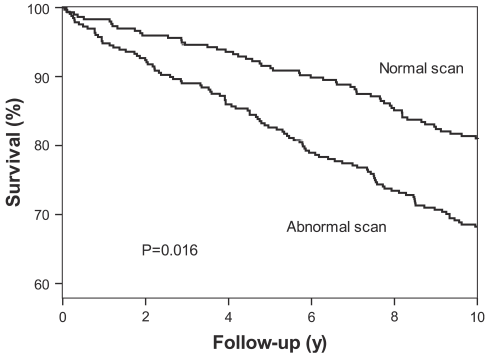

Figure 3. Kaplan Meier survival curves for all-cause mortality and non-fatal myocardial infarction. Event-free survival was significantly different in patients with a normal and patients with abnormal exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT. y = years.

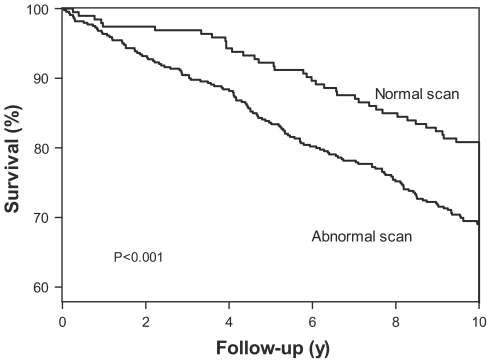

Figure 4. Kaplan Meier survival curves for revascularization. Event-free survival was significantly different in patients with a normal and patients with abnormal exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT. y = years.

Predictors of Outcome

Predictors of major adverse cardiac events are demonstrated in Table 2. Univariable predictors of major adverse cardiac events were age, male gender, hypercholesterolemia, previous myocardial infarction, revascularization, peak heart rate, rate-pressure product, typical angina and all analyzed scan parameters. A multivariable model revealed that myocardial perfusion SPECT had an incremental prognostic value over clinical variables and stress test parameters. The post-imaging models demonstrated that an abnormal scan was a powerful predictor of outcome; there was a direct relation between an abnormal scan and the risk of major adverse cardiac events

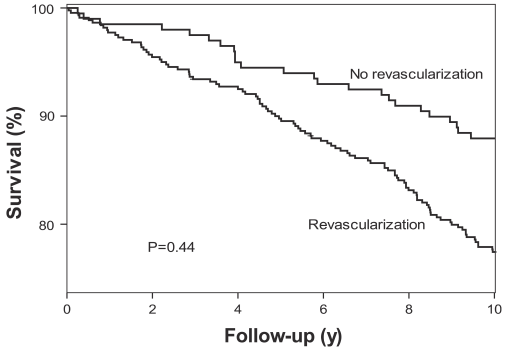

Figure 5. Kaplan Meier survival curves for the combined endpoint of all-cause mortality or non-fatal myocardial infarction according to strata of coronary revascularization. Event-free survival was not significantly different between patients with and without revascularization during follow-up. y = years.

Table 2. Predictors of major adverse cardiac events (cardiac death, nonfatal infarction or revascularization) at univariable and multivariable analysis.

	Univariable analysis	Multivariable analysis			
		Pre-imaging	Post-imaging I	Post-imaging II	Post-imaging III
Age*	1.02 (1.01-1.03)	1.05 (1.03-1.06)	1.03 (1.01-1.04)	1.02 (1.01-1.03)	1.05 (1.03-1.08)
Male gender	1.89 (1.50-2.39)	1.80 (1.29-2.51)	*p=0.11*	1.40 (1.09-1.79)	1.97 (1.25-3.10)
Congestive heart failure	*p=0.69*	*p=0.62*	*p=0.65*	*p=0.78*	*p=0.15*
Diabetes mellitus	*p=0.22*	1.96 (1.26-3.08)	1.74 (1.13-2.69)	p=0.13	2.36 (1.35-4.14)
History of angina	*p=0.26*	*p=0.63*	*p=0.93*	*p=0.66*	*p=0.52*
Hypercholesterolemia	1.30 (1.06-1.60)	*p=0.79*	*p=0.89*	*p=0.17*	*p=0.92*
Hypertension	*p=0.58*	*p=0.82*	*p=0.87*	*p=0.10*	*p=0.80*
Previous infarction	1.58 (1.26-1.97)	1.71 (1.15-2.55)	1.51 (1.10-2.08)	1.33 (1.06-1.68)	*p=0.06*
Revascularization	4.54 (3.63-5.68)	1.93 (1.43-2.60)	3.23 (2.43-4.30)	3.64 (2.93-4.53)	3.11 (2.32-4.16)
Smoking	*p=0.16*	2.25 (1.50-3.38)	1.42 (1.03-1.94)	*p=0.18*	2.41 (1.60-3.64)
Exercise test results					
Peak heart rate	0.87 (0.83-0.91)	*p=0.16*	*p=0.31*	0.98 (0.97-0.99)	*p=0.21*
Peak systolic BP	*p=0.91*	*p=0.29*	*p=0.16*	*p=0.86*	*p=0.11*
Peak RPP	0.96 (0.95-0.98)	*p=0.70*	*p=0.94*	*p=0.56*	*p=0.93*
Typical angina	1.68 (1.30-2.18)	*p=0.40*	*p=0.53*	*p=0.94*	*p=0.60*
ST-segment changes	*p=0.12*	*p=0.10*	*p=0.33*	*p=0.20*	*p=0.41*
Scan parameters					
Abnormal scan	1.68 (1.36-2.08)	-	1.57 (1.12-2.20)	-	-
Reversible defect	1.94 (1.55-2.44)	-	-	1.62 (1.20-2.20)	-
Fixed defect	1.28 (1.03-1.58)	-	-	*p=0.47*	
SRS**	1.02 (1.01-1.02)	-	-	-	1.03 (1.01-1.04)
SDS**	1.05 (1.04-1.07)	-	-	-	*p=0.49*
SSS**	1.27 (1.15-1.46)	-	-	-	-

Statistically significant predictors of outcome are presented as hazard ratio (confidence interval), of all other variables the p-value is presented.

- = not included in the model, *** =** per unit increment, ** = per % myocardium increment, BP = blood pressure, RPP = rate pressure product, SSS = summed stress score, SRS = summed rest score, SDS = summed difference score.

DISCUSSION

The prognostic value of exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT has been reported in previous studies with short-to-medium-term follow up.[4-10] The long-term prognostic value of exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT has not been defined. This study demonstrates that the prognostic value of exercise ^{99m}Tc-tetrofosmin

myocardial perfusion SPECT in predicting major adverse cardiac events, all-cause mortality, and all-cause mortality and nonfatal myocardial infarction was maintained during a long-term follow-up of 11±3.3 years. Univariable and multivariable analyses showed that exercise ^{99m}Tc-tetrofosmin SPECT provided prognostic information incremental to clinical data and exercise test data. Patients with a normal SPECT had a relatively favorable long-term prognosis, in contrast to patients with an abnormal study who had a significantly increased risk of cardiac events. The SPECT parameters abnormal scan, reversible defect, and SRS were strong predictors of long-term outcome.

Comparison to Previous Studies

Previous studies have demonstrated the prognostic value of exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT for the prediction of cardiac events in patients with known or suspected coronary artery disease at short-medium term follow-up.[4-10] Groutars et al.[4] studied 246 patients who had a normal exercise thallium/^{99m}Tc-tetrofosmin myocardial perfusion SPECT. The annualized cardiac event rate was 0.4%/year during a 25±3 month follow-up. Galassi et al.[5] studied 459 patients with exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT. During a median follow-up of 38 months, the annualized event rate (cardiac death/nonfatal infarction) was 0.5%/year in patients with a normal study and 4.9%/year in those with an abnormal study. Shaw et al.[7] reported the results from a multicenter registry and described an excellent prognosis for patients with a normal ^{99m}Tc-tetrofosmin myocardial perfusion SPECT during a mean follow-up of 2.5 years (30 months). Borges-Neto et al.[8] studied 473 patients with ^{99m}Tc-tetrofosmin and 518 patients using ^{99m}Tc-sestamibi exercise myocardial perfusion SPECT. The study demonstrated that the type of ^{99m}Tc-labeled myocardial perfusion agent did not affect interpretation of results for risk stratification and prognostic assessment during the 1.5-year study period. Georgoulias et al.[9] studied 246 asymptomatic patients after percutaneous coronary intervention with exercise ^{99m}Tc-tetrofosmin gated-SPECT. During 8.3±2.9-year follow-up of this selected population, myocardial perfusion SPECT provided incremental prognostic value. However, routine testing in asymptomatic patients is generally not recommended, and the clinical value and cost-effectiveness of routine SPECT after percutaneous coronary intervention need further investigation. Recently, Jain et al.[10] studied 371 patients with exercise or pharmacologic stress ^{99m}Tctetrofosmin gated-SPECT. During a mean follow-up of 3.9 years, SPECT findings significantly improved accuracy of cardiac event rate prediction compared to clinical information alone.

Compared to these previous studies, our study included 638 patients who were followed for 11±3.3 years. The findings of the current study extend the conclusions drawn from the previous medium-term prognostic studies. Previously, we have reported the 4±1.3 year follow-up of these 655 patients who underwent exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT.[6] In the same previous study, patients with a normal study had an annualized event rate (cardiac death, nonfatal infarction, and coronary revascularization) of 1.5%/year and those with an abnormal study of 5.0%/ year. In the current long-term follow-up study, Kaplan-Meier survival curves continued to diverge over time. Patients with normal SPECT had a favorable event-free survival, indicating that the prognostic value of SPECT for the prediction of outcome was maintained during the long-term follow-up period. Hence, patients with normal SPECT scans can be excluded from coronary invasive procedures. In contrast, patients with an abnormal myocardial perfusion SPECT had significantly higher annualized event rates. A total of 294 (46%) patients had known coronary artery disease; this may have caused the relatively high event rate in this patient cohort. Future studies are needed to optimize risk modification to improve outcome in these patients.

The 10 excluded patients who underwent revascularization <60 days after testing represent 1.6% of the overall cohort. This percentage is relatively low because in most of the patients with ischemia according to exercise ^{99m}Tc-tetrofosmin, medical therapy was probably optimized before a decision on referral to percutaneous coronary revascularization or surgical coronary revascularization was made. Kaplan-Meier curves demonstrated that referral to coronary revascularization was relatively low in patients with normal scan results in the first 4 years after testing. Previous studies demonstrate that the timing of revascularization requires careful consideration.[13] Patients with no or mild symptoms and little ischemia can safely be treated with medical treatment alone. Conversely, patients with moderate-to-severe symptoms and/or extensive ischemia should be strongly considered for revascularization therapy.[13] The current analysis demonstrates that event-free survival from all-cause mortality and nonfatal myocardial infarction was not significantly different between patients with coronary revascularization during follow-up and those without. This is in line with results from the COURAGE trial which demonstrated that clinical outcome was not significantly different between patients with stable angina who received an initial therapy of coronary revascularization and optimal medical therapy compared with patients with optimal medical therapy alone.[14]

Limitations

This study has several limitations. First, no attenuation or scatter correction was used during exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT. Application of attenuation or scatter correction may have improved the accuracy of the SPECT studies. Recent data indicate that attenuation correction may further improve risk stratification.[15,16] Second, previous studies have demonstrated that functional data derived from gated myocardial perfusion SPECT provides additional information to predict outcome. At the time of data collection, gated SPECT was not routinely performed. Therefore, in this study, the prognostic value of gated SPECT was not analyzed. Third, coronary angiography was not routinely performed; therefore, the current analysis may be influenced by false-positive and false negative SPECT studies. Fourth, although the feasibility of the test was high, 72 (11%) patients had an inconclusive test (failure to achieve target heart rate and to demonstrate a perfusion abnormality). These 72 studies were considered normal. The feasibility and perhaps the prognostic value could have been higher if beta-blocker therapy was routinely discontinued before the exercise test. Fifth, the results of exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT were available to the treating physicians. Patient management decisions were made at discretion of the treating physicians. It cannot be excluded that patients with an abnormal study received more intensive medical therapy and were referred to coronary revascularization to favorably alter their prognosis. Therefore the prognostic power of exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT may have been underestimated in the present study. Sixth, the present results were obtained in patients who underwent exercise ^{99m}Tc-tetrofosmin imaging, and cannot be automatically be extrapolated to SPECT studies using other isotopes. Finally, clinical data upon which to adjust the multivariable model were relatively limited; this could have influenced the current analysis.

CONCLUSION

Exercise ^{99m}Tc-tetrofosmin myocardial perfusion SPECT has an incremental long-term prognostic value over clinical and stress test parameters for the prediction of major adverse cardiac events. Patients with a normal ^{99m}Tc-tetrofosmin SPECT have a relatively favorable long-term prognosis, in contrast to patients with an abnormal study who have a significantly increased risk of cardiac events.

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Chapter 5

What is the value of stress ^{99m}Tc-tetrofosmin myocardial perfusion imaging for the assessment of very long-term outcome in obese patients?

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ABSTRACT

Objective. There are no data regarding the long-term prognostic value of single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in obese patients. The aim of this study was to examine the value of stress ^{99m}Tc-tetrofosmin MPI findings for the prediction of very long-term outcome in obese patients.

Methods. The study population consisted of 261 patients with a body mass index ≥30 kg/m^2 who underwent exercise or pharmacological stress ^{99m}Tc-tetrofosmin MPI for the assessment of known or suspected coronary artery disease. Endpoints during follow-up 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 was 59±10 years, 42% of the patients was male, and the body mass index was on average 37±7 kg/m^2. MPI findings were normal in 109 patients (42%). Myocardial perfusion abnormalities were fixed in 62 patients (24%) and reversible in 90 patients (34%). During a median 12-year follow-up, 91 (35%) patients died, and 27 (10%) had a nonfatal myocardial infarction. Survival curves were compared using the log-rank test at subsequent follow-up durations. Obese patients with a normal stress ^{99m}Tc-tetrofosmin study had a significantly better prognosis as compared with those with an abnormal study, up to 6 years after the test was performed.

Conclusion. Stress ^{99m}Tc-tetrofosmin MPI provides valuable prognostic information for the prediction of outcome in obese patients. Obese patients with a normal stress ^{99m}Tc-tetrofosmin study have a significantly better prognosis as compared with those with an abnormal study, up to 6 years after the test is performed.

INTRODUCTION

Obesity has reached global epidemic proportions in both adults and children and is associated with numerous comorbidities.[1,2] Obesity, defined as a body mass index (BMI)≥30, has a major impact on the risk of cardiovascular diseases. Obesity may cause premature coronary artery disease by its influence on known risk factors including diabetes, hypertension, and sleep apnea. As a consequence, obese patients are at a significantly increased risk of acute coronary syndromes, and have a reduced life expectancy.[2-5] Multiple studies have shown that stress myocardial perfusion imaging (MPI) yields additional diagnostic and prognostic information for the evaluation of coronary artery disease.[6-8] The extent and severity of abnormalities on MPI allow stratification of patients for future risk of adverse cardiac events. A previous study from our center showed that stress MPI is a useful tool in predicting mortality and cardiac events in obese patients.[9]

Currently, information on the very long-term prognostic value of stress ^{99m}Tc-tetrofosmin MPI in obese patients is not available. The very long-term prognostic value of MPI in these patients may be impaired because their increased underlying cardiovascular risk and accelerated natural progression of coronary artery disease. This creates uncertainties in the clinical management of obese patients. The aim of this study was to assess the role of stress ^{99m}Tc-tetrofosmin MPI for risk stratification in obese patients and to determine the value of this test for the assessment of very long-term outcome.

METHODS

Study Design

The study population consisted of 267 consecutive obese patients who were referred for stress ^{99m}Tc-tetrofosmin SPECT between January 1995 and December 2002, because of known or suspected coronary artery disease. Follow-up was successful in 261 (98%) patients. Patients were considered obese if they had a body mass index ≥30 kg/m^2, according to the criterion of the National Institutes of Health and the World Health Organization. Body mass index was calculated as the body weight divided by the squared height. The study population was similar to that in a previous study from our center.[9] The local medical ethics committee approved the protocol and all patients gave informed consent. A structured interview and clinical history were obtained, including assessment of cardiac risk factors, and the symptoms prior to the stress test.

Stress Testing Protocol

The stress testing protocol has been described previously.[9] In short, the choice of stress test was based on ability to exercise. Exercise stress testing was performed in 70 patients using a symptom-limited upright bicycle ergometer with a stepwise increment of 20 W every minute. Dobutamine-atropine stress testing was performed in 191 patients. Computer averaging of the electrocardiographic complexes was performed for both stress tests. Significant ST-segment depression was defined as a horizontal or downsloping ST-segment depression of more than 1 mm occurring 80 ms after the J point.

Myocardial Perfusion SPECT

Approximately 1 minute before the termination of the stress test an intravenous dose of 370 MBq of ^{99m}Tc-tetrofosmin (Myoview; Amersham) was administered. For resting studies 370 MBq of the same tracer was administered at least 24 hours after the exercise test. Image acquisition was performed using a SPECT camera system (Picker Prism 3000XP camera; Picker, Cleveland, OH). A normal study was defined as absence of perfusion abnormalities. Summed stress score (SSS) and summed rest score (SRS) were calculated by the summation of the scores of the myocardial segments at stress and at rest, respectively. Standard 17-segment-based scores were calculated and converted to percent of the total myocardium (% myocardium) by dividing the summed scores by the maximum potential score, and multiplying by 100.[10]

Patient Follow-Up

Outcome data were obtained by evaluation of hospital records, contacting the patient's general practitioner, and/or review of civil registries. The date of the last review or consultation was used to calculate follow-up time. Endpoints were all-cause mortality, cardiac death, nonfatal myocardial infarction, and coronary revascularization. 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. Hard cardiac events were defined as the occurrence of cardiac death or nonfatal myocardial infarction. Patients who underwent revascularization within 3 months of the stress test were censored, because previous studies have demonstrated that revascularization within 3 months is predominantly based on the test results, whereas revascularization after this period reflects a worsening clinical status.

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-squared test. 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. 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 3 models. In model I, the only SPECT MPI variable entered was the presence of abnormal perfusion. In model II, the variables entered were the presence of a fixed or reversible perfusion defect. In model III, the variables entered were SSS and SRS. The predictive value of each model was expressed using the Chi-squared statistic. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. P value <.05 was considered statistically significant.

Table 1. Clinical characteristics.

Age (years)	59±10
Male gender	110 (42%)
Weight (kg)	101±16
Body mass index (kg/m^2)	37±7
Diabetes mellitus	46 (17%)
Hypertension	156 (59%)
Hypercholesterolemia	109 (41%)
Smoking	60 (23%)
Angina	104 (39%)
Atypical chest pain	102 (38%)
Prior myocardial infarction	73 (28%)
Prior myocardial revascularization	77 (29%)
ACE-inhibitor	88 (33%)
Betablocker	145 (58%)
Calcium channel blocker	102 (38%)
Diuretic	67 (25%)

Data are presented as mean ± standard deviation or number of patients (percentages)

RESULTS

Clinical characteristics

Baseline characteristics of the patients are presented in Table 1. The mean age was 59±10 years and 42% of the patients were male. The body mass index was on average 37±7 kg/m^2. SPECT findings were normal in 109 patients (42%). Myocardial perfusion abnormalities were fixed in 62 patients (24%) and reversible in 90 patients (34%). A total of 34 patients had completely reversible perfusion defects, whereas 56 patients had partially reversible perfusion defects.

Patient Outcome

Kaplan-Meier survival curves and cumulative event rate are presented in Figures 1, 2, 3. Median follow-up duration was 12 years (range 9-16 years). During a mean follow-up of 10.4±4.4 years, 91 (35%) patients died. Cardiac mortality occurred in 28 (11%) patients. Nonfatal myocardial infarction occurred in 27 (10%) patients, and 88 (34%) patients underwent coronary revascularization. The annualized all-cause mortality rate after a normal study was 1.5%, 2.3%, and 1.9%, and after an abnormal study was 3.2%, 2.5%, and 2.7% at, respectively, 5-, 10-, and 15-year follow-up. Annualized cardiac mortality rate after a normal study was 0.6%, 0.6%, and 0.5%, and after an abnormal study was 1.6%, 1.0%, and 0.8% at, respectively, 5-, 10-, and 15-year follow-up. Annualized hard cardiac event rate after a normal study was 1.0%, 0.8%, and 2.3% and after an abnormal study was 2.0%, 1.2%, and 1.9% at respectively 5-, 10-, and 15-year follow-up.

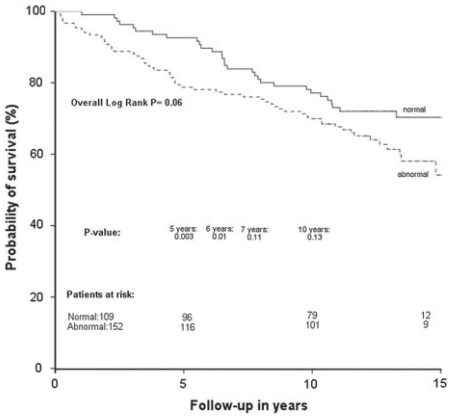

Figure 1. Kaplan-Meier event-free survival for the endpoint of all-cause mortality in patients with normal and abnormal stress ^{99m}Tc-tetrofosmin SPECT.

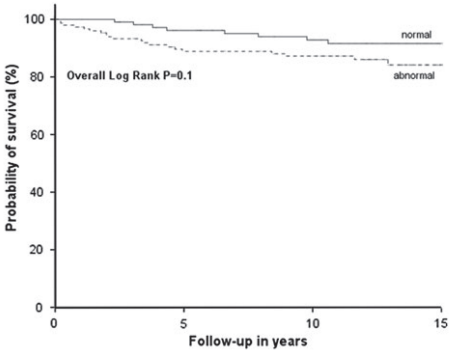

Figure 2. Kaplan-Meier event-free survival for the endpoint of cardiac mortality in patients with normal and abnormal stress ^{99m}Tc-tetrofosmin SPECT.

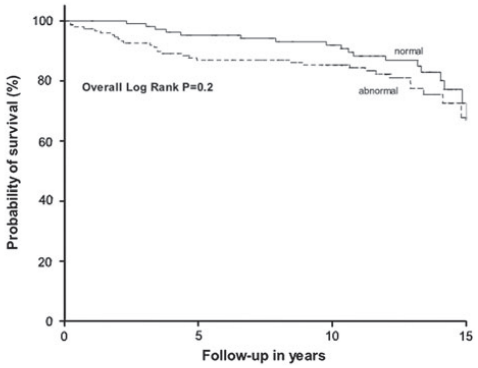

Figure 3. Kaplan-Meier event-free survival for the endpoint of hard cardiac events (cardiac mortality and nonfatal myocardial infarction) in patients with normal and abnormal stress^{99m}Tc-tetrofosmin SPECT.

To determine up to what time point during the follow-up the stress ^{99m}Tc-tetrofosmin SPECT study holds its prognostic value, the log-rank test was performed at subsequent follow-up durations (Figure 1). This analysis demonstrates that obese patients with a normal stress ^{99m}Tc-tetrofosmin study have a significantly better prognosis as compared with those with an abnormal study, up to 6 years after the test is performed. The perishable date of stress ^{99m}Tc-tetrofosmin SPECT for the prediction of outcome in obese patients is approximately 6 years.

Risk Stratification

Univariate analysis demonstrated that during the very long-term follow-up, age, prior heart failure, diabetes mellitus, prior myocardial infarction, and smoking were predictors of all-cause mortality (Table 2). Age, prior heart failure, diabetes mellitus, prior myocardial infarction were univariate predictors of cardiac mortality (Table 3). Age, prior heart failure, and prior myocardial infarction were significant univariate predictors of hard cardiac events (Table 4). Univariate analyses demonstrated that ^{99m}Tc-tetrofosmin SPECT parameters were not predictive of very long-term outcome. Multivariate analyses demonstrated that SPECT parameters had no incremental value over clinical variables for the prediction of all-cause mortality, cardiac mortality, and hard cardiac during the entire 12-year follow-up.

Table 2. Univariate and multivariate predictors of all-cause mortality.

		Multivariate		
Parameter	**Univariate**	**Model I**	**Model II**	**Model III**
Age	1.07 (1.05–1.09)	1.08 (1.06–1.1)	1.07 (1.05–1.11)	1.08 (1.06–1.11)
Prior heart failure	2.5 (1.5–4.2)	2.0 (1.2–3.5)	2.0 (1.2–3.5)	2.0 (1.2–3.5)
Diabetes	2.1 (1.4–3.2)	2.3 (1.4–3.7)	2.3 (1.5–3.6)	2.3 (1.5–3.7)
Prior myocardial infarction	1.7 (1.1– 2.6)	2.1 (1.3–3.4)	2.2 (1.4–3.4)	2.1 (1.3–3.4)
Current smoking	1.5 (0.9–2.3)	1.5 (0.9–2.5)	1.6 (1.0–2.6)	1.6 (1.0–2.6)
Abnormal perfusion	1.5 (0.98–2.4)	1.1 (0.7–1.8)	-	-
Fixed	1.1 (0.7–1.8)	-	0.9 (0.6-1.3)	-
Reversible	1.3 (0.8-2.0)	-	1.0 (0.6-1.5)	-
SSS*	1.1 (0.9-1.2)	-	-	1.0 (0.9-1.2)
SRS*	1.1 (1.0-1.2)	-	-	0.99 (0.84-1.17)
Total Chi-square	-	75	72	72

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 variables entered were the presence of a fixed or reversible perfusion defect. In model III, the variables entered were SSS and SRS.

* Per 5.6% of the total myocardium increment.

Table 3. Univariate and multivariate predictors of cardiac mortality.

		Multivariate		
Parameter	**Univariate**	**Model I**	**Model II**	**Model III**
Age	1.05 (1.02–1.09)	1.07 (1.02–1.11)	1.06 (1.02–1.11)	1.07 (1.02–1.12)
Prior heart failure	4.4 (2.0–9.7)	2.8 (1.2–6.4)	2.9 (1.3–6.9)	2.4 (1.1–5.7)
Diabetes	3.3 (1.5–6.9)	3.3 (1.5–7.3)	3.3 (1.5–7.3)	3.7 (1.7–8.0)
Prior myocardial infarction	3.3 (1.5–6.9)	3.7 (1.6–8.3)	4.0 (1.8–8.8)	2.9 (1.2–6.8)
Abnormal perfusion	2.0 (0.9–4.5)	1.2 (0.5–2.9)	-	-
Fixed	1.2 (0.6–2.6)	-	0.9 (0.4–2.1)	-
Reversible	1.3 (0.6–2.8)	-	0.9 (0.4–2.0)	-
SSS*	1.2 (1.1–1.4)	-		1.1 (0.9–1.4)
SRS*	1.2 (1.1–1.4)	-	-	1.0 (0.8-1.3)
Total Chi-square	-	42	43	45

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 variables entered were the presence of a fixed or reversible perfusion defect. In model III, the variables entered were SSS and SRS.

* Per 5.6% of the total myocardium increment.

DISCUSSION

The main finding of this study is that stress ^{99m}Tc-tetrofosmin MPI provides useful information for the prediction of outcome in obese patients. Obese patients with a normal stress ^{99m}Tc-tetrofosmin study have a significantly better prognosis as compared with those with an abnormal study, up to 6 years after the test is performed. After this 6-year period, stress ^{99m}Tc-tetrofosmin MPI does not hold its value for the prediction of all-cause mortality, cardiac mortality, and hard cardiac events in obese patients. The perishable date of stress ^{99m}Tc-tetrofosmin SPECT for the prediction of outcome in obese patients is approximately 6 years. Although multiple studies have shown that stress MPI has an incremental prognostic value over clinical data for the prediction of mortality and cardiac events,[6-8] no previous reports have assessed the very long-term prognostic value in obese patients.

Table 4. Univariate and multivariate predictors of hard cardiac events.

		Multivariate		
Parameter	**Univariate**	**Model I**	**Model II**	**Model III**
Age	1.05 (1.02-1.08)	1.06 (1.03-1.08)	1.06 (1.03-1.09)	1.05 (1.02-1.08)
Prior heart failure	2.8 (1.4-5.5)	2.4 (1.2-4.7)	2.5 (1.2-5.0)	2.3 (1.1-4.7)
Prior myocardial infarction	2.2 (1.3-3.8)	2.2 (1.3-4.0)	2.5 (1.4-4.5)	2.1 (1.1-3.8)
Abnormal perfusion	1.7 (1.0-3.0)	1.2 (0.6-2.1)	-	-
Fixed	1.0 (0.6-1.8)	-	0.7 (0.4-1.2)	-
Reversible	1.6 (0.9-2.8)	-	1.1 (0.6-2.0)	-
SSS*	1.1 (1.0-1.3)	-	-	1.1 (0.9-1.2)
SRS*	1.1 (1.0-1.3)	-	-	1.0 (0.8-1.2)
Total Chi-square	-	30	33	28

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 variables entered were the presence of a fixed or reversible perfusion defect. In model III, the variables entered were SSS and SRS.
* Per 5.6% of the total myocardium increment.

There is overwhelming evidence supporting the importance of obesity in the pathogenesis and progression of coronary artery disease. Studies have shown that obesity is associated with more morbidity than smoking, alcoholism, and poverty.[1-5] Obesity may have influence on insulin resistance, hypertension, hyperlipidemia, inflammatory markers, thromboembolism, and sleep apnea. These are established risk factors for coronary

artery disease. Conversely, other studies have reported on an obesity paradox, that is: lower mortality in obese patients.[11,12] A recent study by Boiten et al[13] described the very long-term outcome of ^{99m}Tc-tetrofosmin SPECT in 655 consecutive patients. During an 11.0 ± 3.3-year follow-up, all-cause mortality was approximately 1%/year in patients with a normal study and 2%/year in those with an abnormal study. In this study, all-cause mortality was 1.9%/year in obese patients with a normal study and 2.7%/year in those with an abnormal study.

The evaluation of coronary artery disease in obese patients is challenging. The baseline ECG in these patients is often influenced by the presence of obesity (false-positive for inferior myocardial infarction, microvoltages, and nonspecific repolarization abnormalities). Additionally, obese patients may have an impaired maximal exercise testing capacity (due to dyspnea, orthopedic limitations, left ventricular diastolic dysfunction). This is confirmed by this study in which 27% of the obese population was able to perform an exercise test, whereas the remaining 73% was unable to perform an exercise test and underwent a pharmacological stress study.

A few previous studies have reported on the short to medium-term prognostic value of SPECT MPI in obese patients. Duvall et al[14] studied 433 obese patients with a mean body mass index of 47.3 ± 8 kg/m2. A total of 98 patients performed an exercise test and 335 underwent pharmacological stress testing in conjunction with ^{99m}Tc-SPECT. The patients had a mean follow-up of 24.9 ± 11.3 months, there was a statistically significant difference in the Kaplan-Meier curves at 1-year follow-up; however, at 2-year follow-up there was no significant risk stratification. The authors stated that this lack of prognostic value at 2 years may have been the result of the retrospective nature of the study or the sample size and relative short follow-up length. Alternatively, obesity may have resulted in a more rapidly progression of the atherosclerotic process. Uretsky et al[12] previously described the impact of weight on long-term survival in 3673 patients without known CAD and with normal stress SPECT MPI. During a 7.5±3-year follow-up, overweight and obese patients had a lower risk of all-cause mortality compared to normal weight patients. Hence, that study supported the obesity paradox (lower mortality in obese patients). In this study, event rates were substantially higher which was caused by the clinical profile of the patients (28% had previous myocardial infarction, 29% had previous myocardial revascularization) that was different from the patients studied by Uretsky et al.[12] An earlier study from our center[9] demonstrated that stress ^{99m}Tc-tetrofosmin MPI was independently predictive of cardiac mortality and all-cause mortality in obese patients during a mean follow-up of 5.5±2 years. This study differs from previous

studies because the median follow-up duration was 12 years (range 9-16 years). This study extends the results from previous studies and demonstrates that the prognostic value is maintained up to 6 years after the date of the SPECT MPI.

Several factors may explain why the value of SPECT MPI has no incremental prognostic value at 6-15-year follow-up. Hachamovitch et al[15] have demonstrated previously that a warranty period after normal 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 SPECT MPI. In that study of Hachamovitch et al,[15] overall, patients with a normal study had a favorable outcome. However, there were patients with a normal study that had an adverse outcome. Pharmacological stress testing, a history of coronary artery disease, diabetes, gender, and increasing age were significant predictors of adverse outcome. Clinical characteristics, such as hypertension, diabetes, and the lesions from a previous myocardial infarction, might change and become worse in these years and can affect the risk on death and cardiac events. Moreover,this population of patients with obesity may have an accelerated progression of coronary artery disease as compared to patients without obesity. Because the prognostic value of SPECT MPI in obese patients is maintained up to 6 years after testing, more frequent monitoring of obese patients after this period may be justified. Repeated testing after 6 years may be considered depending on the patient's symptoms and clinical status. The appropriateness criteria for cardiac radionuclide imaging should be used to determine whether repeated testing is necessary.[16]

SPECT MPI provides clinically useful information for patients' management and decisions on further testing in obese patients. This study demonstrates that obese patients with a normal SPECT MPI have a favorable prognosis. In these patients, a watchful waiting approach to care is justified, and additional diagnostic strategies including invasive coronary angiography can be avoided. Previous studies have demonstrated that this type of management strategy may be both clinically effective and cost-effective.[17,18] In obese patients with an abnormal SPECT MPI study, medical therapy should be optimized and further testing including invasive coronary angiography should be considered. Clearly, clinical judgment remains important in deciding patient management decisions, especially in obese patients.

This study has some limitations. First, the studied population was relatively small. Second, obesity may cause false positive SPECT MPI results because of attenuation. In this study, attenuation correction was not routinely performed. This may have influenced the prognostic value of SPECT MPI in this study population.

Recent data indicate that attenuation correction may further improve diagnostic accuracy of myocardial perfusion SPECT. Third, no information on medical therapy changes was available.

CONCLUSION

Stress ^{99m}Tc-tetrofosmin MPI provides valuable prognostic information for the prediction of outcome in obese patients. Obese patients with a normal stress ^{99m}Tc-tetrofosmin study have a significantly better prognosis as compared with those with an abnormal study, up to 6 years after the test is performed.

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Chapter 6

Prediction of long-term (>10 year) cardiovascular outcomes in heart transplant recipients: value of stress technetium-99m tetrofosmin myocardial perfusion imaging

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ABSTRACT

Background. Myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) is useful in the evaluation of cardiac allograft vasculopathy (CAV) in heart transplant (HTx) recipients. The current study evaluated the long-term prognostic value of stress SPECT MPI for predicting all-cause mortality and cardiac events in HTx recipients.

Methods. The study population consisted of 166 HTx recipients (mean age 54 ±10 years, 84% male) who underwent exercise or dobutamine stress ^{99m}Tc-tetrofosmin SPECT MPI for the assessment of CAV. An abnormal SPECT MPI was defined as the presence of a fixed or a reversible perfusion defect. Endpoints were all-cause mortality, cardiac mortality and nonfatal myocardial infarction (MI).

Results. MPI abnormalities were detected in 55 patients (33%), including fixed defects in 28 patients (17%), partially reversible in 17 patients (10%) and completely reversible defects in 10 patients (6%). During a median follow-up of 12.8 years (range 0-15), 109 (66%) patients died (all-cause mortality), of which 67 (40%) were due to cardiac causes. A total of 5 (3%) patients experienced a non-fatal MI. HTx recipients with a normal stress ^{99m}Tc-tetrofosmin SPECT MPI had a significantly better prognosis as compared with those with an abnormal study, up to 5 years after the initial test. The presence of a reversible perfusion defect was a significant predictor of all-cause mortality, cardiac mortality and major cardiac events, during the entire follow-up period.

Conclusions. Stress ^{99m}Tc-tetrofosmin SPECT MPI provides valuable prognostic information for the prediction of long-term outcome in HTx recipients. Patients with a normal stress ^{99m}Tc-tetrofosmin SPECT MPI have a significantly better prognosis as compared with those with an abnormal study, up to 5 years after initial testing.

Key Words: heart transplant recipients - cardiac allograft vasculopathy - long-term prognosis - stress SPECT MPI.

INTRODUCTION

Heart transplantation (HTx) is the first choice in treatment of patients with end-stage heart failure. However, the long-term outcome is severely hampered by cardiac allograft vasculopathy (CAV), occurring up to 50% of the patients[1] and is associated with an increased risk of mortality.[2-4] As a result of denervation of the transplanted heart, angina symptoms resulting from CAV are usually absent and the first clinical sign of CAV can be heart failure, myocardial infarction, ventricular arrhythmias or sudden death.[5] Serial coronary angiography (CA) and intravascular ultrasound (IVUS) are used for the evaluation of significant CAV.[6] However these are invasive procedures with inherent risks. Among noninvasive modalities, myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) is a useful clinical tool to evaluate CAV. Several studies have demonstrated that stress SPECT MPI has diagnostic and prognostic value in HTx recipients.[7-9] However, information regarding the value of stress SPECT MPI for the prediction of long-term cardiovascular outcomes in HTx recipients is limited.[10] Due to the relatively high prevalence and progression of CAV in these patients[1], the long-term prognostic value of stress SPECT MPI may be impaired. This creates uncertainties in the clinical management of these patients. Accordingly, the aim of this study was to assess the long-term prognostic value of stress SPECT MPI for predicting all-cause mortality and cardiac events in HTx recipients.

METHODS

Patient Selection

The study population consisted of 166 HTx recipients who underwent exercise (n=65) or dobutamine (n=101) stress SPECT MPI >2 years after transplantation at the Thoraxcenter, Rotterdam, The Netherlands between 1992 and 1998. The current study details the results of a long-term follow-up from a prior study at our center.[11] The reason for performing this repeat follow-up study was to assess the long-term (>10 year) prognostic value of stress SPECT MPI in HTx recipients. Follow-up was successful in all of the 166 patients. The Hospital Ethics Committee approved the study protocol. The study was conducted according to the Helsinki Declaration.[12] All patients consented to participation in this study. Before the stress test, a structured interview and clinical history were obtained, including assessment of cardiac risk factors. Hypertension was defined

as a blood pressure of ≥140/90 mmHg or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level of ≥7.8 mmol/L or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol of ≥6.4 mmol/L or treatment with lipid-lowering medication.

Stress Test Protocol

The exercise or dobutamine stress test was performed as described previously.[11] Dobutamine was infused through an antecubital vein starting at a dose of 5 µg/kg/min, followed by 10 µg/kg/min at 3 minutes, increasing by 10 µg/kg/min every 3 minutes to a maximum of 40 µg/kg/min. Atropine was given to patients who could not achieve the 85% age-predicted heart rate at the maximal dobutamine dose. The test was discontinued if severe chest pain, ST-segment depression >2 mm, significant arrhythmia, hypertension (blood pressure ≥240/120 mm Hg), systolic blood pressure decrease of >40 mm Hg, or any intolerable side effect regarded as being due to dobutamine occurred during the test. Metoprolol (1 to 5 mg) was used intravenously to reverse the adverse effects of dobutamine/atropine. An ischemic electrocardiographic response was defined as ≥1 mm horizontal or downsloping ST-segment depression persisting 80ms after the J point. Symptom-limited upright bicycle ergometry test was performed with stepwise increments of 20 W each minute. Blood pressure and electrocardiographic recordings were performed as described for the dobutamine stress test.

SPECT MPI

The single-photon emission computed tomography protocol has been described previously.[11] An intravenous dose of 370 MBq of technetium-99m tetrofosmin (Myoview, Amersham, Buckinghamshire, United Kingdom) was administered approximately 1 minute before the termination of the dobutamine or the exercise stress test.[13] Acquisition of images began 1 hour after the stress test. For studies taken at rest, images were acquired 24 hours after the stress study, 1 hour after injection of 370 MBq of tetrofosmin. Image acquisition was performed with a triple-head gamma camera system (Picker Prism 3000 XP, Cleveland, Ohio). For each study, 6 oblique (short-axis) slices from the apex to the base and 3 sagittal (vertical long-axis) slices from the septum to the lateral wall were defined. Each of the 6 short-axis slices was divided into 8 equal segments. The interpretation of the scan was semiquantitatively performed by visual analysis assisted by circumferential profiles analysis. Stress and resting 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 a stress image that partially or completely resolved at rest in ≥2 contiguous segments or slices. A fixed perfusion defect was defined as a perfusion defect on stress images in ≥2 contiguous segments or slices that persisted on images taken at rest. An abnormal study was considered in the presence of a fixed and/or reversible perfusion defect. To assess the severity of perfusion abnormalities, the left ventricular myocardium was divided into 6 segments: anterior, inferior, septal anterior, septal posterior, posterolateral, and apical. Each of the 6 major left ventricular segments was scored using a 4-grade method (0 = normal, 1 = mildly reduced, 2 = moderately reduced, and 3 = severely reduced or absent uptake). The perfusion defect scores were derived by the summation of the score of the six myocardial segments at rest (summed rest score (SRS) and at stress (summed stress score (SSS)). The difference was expressed as the summed difference score (SDS). These indices were expressed as the percent of the total myocardium (% myocardium) as described previously.[14]

Patient Follow-up

Follow-up data were obtained in 2011. The patient's survival status was determined by contacting the municipal civil registry. For those patients who were still alive, follow-up was obtained by contacting the patients, the patient's general practitioner or by reviewing hospital records. The date of the last review or consultation was used to calculate the follow-up time. Endpoints were all-cause mortality, cardiac mortality and nonfatal myocardial infarction (MI). Causes of death were obtained from the Central Bureau of Statistics Netherlands (www.cbs.nl). Cardiac mortality 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 mortality. Major cardiac events were defined as cardiac mortality and nonfatal MI.

Statistical Analysis

All statistical analyses were performed using SPSS, version 21.0 (Chicago, IL, USA). Continuous data were expressed as mean value ± SD and compared using the Student s t-test. Categorical data were expressed in numbers and percentages and compared using the Chi-squared test. The probability of survival was calculated using the Kaplan-Meier method. Survival curves were compared using the log-rank test. To investigate whether

SPECT MPI has additional prognostic value in predicting long-term prognosis, the Cox proportional-hazards regression model was used. To determine the perishable date of SPECT MPI in HTx recipients, the Kaplan-Meier method and multivariable analysis was repeated at 1, 2, 3, and so on years of follow-up. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). The incremental value of SPECT MPI over the clinical variables in the prediction of the endpoints of interest was performed according to 4 models. In Model 1, the presence of an abnormal SPECT MPI was entered. In Model 2 the presence of a reversible or fixed defect was entered. In Model 3, the variable entered was SDS and in Model 4, the variable entered was SSS. The predictive value of each model was expressed using the Chi-squared statistic.

Table 1. Clinical characteristics

	(n=166)
Age (years)	54 ± 10
BMI (kg/m^2)	26.4 ± 4.5
Male gender	140 (84%)
Hypertension	117 (71%)
Diabetes mellitus	18 (11%)
Smoking	24 (15%)
Hypercholesterolemia	70 (42%)
Beta blocker use	23 (14%)
Target heart rate reached*	117 (70%)

Data are presented as mean ± SD or numbers (percentages).

BMI = body mass index.

*Target heart rate reached is defined as 85% of the maximal predicted heart rate.

RESULTS

Clinical Characteristics

The baseline characteristics of the 166 patients are presented in Table 1. Mean age was 54 ±10 years and 84% of the patients were male. SPECT MPI findings were normal in 111 patients (67%). Myocardial perfusion abnormalities were fixed in 28 patients (17%), partially reversible in 17 patients (10%) and completely reversible defects in 10 patients (6%). During the stress test there was a significant increase in heart rate (93±13 to 140±17 beats per minute, p <0.001) and systolic blood pressure (146±18 to 166±30 mmHg,

p<0.001). Two patients developed atypical and 1 patient developed typical chest pain during the stress test. A total of 117 patients (70%) reached the target heart rate (85% of the age-predicted maximal exercise heart rate). Minor side effects of dobutamine administration included nausea in 3 patients (3%), flushing in 4 patients (4%), headache in 5 patients (5%), and chills in 3 patients (3%). Non-sustained ventricular tachycardia during exercise stress testing was observed in 1 patient.

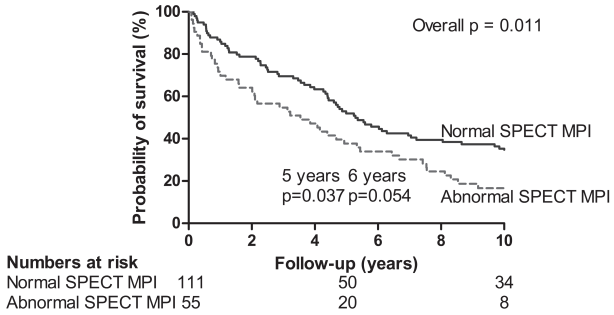

Figure 1. Kaplan-Meier event-free survival for all-cause mortality in HTx recipients with normal and abnormal SPECT MPI.

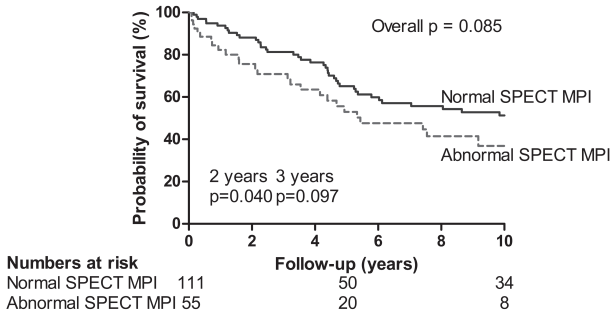

Figure 2. Kaplan-Meier event-free survival for cardiac mortality in HTx recipients with normal and abnormal SPECT MPI.

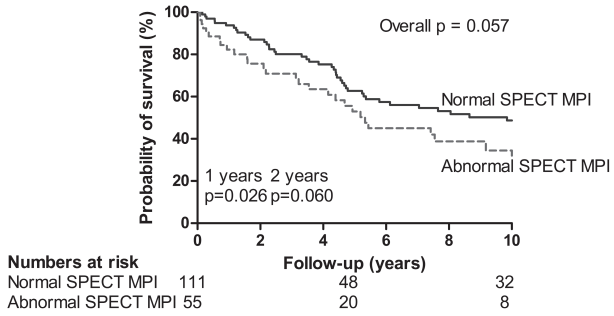

Figure 3. Kaplan-Meier event-free survival for major cardiac events in HTx recipients with normal and abnormal SPECT MPI.

Patient Outcomes

During a median follow-up time of 12.8 years (range 0-15), 109 (66%) patients died (all-cause mortality), of which 67 (40%) were due to cardiac causes. A total of 5 (3%) patients experienced a non-fatal myocardial infarction. Kaplan-Meier survival curves for all-cause mortality, cardiac mortality and major cardiac events are presented in Figures 1, 2 and 3, respectively. The survival curves showed a significantly better long-term survival of HTx recipients with a normal SPECT MPI compared to patients with an abnormal SPECT MPI (annualized all-cause mortality rate: 9 vs 15% at 3 years, 8 vs 11% at 6 years and 6 vs 9% at 9 years, overall P=0.011, Figure 1). To determine up to what time point during follow-up the stress SPECT MPI holds its prognostic value, the log-rank test was performed at subsequent follow-up durations (Figure 1, 2 and 3). This analysis demonstrated that HTx recipients with a normal stress SPECT MPI had a significantly better prognosis as compared with those with an abnormal stress SPECT MPI, up to 5 years after the test is performed for all-cause mortality. The "warranty period" of stress SPECT MPI in HTx recipients for the prediction of all-cause mortality was approximately 5 years. According to cardiac mortality and major cardiac events, patients with a normal stress SPECT MPI had a significantly better prognosis as compared with patients with an abnormal stress SPECT MPI, up to 2 years and 1 year after testing, respectively.

Table 2. Univariable and multivariable predictors of all-cause mortality at 5-year follow-up

Variable	Univariable	Multivariable					
		Clinical variables	Clinical and stress variables	Model 1	Model 2	Model 3	Model 4
Age*	**1.03 (1.01-1.06)**	**1.04 (.101-1.06)**	**1.04 (1.01-1.06)**	**1.03 (1.01-1.06)**	**1.03 (1.01-1.06)**	**1.04 (1.02-1.07)**	**1.04 (1.01-1.07)**
Gender	2.60 (1.20-5.66)	2.10 (0.94-4.69)	2.13 (0.96-4.76)	2.05 (0.92-4.56)	2.15 (0.97-4.79)	2.06 (0.92-4.64)	1.96 (0.87-4.41)
Diabetes	0.80 (0.39-1.66)	0.64 (0.30-1.35)	0.66 (0.31-1.39)	0.61 (0.29-1.30)	0.61 (2.8-1.29)	0.63 (0.29-1.34)	0.61 (0.29-1.31)
Hypertension	1.14 (0.70-1.85)	1.13 (0.67-1.91)	1.10 (0.65-1.87)	1.24 (0.72-2.14)	1.24 (0.73-2.10)	1.07 (0.61-1.85)	1.08 (0.62-1.89)
Smoking	1.41 (0.79-2.52)	1.54 (0.85-2.79)	1.59 (0.87-2.90)	1.59 (0.87-2.92)	1.52 (0.83-2.79)	1.84 (0.97-3.46)	1.86 (0.98-3.51)
Hypercholesterolemia	0.92 (0.59-1.44)	0.78 (0.49-1.27)	0.77 (0.48-1.25)	0.71 (0.43-1.16)	0.77 (0.47-1.25)	0.80 (0.49-1.31)	0.75 (0.45-1.24)
ST-segment changes	1.26 (0.69-2.28)	-	1.25 (0.67-2.34)	1.20 (0.64-2.26)	1.20 (0.64-2.25)	1.18 (0.62-2.25)	1.24 (0.66-2.34)
Abnormal SPECT MPI	**1.59 (1.02-2.49)**	-	-	**1.61 (1.01-2.56)**	-	-	-
Reversible defect	1.66 (0.96-2.87)	-	-	-	**1.87 (1.03-3.38)**	-	-
Fixed defect alone	1.28 (0.75-2.19)	-	-	-	1.39 (0.78-2.47)	-	-
SDS**	1.11 (0.93-1.33)	-	-	-	-	1.15 (0.93-1.41)	-
SSS**	1.05(0.97-1.14)	-	-	-	-	-	1.06 (0.95-1.18)
Total Chi-square	-	16.1	16.5	20.6	20.7	19.3	19.1

Values are expressed as Cox proportional hazard ratio with 95% confidence interval.

SPECT MPI = single-photon emission computed tomography myocardial perfusion imaging.

SDS = summed difference score

-SSS = summed stress score.

- = variable excluded. Bolt values are significant.

*per unit increment

**per 5.6% of the total myocardium increment.

Predictors of long-term outcome

Univariable and multivariable predictors of all-cause mortality are summarized in Table 2. Based on the maximum length of prognostic value at Kaplan-Meier analysis the univariable and multivariable predictors are shown at a follow-up duration of 5 years. Univariable predictors of all-cause mortality were age, gender and an abnormal SPECT MPI (Table 2). The presence of a reversible perfusion defect and SDS were univariable predictors of cardiac mortality and an abnormal SPECT MPI, the presence of a reversible perfusion defect and SDS were univariable predictors of major cardiac events.

Multivariable analyses were performed to determine the maximum length of the prognostic value, or the "warranty period", of SPECT MPI. An abnormal SPECT MPI and the presence of a reversible defect provided incremental prognostic information for the prediction all-cause mortality up to a follow-up duration of 5 years, (Table 2). An abnormal SPECT MPI provided incremental prognostic information for the prediction of cardiac mortality up to a follow-up duration of 2 years. The presence of a reversible defect was a significant predictor of cardiac mortality during the entire follow-up. For the prediction of major cardiac events, an abnormal SPECT MPI was a significant predictor up to 2 years of follow-up. The presence of a reversible defect was a significant predictor of major cardiac events during the entire follow-up duration.

DISCUSSION

The present study evaluated the long-term prognostic value of SPECT MPI in HTx recipients, examining the incremental prognostic value of SPECT MPI over clinical and stress test variables. The results show that stress SPECT MPI provides useful prognostic information for the prediction of cardiovascular outcomes in HTx recipients. HTx recipients with a normal stress SPECT MPI have a significantly better prognosis as compared to patients with an abnormal stress SPECT MPI, up to 5-years after initial testing. After that period, the risk of adverse events does not significantly differ in patients with both normal and abnormal SPECT MPI. So, the warranty period of stress SPECT MPI in HTx recipients is approximately 5 years. As the multivariable analysis showed, the presence of a reversible perfusion defect was a significant predictor of all-cause mortality and cardiac events during the entire follow-up.

SPECT MPI using either exercise or pharmacological stress is a commonly used non-invasive technique for the evaluation of known or suspected CAD. The prognostic value of dobutamine stress SPECT MPI has been firmly established in non-transplant patients.[15-17] However, there are scarce data regarding the utility of stress SPECT MPI for the prediction of long-term outcome in HTx recipients.[10] This creates uncertainties in the prognostic stratification in these patients. Previous studies have reported the short- and medium term outcome of SPECT MPI in HTx recipients.[10, 11, 18-20] Bacal et al.[18] studied 39 patients (mean age was 48±13 years) after orthotopic HTx who underwent thallium SPECT MPI for the detection of CAV. In this small number of patients, thallium SPECT MPI was not a significant predictor of outcomes during the 4-year follow-up period. Hacker et al.[8] followed 77 HTx recipients with a mean age of 53±11 years (80% males) who underwent dobutamine stress technetium SPECT MPI. Cardiac events (revascularization, heart failure, death and/or MI) occurred in 32% of the patients with an abnormal SPECT MPI during a mean follow-up duration of 22 months. The authors concluded that dobutamine stress SPECT MPI identified patients at risk for future cardiac events. A normal SPECT MPI was associated with a negative predictive value of 98% for cardiac events. Wu et al.[20] investigated the value of dobutamine thallium SPECT to detect CAV and to predict clinical events in 47 HTx recipients. Mean age was 51.6±11.7 years (79% males). During a mean follow-up period of 40 months, a total of 6 patients died, of whom 4 patients due to cardiac causes. Only large reversible perfusion defects on stress SPECT MPI were associated with a significant risk of cardiac mortality (p=0.002). In 110 HTx recipients, Manrique et al.[19] investigated the diagnostic and prognostic value of thallium and technetium SPECT MPI. Mean age was 53±13 years (85% males). During a mean follow-up period of 4.8 years, a stress perfusion defect >3 segments was an independent predictor of cardiac mortality. SPECT MPI identified patients with a high risk of poor outcome. As the authors noted, a normal SPECT MPI might alleviate the need for coronary angiography. More recently, Wenning et al.[10] studied 104 HTx recipients (mean age 50.7±12.2 years and 85% were male) who underwent ^{99m}Tc-tetrofosmin SPECT. During a mean follow-up of 9.4 years no difference was observed according to all-cause mortality between patients with homogeneous perfusion (defined as <10% decreased tracer uptake of the myocardial segments) and inhomogeneous perfusion (defined as decreased tracer uptake of >20% of the myocardial segments).

The present study differs from these previous studies for several reasons. First, these previous studies used thallium-201[18, 20], ^{99m}Tc-tetrofosmin[10], ^{99m}Tc-sestamibi[8] or both thallium-201 and ^{99m}Tc-sestamibi[19] as radionuclide tracers. The current study evaluated SPECT MPI in HTx recipients using ^{99m}Tc-tetrofosmin as a tracer, which is currently the

most commonly used tracer along with ^{99m}Tc-sestamibi.[21] Second, some of these previous studies[8, 19, 20] concluded that SPECT MPI provides prognostic information for the prediction of cardiac events in HTx recipients, whereas other studies found no significant prognostic information.[10, 18] The latter studies[10, 18] had a relatively longer follow-up period (9.4 and 4 years respectively). All these previous studies have not investigated the warranty period of stress SPECT MPI in HTx recipients. The current study found that the warranty period of stress SPECT MPI in HTx recipients is approximately 5 years. Third, the range of follow-up duration in these previous studies varies between 22 months and 9.4 years. In a previous study of our center[11] the same population was studied with a median follow-up of 2.5 years. The current study evaluated the long-term outcome (>10years) after SPECT MPI in HTx recipients and extends the conclusions drawn from these previous studies. The results shows that SPECT MPI has a limited predictive value of adverse outcome in these patients. HTx recipients with a normal stress SPECT MPI have a relatively favorable outcome compared to patients with an abnormal stress SPECT MPI up to 5 years after the test. This is in line with previous studies indicating that a warranty period exists after a normal SPECT MPI.[22] CAV apparently is a chronic progressive disease in HTx recipients that may alter the risk status of the patients over time.

In the annually published report of the International Society for Heart and Lung Transplantation (ISHLT) the median survival of HTx recipients between 1982 and 2013 was 11 years.[23] Due to advanced immunosuppressive therapy and prevention and treatment of opportunistic infections survival of patients after HTx has improved.[23, 24] The median survival in the present study was 12.8 years. Patients in the current study were enrolled form 1992. So, according to the median survival the present findings are comparable with this ISHLT report.

Due to denervation of the allograft and incomplete reinnervation, angina pectoris is usually lacking in HTx recipients. First clinical signs of CAV in HTx recipients include heart failure, silent MI and sudden death.[25] As a consequence, screening for early detection of CAV is required. Therefore, in most centers HTx recipients undergo an annual or biannual coronary angiography during the first five years following cardiac transplantation to search for asymptomatic CAV.[26] However, many HTx recipients with clinical cardiac events do not have significant disease on coronary angiography.[27] Moreover, invasive coronary angiography has inherent risks. As a result, there is a continuing need for noninvasive techniques to evaluate CAV. The results of the current study shows that dobutamine stress SPECT MPI is useful is risk stratifying HTx recipients up to 5 years after testing.

The ISHLT guidelines for the care of HTx recipients[28] state that SPECT MPI may be useful for diagnosing CAV in HTx recipients unable to undergo invasive evaluation. The sensitivity of dobutamine SPECT MPI has been reported to be 90% and a specificity of 60% in this patient cohort. The negative predictive value of the test was found to be 79%.[13] During the first five years after transplantation annual coronary angiography is recommended. In patients with kidney disease, dobutamine stress echocardiography (DSE) represents an alternative. After five years following transplantation, DSE is recommended annually in low-risk patients (defined as normal coronary angiography at five years). For patients with poor echocardiographic quality dobutamine stress SPECT MPI is a feasible alternative.[28] The present findings support the frequent monitoring of HTx recipients and the role of noninvasive dobutamine stress SPECT MPI in order to avoid coronary angiography when possible. In our center, we conduct in the first and fourth year after HTx a coronary angiogram, followed by yearly SPECT MPI from the sixth year after HTx. CAG was performed after the fourth year if the annual perfusion scintigraphy was positive, or when ischemia was suspected due to cardiac markers or clinical, electrocardiographic or echocardiographic criteria.

This study has some limitations. First, at time of SPECT MPI gated SPECT was not routinely performed. Functional data derived from gated SPECT provides additional information. Second, no attenuation or scatter correction was used for SPECT MPI. Application of attenuation or scatter correction may have further improved the accuracy of this technique. Third, CAV is a major complication associated with higher mortality in HTx recipients.[3] In the present study, angiographic data to examine CAV were not evaluated. However, the endpoints used in this study are cardiac events related to CAV.

In conclusion, stress ^{99m}Tc-tetrofosmin SPECT MPI provides valuable prognostic information for the prediction of outcome in HTx recipients. Patients with a normal stress ^{99m}Tc-tetrofosmin SPECT MPI have a significantly better prognosis as compared with those with an abnormal study, up to 5 years after initial testing.

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Chapter 7

Eleven-year prognostic value of dobutamine stress ^{99m}Tc-sestamibi myocardial perfusion imaging in patients with limited exercise capacity

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ABSTRACT

Myocardial perfusion single-photon emission computed tomography is a routine technique for the evaluation of coronary artery disease. However, information on the very long term prognostic value of dobutamine stress single-photon emission computed tomographic myocardial perfusion imaging (MPI) in patients with limited exercise capacity is scarce. The aim of this study was to assess the long-term prognostic value of dobutamine stress technetium-99m (^{99m}Tc)sestamibi MPI in these patients. The study population consisted of a high-risk cohort of 531 consecutive patients with limited exercise capacity who underwent dobutamine stress ^{99m}Tc-sestamibi MPI for the assessment of known or suspected coronary artery disease. Follow-up was successful in 528 patients. Because of early revascularization, 55 patients were excluded. The present data are based on 473 patients. The end points were all-cause mortality, cardiac death, nonfatal myocardial infarction, and late (>60 days) coronary revascularization. Kaplan-Meier survival curves were performed and univariate and multivariate analyses were performed to identify predictors of very long term outcome. The mean age of the patients was 61±12 years, and 58% were men. Abnormal results (defined as the presence of reversible or fixed defects) were observed in 312 patients (66%). During a mean follow-up period of 11.3±6.7 years, 287 patients (61%) died (all-cause mortality), of whom 125 (26%) died due to cardiac causes. Nonfatal myocardial infarction occurred in 59 patients (12%). Late coronary revascularization was performed in 61 patients (13%). Univariate predictors of major cardiac events included age, male gender, previous infarction, diabetes mellitus, history of angina, heart failure, ST-segment changes, abnormal results on ^{99m}Tc-sestamibi scan, reversible defect, fixed defect, summed rest score, and summed stress score. Multivariate analysis identified abnormal results on MPI as a strong independent predictor of major adverse cardiac events.

In conclusion, in patients with limited exercise capacity, dobutamine stress ^{99m}Tc-sestamibi single-photon emission computed tomography provides incremental prognostic information in addition to clinical and stress test parameters for the prediction of very long term outcomes.

INTRODUCTION

Globally, coronary artery disease (CAD) remains a major cause of both morbidity and mortality.[1] Myocardial perfusion imaging with single-photon emission computed tomography (SPECT) is a routine technique for the diagnosis and risk stratification of patients with known or suspected CAD.[2,3] Technetium-99m (^{99m}Tc)-sestamibi is a widely used tracer in conjunction with SPECT. In patients with limited exercise capacity because of disease complications such as stroke, neuropathy, or peripheral vascular disease, dobutamine stress testing represents an achievable alternative to vasodilator stress. The prognostic value of dobutamine stress ^{99m}Tc-sestamibi myocardial perfusion imaging (MPI) for detecting CAD has been well documented in various patient groups for short- and medium-term follow-up.[4-10] However, very long term prognostic data on dobutamine stress ^{99m}Tc-sestamibi MPI are lacking. Accordingly, the aim of this study was to determine the long-term prognostic value of dobutamine stress ^{99m}Tc-sestamibi MPI for the prediction of adverse events in a high-risk cohort of patients with limited exercise capacity.

METHODS

The study population consisted of 531 consecutive patients with limited exercise capacity as previously described.[10] These patients were referred between 1990 and 1995 for dobutamine stress ^{99m}Tc-sestamibi SPECT for the evaluation of suspected or known CAD. Follow-up was successful in 528 (99.4%) of 531 patients. All patients gave informed consent before testing and the local ethics committee approved the study protocol. Fifty-five patients underwent early coronary revascularization 60 days after MPI and were excluded from analysis (35 with coronary arterial bypass graft placement and 20 with percutaneous transluminal coronary angioplasty). This exclusion was based on the previously published data indicating that referral to coronary revascularization in the first 60 days after nuclear testing tends to be based on the results of the scan and that referral to revascularization >60 days after nuclear testing tends to be based on the worsening of the patient's clinical status.[11] In September 2012 follow-up was performed. As a result, the current data are based on 473 patients with complete follow-up. A structured interview and clinical history were obtained, including assessment of cardiac risk factors, prior to dobutamine stress testing. A blood pressure ≥140/90 mmHg, or treatment with antihypertensive medication was considered as hypertension. A fasting glucose

level ≥7.8 mmol/L or the need for insulin or oral hypoglycemic agents was considered as diabetes mellitus. Hypercholesterolemia was defined as a total cholesterol ≥6.4 mmol/L, or treatment with lipid-lowering medication.

The stress testing protocol after dobutamine administration has been described previously.[10] Dobutamine was injected intravenously up to a maximum dose of 40 µg/kg/min. If the test end point was not reached at a maximum dose of dobutamine, up to 1 mg of atropine was administered intravenously. During stress testing, blood pressure, heart rate and electrocardiographic leads were continuously monitored. Test end points were achievement of target heart rate (85% of maximum age and sex-predicted heart rate); horizontal or downsloping ST segment depression of > 2 mm at an interval of 80 msec after the J point, as compared with the baseline measurement; ST segment elevation >1 mm in patients without previous myocardial infarction (MI); severe angina; systolic blood pressure decrease >40 mm Hg, as compared with the baseline measurement; blood pressure >240/120 mm Hg; or clinically important cardiac arrhythmias. To overcome the side effects of dobutamine, metoprolol was intravenously administered and atropine was used if the effects did not revert spontaneously after termination of dobutamine infusion.

A dose of 370 MBq of ^{99m}Tc-sestamibi (Cardiolite; Bristol-Myers Squibb Pharma Belgium, Brussels, Belgium) was administered intravenously approximately 1 minute before cessation of the stress test. For studies performed with the patient at rest, 370 MBq of sestamibi was injected ≥24 hours after stress testing. Images were acquired with a Gammasonics singlehead Rota camera (Orbiter; Siemens, Iselin, NJ) without attenuation or scatter correction, by using a low-energy all-purpose collimator. Thirty-two projections were obtained over a 180° arc, from left posterior oblique to right anterior oblique, with an acquisition time of 45 seconds per projection. Data were collected in a 64x64 matrix (word mode), and images were reconstructed by using a filtered back-projection algorithm and a ramp reconstruction filter. Transverse images were reconstructed by using a software package (SPETS; Nuclear Diagnostics, Hägersten, Sweden). From the 3-dimensional data, oblique (shortaxis) and sagittal (vertical long-axis) images obtained perpendicular and parallel to the long axis, respectively, were reconstructed. The scan interpretation were semiquantitatively performed by using visual analysis assisted by circumferential profile analysis. Profile curves 2.5 SDs below normal perfusion were considered abnormal. Images obtained at stress and rest were reviewed side by side at a computer display with consensus reading by 2 experienced observers who were blind to the patients' clinical data. A third observer was consulted in case of disagreement of a decision. In this study, the original interpretations of the images were

used. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest on ≥2 contiguous segments or sections. A fixed perfusion defect was defined as a perfusion defect on stress images on ≥2 contiguous segments or sections which persist on rest images. The presence of a fixed and/or reversible perfusion defect was considered as an abnormal scan. Each myocardial segment was assigned a score from 0 to 3 (0=normal, 1=slightly reduced, 2=moderately reduced, 3=severely induced / absent uptake). Summed stress score (SSS) and summed rest score were calculated by the summation of the scores at stress and rest, respectively. The SDS (summed difference score) was considered representative of the extent and severity of myocardial ischemia. Standard 17-segment-based scores were calculated and converted into % per myocardium by dividing the summed scores by the maximum potential score, and multiplying by 100.[12]

Clinical outcome data were obtained by contacting the patient, the patients' general practitioners, civil registries and reviewing hospital records. Endpoints were cardiac death, nonfatal myocardial infarction and late coronary revascularization. Cardiac death included death caused by acute myocardial infarction, significant arrhythmias or refractory congestive heart failure and sudden death occurring without another explanation. Using the participants' civil registration number, we linked individual level information to differentiate cardiac death from non-cardiac death. Hard cardiac events were defined as the occurrence of cardiac death or nonfatal myocardial infarction. The combined endpoint of cardiac death, nonfatal myocardial infarction or coronary revascularization was considered as major adverse cardiac events (MACE).

IBM SPSS statistical software version 22 was used to analyze data. Variables were expressed as mean±SD or number. Continuous data were compared by using the Student's t test. Chi-square tests were used to compare categorical variables. Univariable and multivariable Cox proportional hazards regression models were used to identify independent predictors of late cardiac events. Variables were selected in a stepwise forward selection manner with entry and retention set with a p value of 0.05. A variable's risk was expressed as a hazard ratio with a corresponding 95% confidence interval. The incremental value of abnormal myocardial perfusion scintigraphy over the clinical variables was determined using a multivariate analysis according to 3 models. In model 1, an abnormal scan was entered as a scanning variable. In model 2, the scanning variables, the presence of a fixed and reversible defect, were entered. In model 3, SRS and SDS were entered. The probability of survival was calculated by using the Kaplan-Meier method, and survival curves were compared by using the log-rank test. A $p < 0.05$ was considered statistically significant.

RESULTS

The clinical data of the 473 patients are presented in Table 1. During dobutamine stress testing there was a significant increase in heart rate (from 70±14 to 136±17 beats/min, p<.001) and systolic blood pressure (140±23 mmHg to 146±31 mmHg, P < .001). The highest dobutamine dose was 10 µg/kg/min in 3 (1%), 20 µg/kg/min in 15 (3%), 30 µg/kg/min in 66 (14%), and 40 µg/kg/min in 389 patients (82%). Atropine was added in 196 (41%) patients. Patients who received ß-blockers (120 [65%] of 185) more frequently received atropine compared to those who not received ß-blockers (76 [26%] of 288, P<.001). Test findings were inconclusive (failure to achieve target heart rate in the absence of perfusion abnormalities) in 43 (9%) patients. These patients were not excluded from the prognostic data reported. There were no patients who experienced myocardial infarction or ventricular fibrillation. Side effects were atrial fibrillation in five patients (1%), short ventricular tachycardia (<10 complexes) in 19 patients (4%), severe hypotension (decrease in systolic pressure >40 mm Hg) and severe hypertension (blood pressure >240/130 mm Hg) both in 3 patients (0.6%). As minor side effects nausea occurred in 18 (4%), chills in 22 (5%), and headache in 29 patients (6%).

Table 1. Baseline characteristics

n = 473	**Number (%)**
Age (years)	61 ± 12
Men	273 (58%)
Hypertension	214 (45%)
Diabetes mellitus	69 (15%)
Smoker	122 (26%)
Hypercholesterolemia	116 (25%)
Congestive heart failure	84 (18%)
Beta blocker therapy	185 (39%)
Prior myocardial infarction	210 (44%)
Previous coronary artery bypass graft	92 (19%)
Previous percutaneous coronary intervention	75 (16%)

The results of SPECT were abnormal in 312 patients (66%). Perfusion abnormalities were reversible defects in 72 patients (15%). Most of the patients had fixed defects (126 patients [27%]), suggesting that they had myocardial damage. One hundred fourteen patients (24%) had fixed and reversible (or partially reversible) defects. During a mean follow-up period of 11.3±6.7 years, 287 patients (61%) died (all-cause mortality), of whom 125 (26%) died due to cardiac causes. Nonfatal myocardial infarction occurred in 59 patients (12%). Late (>60 days) coronary revascularization was performed in 61 patients (13%).

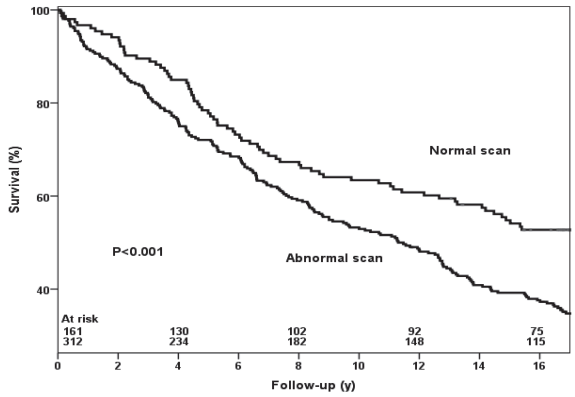

Figure 1. Kaplan-Meier survival curves for all-cause mortality. Survival was significantly different between patients with normal and those with abnormal results on dobutamine stress ^{99m}Tc-sestamibi myocardial perfusion SPECT.

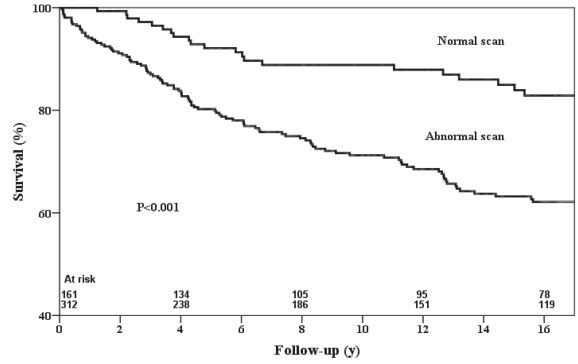

Figure 2. Kaplan-Meier survival curves for cardiac death. Survival was significantly different between patients with normal and those with abnormal results on dobutamine stress ^{99m}Tc-sestamibi myocardial perfusion SPECT.

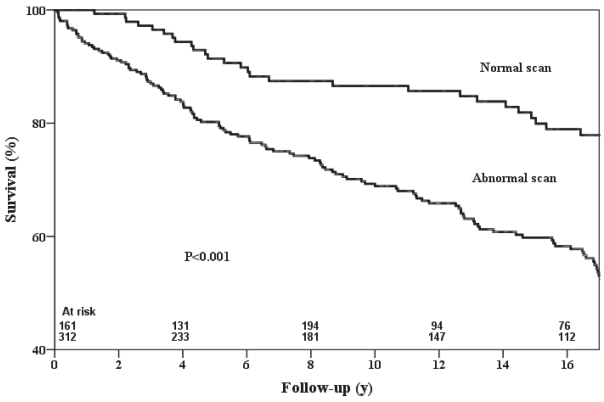

Figure 3. Kaplan-Meier survival curves for hard cardiac events (cardiac death and non fatal myocardial infarction). Event-free survival was significantly different between patients with normal and those with abnormal results on dobutamine stress ^{99m}Tc-sestamibi myocardial perfusion SPECT.

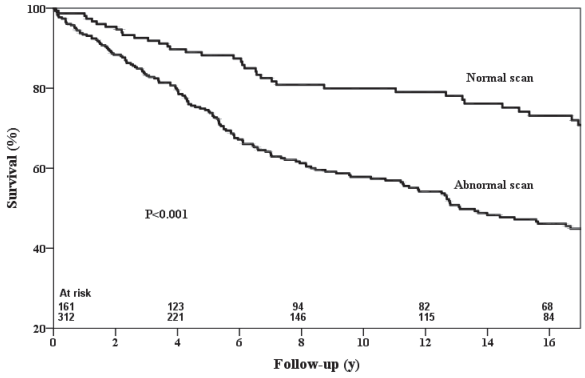

Figure 4. Kaplan-Meier survival curves for major adverse cardiac events (cardiac death, non fatal myocardial infarction or revascularization). Event-free survival was significantly different between patients with normal and those with abnormal results on dobutamine stress ^{99m}Tc-sestamibi myocardial perfusion SPECT.

Kaplan-Meier curves in relation to all-cause mortality, cardiac death, hard cardiac events, and major adverse cardiac events are presented in Figures 1 to 4. The survival curves demonstrate that patients with normal results on SPECT had a relatively low risk for all-cause mortality, cardiac death, hard cardiac events, and major cardiac events compared with those with abnormal findings. The annualized event rates for cardiac death for patients with normal results on SPECT were significantly lower than for those with abnormal findings (1.2% vs 2.5%, p <0.001). The annualized hard cardiac event rate for patients with normal results on SPECT was also significantly lower (3.4%) compared

with patients with abnormal findings ([4.3%] p <0.001). The annualized rates for major adverse cardiac events were 2.2% in patients with normal results on SPECT and 4.4% in those with abnormal findings (p <0.001).

Univariate predictors of major cardiac events were age, male gender, prior myocardial infarction, diabetes mellitus, history of angina and congestive heart failure, ST-segment changes, abnormal results on SPECT, presence of reversible defect, presence of fixed defect, summed rest score, and summed stress score (Table 2). Multivariate analysis demonstrated that clinical data (age, male gender, previous myocardial infarction, and congestive heart failure) were predictors of very long-term outcomes. Model 1 demonstrates that abnormal results on SPECT were an independent predictor of major adverse cardiac events (hazard ratio 1.53, 95% confidence interval 1.02 to 2.30).

Table 2. Predictors of major cardiac events (cardiac death, nonfatal infarction or revascularization) at univariable and multivariable analysis

		Multivariable HR (CI)			
Variable	**Univariable HR (CI)**	**Clinical data**	**Model I**	**Model II**	**Model III**
Age*	1.02 (1.01-1.04)	1.03 (1.01-1.04)	1.03 (1.01-1.04)	1.03 (1.01-1.04)	1.03 (1.01-1.04)
Men	1.93 (1.43-2.60)	1.69 (1.22-2.34)	1.61 (1.16-2.23)	1.69 (1.22-2.34)	1.69 (1.22-2.34)
Prior MI	2.19 (1.65-2.91)	1.63 (1.20-2.22)	1.46 (1.05-2.03)	1.63 (1.20-2.22)	1.63 (1.20-2.22)
Diabetes mellitus	1.70 (1.19-2.43)	*P=0.13*	*P=0.11*	*P=0.13*	*P=0.13*
Hypertension	*P=0.95*	*P=0.30*	*P=0.49*	*P=0.30*	*P=0.30*
Hypercholesterolemia	*P=0.22*	*P=0.34*	*P=0.30*	*P=0.34*	*P=0.34*
Angina pectoris	1.38 (1.02-1.87)	*P=0.66*	*P=0.43*	*P=0.66*	*P=0.66*
Smoking	*P=0.84*	*P=0.76*	*P=0.76*	*P=0.76*	*P=0.76*
Congestive HF	2.37 (1.71-3.29)	1.83 (1.30-2.58)	1.75 (1.24-2.48)	1.83 (1.30-2.58)	1.83 (1.30-2.58)
Stress test results					
Typical angina pectoris	*P=0.17*	*P=0.20*	*P=0.21*	*P=0.20*	*P=0.20*
ST-segment changes	1.60 (1.19-2.14)	1.35 (1.00-1.82)	P=0.09	1.35 (1.00-1.82)	1.35 (1.00-1.82)
Scan parameters					
Abnormal scan	2.40 (1.70-3.39)	-	1.53 (1.02-2.30)	-	-
Reversible defect	1.42 (1.07-1.87)	-	-	*P=0.38*	-
Fixed defect	1.49 (1.11-1.99)	-	-	*P=0.64*	-
SRS**	1.50 (1.23-1.95)	-	-	-	*P=0.55*
SDS**	*P=0.35*	-	-	-	*P=0.97*
SSS**	1.03 (1.01-1.04)	-	-	-	-

Statistically significant predictors of outcome are presented as hazard ratio (confidence interval), of all other variables the p-value is presented.

- = not included in the model; * = per unit increment; ** = per % myocardium increment; SDS = summed difference score; SRS = summed rest score; SSS = summed stress score.

DISCUSSION

We assessed the very long term prognostic value of dobutamine stress ^{99m}Tc-sestamibi MPI for the prediction of hard and major adverse cardiac events in a high-risk cohort of 473 patients with limited exercise capacity. Patients with normal results on stress ^{99m}Tc-sestamibi MPI had significantly better outcomes compared with those with abnormal findings. The survival curves continued to diverge during the follow-up period of 11.3±6.7 years, indicating a maintained prognostic value of ^{99m}Tc-sestamibi SPECT. Patients with abnormal results on SPECT had a significantly increased cardiac event rate compared with patients with normal findings. This study showed relatively high event rates during the long-term follow-up period. The high event rates may be explained by several factors. First, the study population was relatively old, and 44% had previous myocardial infarctions. Second, all patients underwent dobutamine stress testing because they were unable to perform adequate exercise tests. The inability to perform an exercise test is an adverse prognostic marker. Third, during the long-term follow-up period, which was complete for nearly all patients, natural progression of CAD may have occurred.

Previous studies have examined the prognostic value of dobutamine stress SPECT for the prediction of cardiac events during short- to medium-term follow-up.[4-10] It has been demonstrated that normal results on stress SPECT are associated with a benign prognosis. Shaw and Iskandrian[13] performed a pooled analysis of 19 studies including 39,173 patients and reported a hard event rate of 0.6%/year for patients with normal results on SPECT. Senior et al[4] followed 61 patients who underwent coronary arteriography for the evaluation of chest pain who underwent dobutamine stress ^{99m}Tc-sestamibi single-photon emission computed tomographic MPI for a median follow-up of 19 months. The investigators concluded that dobutamine stress ^{99m}Tc-sestamibi SPECT is a good predictor of future cardiac events. Calnon et al[5] studied 308 patients who underwent dobutamine stress ^{99m}Tc-sestamibi SPECT. During a mean time period of 1.9 years, cardiac event rates were significantly higher in patients with abnormal results on SPECT (10%/year) compared with those with normal findings (2.3%/year). Navare et al[8] described 1,367 patients with known or suspected CAD who underwent dobutamine stress ^{99m}Tc-sestamibi SPECT. During an average follow-up period of 25 months, the annualized cardiac event rate was 2.5% in patients with normal results on SPECT and 7.6% in those with abnormal findings.

In the present study, the incremental prognostic value of dobutamine stress SPECT over clinical data was maintained during the long-term follow-up period in patients

with limited exercise capacity. Previously, we reported 8-year follow-up in these 473 patients who underwent dobutamine stress ^{99m}Tc-sestamibi SPECT.10 In that study, patients with normal results on SPECT maintained a low event rate during entire follow-up period. In the present very long term follow-up study, patients with normal results on SPECT maintained favorable event-free survival in contrast to patients with abnormal findings, who had significantly higher annualized event rates. So, the findings of the present study extend the conclusions drawn from the previous prognostic studies on short-, medium-, and long-term follow-up.[4-10]

This study had some limitations. First, 9% of the patients failed to achieve target heart rates in the absence of perfusion abnormalities. The prognostic value could have been higher if ß blockers were ceased before stress testing. Second, no attenuation or scatter correction was used for SPECT. Recent data indicate that attenuation correction may improve risk stratification.[14,15] Third, previous data have demonstrated the superiority of gated SPECT to nongated SPECT in outcome prediction. However, in this study, we analyzed the prognostic value of nongated SPECT. Fourth, recent data[16] showed that stress MPI underestimates the extent of CAD, possibly because of the low myocardial extraction relative to hyperemic flow changes of the ^{99m}Tc-labeled tracers and the fact that only relative perfusion is evaluated.[17] This evidence could have influenced the outcome of this study. Finally, in this study, 1 of the end points was major adverse cardiac events, a composite end point of cardiac death, nonfatal myocardial infarction, and coronary revascularization. The use of a composite end point has inherent limitations.

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Chapter 8

Prediction of 14-year cardiovascular outcomes by dobutamine stress ^{99m}Tc-tetrofosmin myocardial perfusion SPECT in elderly patients unable to perform exercise testing

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ABSTRACT

Background. Dobutamine stress myocardial perfusion imaging (MPI) is a useful alternative for the evaluation of coronary artery disease (CAD) in elderly patients who are unable to perform an exercise stress test. However, data on the long-term prognostic value of stress MPI in elderly patients are lacking. Therefore, this study evaluated the long-term prognostic value of dobutamine stress MPI in elderly patients unable to perform an exercise test.

Methods. The study population consisted of 247 elderly patients (mean age 71±5 years) who underwent dobutamine stress single-photon emission computed tomography (SPECT) MPI. An abnormal SPECT study was defined as the presence of fixed and/or reversible perfusion defects. A summed stress score (SSS) was obtained to estimate the extent and severity of perfusion defects. End points during follow-up were all-cause mortality, cardiac mortality, and nonfatal myocardial infarction (MI).

Results. During a median follow-up of 14 years (range 12-16), 168 (68%) patients died (all-cause mortality), of which 56 (23%) were due to cardiac causes. Nonfatal MI occurred in 19 (8%) patients. Kaplan-Meier survival curves showed that MPI provided optimal risk stratification in patients with normal and abnormal MPI. Multivariable analysis identified an abnormal MPI as a strong significant predictor of all-cause mortality and cardiac events. A multivariable analysis also revealed that a reversible defect and SSS were strong long-term predictors of cardiac mortality and hard cardiac events.

Conclusion. Dobutamine stress ^{99m}Tc-tetrofosmin SPECT provides incremental prognostic information for the prediction of long-term cardiovascular outcomes in elderly patients, unable to perform exercise testing. Dobutamine stress MPI is useful in risk classifying elderly patients.

Key Words: ^{99m}Tc-Tetrofosmin – dobutamine stress SPECT – long-term prognosis – coronary artery disease – elderly

INTRODUCTION

Globally, deaths from cardiovascular disease are increasing, in particular due to the aging population. Between 1990 and 2013, the number of global deaths caused by cardiovascular disease has increased by 41%.[1] As a result of ageing of the population, more elderly patients are referred for diagnostic and prognostic cardiac evaluation. Stress myocardial perfusion imaging (MPI) is useful for the evaluation of coronary artery disease (CAD) in elderly patients.[2,3] A substantial proportion of the elderly population is unable to perform exercise stress testing, because of conditions such as degenerative joint disease or peripheral vascular disease. In such patients vasodilator stress testing is a useful alternative. In patients who also have contraindications for vasodilator stress (such as reactive airway disease or high-grade atrioventricular nodal block) dobutamine stress MPI is recommended according to the ASNC imaging guidelines for nuclear cardiology.[4] The prognostic value of MPI using single-photon emission computed tomography (SPECT) with ^{99m}Tc-tetrofosmin or ^{99m}Tc-sestamibi as tracers in elderly patients has been studied previously for short and medium term follow-up.[5-9] Long-term prognostic data to define the role of stress MPI for the prediction of cardiovascular outcomes in elderly patients are lacking. The long-term prognostic value of stress MPI in elderly patients may be impaired because of their increased underlying cardiovascular risk. Accordingly, the aim of the current study was to assess the long-term prognostic value of dobutamine stress ^{99m}Tc-tetrofosmin MPI for the prediction of cardiovascular outcomes in elderly patients unable to perform exercise testing.

METHODS

Study Population

This study included 272 consecutive elderly patients ≥65 years old who were unable to perform exercise testing and underwent dobutamine stress ^{99m}Tc-tetrofosmin SPECT for the evaluation of suspected or known CAD. The age cut-off was based on previous studies.[3,10] The current study is a continuation of a previous study[8] in which this population of elderly patients was evaluated with a mean follow-up of 3 years The reason to perform the current follow-up study was to assess the very long-term prognostic value of dobutamine stress SPECT. At the time of this study dobutamine was the preferred stressor in our nuclear cardiology laboratory and the mode of stress was determined by

the referring physician. Patients were enrolled between 1995 and 1999. Follow-up was complete for 270 (99.3%) patients. Twenty-three patients underwent coronary artery revascularization < 60 days of the test and were excluded. This exclusion was based on previous data indicating that in the first 60 days after the test, referral for coronary artery revascularization tends to be based on the SPECT results, whereas > 60 days after testing, referral for coronary artery revascularization tends to be based on deterioration of the patient's clinical status.[11] The present data are based on 247 patients. This study was not subject to the Dutch Medical Research Involving Human Subjects Act.[12,13] Therefore, approval from the local research ethics committee to conduct this retrospective study was not required at the time of enrollment. Moreover, the study was conducted according to the Declaration of Helsinki.[14] All patients consented participation in this study.

Clinical Data

Before dobutamine stress testing, a structured clinical interview and history were acquired and cardiac risk factors were assessed. Hypertension was defined as a blood pressure ≥140/90 mmHg or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level ≥7.8 mmol/L or the need for insulin or oral hypoglycemic medication. Hypercholesterolemia was defined as a total cholesterol ≥6.4 mmol/L or treatment with lipid-lowering medication.

Dobutamine Stress Testing

Dobutamine stress testing was performed according to a standard protocol as previously reported.[15] Dobutamine was infused through the antecubital vein, starting at a dose of 10 µg/kg/min for 3 min and increasing by 10 µg/kg/min every 3 min up to a maximum dose of 40 µg/kg/min. If the test endpoint was not reached at a dobutamine dose of 40 µg/kg/min, atropine (up to 1mg) was given intravenously. Blood pressure and heart rate were monitored and electrocardiography was recorded constantly. Test endpoints were: achievement of target heart rate (85% of maximum age- and sex-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; a systolic blood pressure fall >40 mm Hg, compared with baseline; blood pressure >240/120 mmHg; or significant cardiac arrhythmias. Metoprolol was available to reverse the adverse effects of dobutamine/atropine.

^{99m}Tc-Tetrofosmin SPECT MPI

Approximately 1 min before the termination of the dobutamine stress test, an intravenous dose of 370 MBq of ^{99m}Tc-tetrofosmin was administered. For resting studies, 370 MBq of tetrofosmin were injected at least 24 h after the stress study. Image acquisition was performed with a triple-head γ-camera system (Prism 3000 XP; Picker International). 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. Owing to corresponding of the septal part of the 2 basal slices to the fibrous portion of the interventricular septum and normally exhibits reduced uptake, this region was excluded from analysis. As a consequence, 47 segments were identified (3 long axis and 44 short axis). The interpretation of the scan was semiquantitatively performed by visual analysis and aided by circumferential profiles analysis. Stress and rest tomographic views were reviewed side by side by an experienced observer who had no knowledge of the patients' clinical information. A reversible perfusion defect was defined as a perfusion defect on the exercise images that partially or completely resolved at rest in ≥2 contiguous segments or slices. A fixed perfusion defect was defined as a perfusion defect on exercise images in 2 or more contiguous segments or slices, which persists on rest images. The presence of a fixed and / or reversible perfusion defect was considered as an abnormal study. Each myocardial segment was assigned a score from 0 to 3 (0 = normal; 1 = slightly reduced; 2 = moderately reduced; 3 = severely reduced or absent uptake). Summed stress score (SSS) was calculated by the summation of the scores of the myocardial segments at stress. Standard 17-segment based scores were calculated and converted to percent of the total myocardium (% myocardium) by dividing the summed scores by the maximum potential score, and multiplying by 100.[16]

Patient follow-up

Collection of follow-up data was performed by contacting the patient, the patient's general practitioner, civil registries, and review of hospital records. Follow-up data were obtained in September 2011. The date of the last review or consultation was used to determine follow-up time. Endpoints were all-cause mortality, cardiac mortality and nonfatal myocardial infarction (MI). Causes of death were obtained from the Central Bureau of Statistics Netherlands. Cardiac mortality was defined as death caused by myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac mortality. Nonfatal MI was described by chest pain complaints, a rise and fall of cardiac marker levels and

typical changes on electrocardiography (ECG). Hard cardiac events were defined as the occurrence of cardiac mortality or nonfatal MI.

Statistical Analysis

Continuous data were expressed as mean±SD, and percentages were rounded. Continuous variables were compared using the Student t test for unpaired samples. The cumulative survival was calculated using the Kaplan Meier method. Survival curves were compared with the log-rank test. Univariable and multivariable Cox proportional hazards regression models were used to investigate the additional value of MPI parameters. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval. First, clinical data were selected in a stepwise forward selection manner with entry and retention set of a significance level of 0.05. Significant clinical data were then used for including in the multivariable analysis. The incremental value of MPI over the clinical variables in the prediction of events was determined according to 3 models. In Model 1, the incremental value of abnormal MPI over the clinical data and stress test information was assessed. In Model 2, the presence of a fixed or reversible defect was entered. In Model 3 the SSS was entered. A p-value < 0.05 was considered statistically significant.

Table 1. Clinical characteristics.

N = 247	Number (%)
Age (years)	71 ± 5
Male gender	129 (52)
Hypertension	102 (41)
Smoking	52 (21)
Hypercholesterolemia	74 (30)
Heart failure	40 (16)
LBBB	15 (6)
Beta-blockers	105 (43)
Calcium channel blockers	111 (45)
ACE-inhibitors	69 (28)
Diuretics	66 (27)
Nitroglycerine	101 (41)
Digoxine	23 (9)
History of myocardial infarction	89 (36)
History of coronary angioplasty	44 (18)
History of coronary artery bypass surgery	48 (19)

ACE = angiotensin-converting-enzyme
LBBB = left bundle branch block

RESULTS

Demographics and Stress Test Results

Clinical characteristics of the 247 patients are presented in Table 1. The mean age of the study population was 71±5 years (range 65 and 86 years). A total of 48 patients (19%) were >75 years old. Dobutamine stress increased heart rate significantly (from 72±15 to 128±16 bpm, P < 0.001) and increased systolic blood pressure modestly (from 140±23 to 146±31 mm Hg, P < 0.001). The highest dobutamine dose was 10 µg/kg/min in 1 patient (0.4%), 20 µg/kg/min in 44 (18%), 30 µg/kg/min in 45 (18%), and 40 µg/kg/min in 157 (64%). In 88 patients (36%), atropine was added. Patients who were using beta blocker therapy during the dobutamine stress test more frequently received atropine than did patients not receiving beta blocker therapy (54 of 105, 51%, vs. 34 of 142, 24%, P < 0.001). A total of 181 patients (73%) achieved target heart rate. Achieving the target heart rate was not significantly different between patients with and without cardiac mortality (79 vs 72%, P=0.96) and hard cardiac events (75 vs 80%, P=0.42).

Side effects that occurred during dobutamine stress testing were generally self-limiting. These included atrial fibrillation in 5 patients (2%), short ventricular tachycardia (<10 complexes) in 6 patients (2.4%), and severe hypotension (decrease in systolic blood pressure >40 mm Hg) in 4 patients (1.6%). Minor side effects included nausea in 4 (1.6%), flushing in 3 (1.2%), and headache in 13 (5.3%). No patient experienced a myocardial infarction or ventricular fibrillation during or immediately after the stress test.

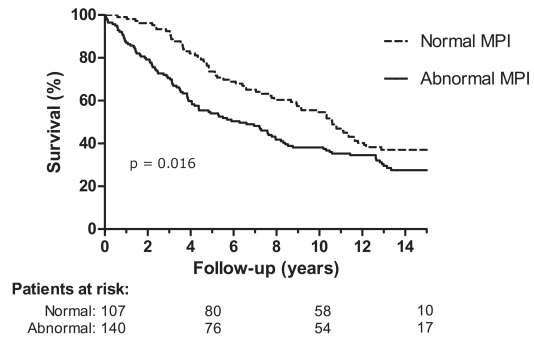

Figure 1. Kaplan-Meier survival curves for all-cause mortality.

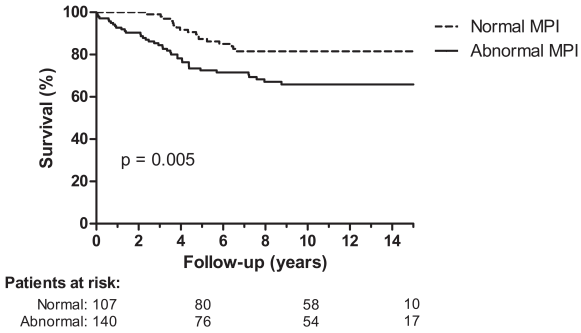

Figure 2. Kaplan-Meier survival curves for cardiac mortality.

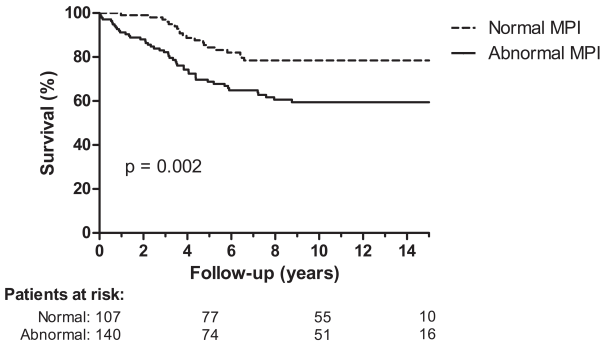

Figure 3. Kaplan-Meier survival curves for hard cardiac events (cardiac mortality and nonfatal myocardial infarction).

SPECT Results and Outcome

Abnormal MPI was detected in 140 patients (57%). A total of 20 (8%) patients showed reversible defects, 67 patients (27%) showed a fixed defect, while 53 patients (22%) showed both fixed and reversible defects. During a median follow up of 14 years (range 12-16), 168 (68%) patients died (all-cause mortality), of which 56 (23%) were due to cardiac causes. Nonfatal MI occurred in 19 (8%) patients. The Kaplan-Meier survival curves are shown in Figures 1- 3. The survival curves show that a normal MPI was associated with relatively low risk of all-cause mortality, cardiac mortality and hard cardiac events. Conversely, elderly patients with an abnormal MPI had a significantly increased risk of all-cause mortality and cardiac events.

Table 2. Univariable and multivariable predictors of all-cause mortality.

		Multivariable			
Variable	**Univariable**	**Clinical data**	**Model 1**	**Model 2**	**Model 3**
Men	1.84 (1.30-2.61)	1.69 (1.19-2.38)	P=0.12	P=0.07	1.49 (1.02-2.19)
Prior MI	*P=0.50*	*P=0.43*	-	-	-
Diabetes mellitus	1.58 (1.05-2.38)	*P=0.07*	-	-	-
Hypertension	1.88 (1.34-2.64)	1.76 (1.25-2.46)	1.83 (1.29-2.60)	1.77 (1.25-2.51)	1.72 (1.21-2.45)
Hypercholesterolemia	*P=0.97*	*P=0.66*	-	-	-
Smoking	1.49 (1.01-2.20)	*P=0.06*	-	-	-
Heart failure	1.99 (1.32-3.01)	1.75 (1.16-2.65)	1.72 (1.13-2.61)	1.69 (1.10-2.57)	1.63 (1.06-2.51)
Stress test results					
Angina pectoris	*P=0.46*	-	*P=0.19.*	*P=0.28*	*P=0.24*
ST-segment changes	*P=0.41*	-	*P=0.99*	*P=0.80*	*P=0.75*
Peak heart rate	*P=0.37*	-	*P=0.19*	*P=0.60*	*P=0.64*
Scan parameters					
Abnormal MPI	1.76 (1.24-2.51)	-	1.79 (1.22-2.64)	-	-
Fixed defect	*P=0.14*	-	-	*P=0.09*	-
Reversible defect	1.76 (1.24-2.51)	-	-	1.64 (1.13-2.38)	-
SSS*	1.20 (1.11-1.38)	-	-	-	*P=0.11*

Statistically significant predictors of outcome are presented as hazard ratio (confidence interval), of all other variables the P-value is presented. -, not included in the model.* per % myocardium increment.
MI = myocardial infarction. MPI = myocardial perfusion imaging. SSS = summed stress score.

Predictors of Outcome

Univariable and multivariable predictors of all-cause mortality, cardiac mortality and hard cardiac events are shown in Tables 2, 3 and 4 respectively. Among clinical variables, men, diabetes mellitus, hypertension, smoking and heart failure were significant predictors of all-cause mortality (Table 2). Diabetes mellitus, hypertension and heart failure were significant predictors of cardiac mortality (Table 3). Men, diabetes mellitus, hypertension and heart failure were univariable predictors of hard cardiac events (Table 4). A multivariable model revealed that an abnormal MPI and reversible defect were powerful predictors of all-cause mortality (Table 2). A multivariable analysis also revealed that an abnormal MPI, reversible defect and SSS provided incremental prognostic information over that provided by clinical and stress test variables for predicting cardiac mortality (Table 3) and hard cardiac events (Table 4).

Table 3. Univariable and multivariable predictors of cardiac mortality.

		Multivariable			
Variable	**Univariable**	**Clinical data**	**Model 1**	**Model 2**	**Model 3**
Men	*P=0.16*	*P=0.31*	-	-	-
Prior MI	*P=0.51*	*P=0.63*	-	-	-
Diabetes mellitus	2.17 (1.22-3.89)	*P=0.07*	-	-	-
Hypertension	2.55 (1.19-4.37)	2.43 (1.42-4.17)	2.41 (1.40-4.17)	2.28 (1.32-3.92)	2.32 (1.34-4.01)
Hypercholesterolemia	*P=0.47*	*P=0.60*	-	-	-
Smoking	*P=0.25*	*P=0.09*	-	-	-
Heart failure	2.79 (1.56-4.99)	2.60 (1.45-4.65)	2.39 (1.32-4.30)	2.37 (1.31-4.27)	2.18 (1.19-4.00)
Stress test results					
Angina pectoris	*P=0.93*	-	*P=0.65*	*P=0.88*	*P=0.70*
ST-segment changes	*P=0.50*	-	*P=0.53*	*P=0.76*	*P=0.76*
Peak heart rate	*P=0.87*	-	*P=0.99*	*P=0.90*	*P=0.96*
Scan parameters					
Abnormal MPI	2.23 (1.26-3.94)	-	2.49 (1.39-4.48)	-	-
Fixed defect	*P=0.34*	-	-	*P=0.17*	-
Reversible defect	1.94 (1.14-3.33)	-	-	1.92 (1.11-3.33)	-
SSS*	1.11 (1.00-1.12)	-	-	-	1.09 (1.01-1.18)

Statistically significant predictors of outcome are presented as hazard ratio (confidence interval), of all other variables the P-value is presented. -, not included in the model. * per % myocardium increment.

MI = myocardial infarction. MPI = myocardial perfusion imaging. SSS = summed stress score.

DISCUSSION

The main finding of this study is that dobutamine stress ^{99m}Tc-tetrofosmin SPECT provides long-term prognostic information for the prediction of all-cause mortality and cardiac events in elderly patients unable to perform exercise testing. Dobutamine stress MPI provided prognostic information incremental to clinical data and stress test results. Patients with a normal MPI had a relatively favorable long-term prognosis, in contrast to patients with an abnormal study who had a significantly increased risk of all-cause mortality and cardiac events. An abnormal MPI and the scan result reversible perfusion defect were strong significant predictors of all-cause mortality and cardiac events. Also the SSS was a strong long-term predictors of cardiac mortality and hard cardiac events.

Table 4. Univariable and multivariable predictors of hard cardiac events.

		Multivariable			
Variable	**Univariable**	**Clinical data**	**Model 1**	**Model 2**	**Model 3**
Men	1.70 (1.04-2.76)	P=0.07	-	-	-
Prior MI	P=0.73	P=0.83	-	-	-
Diabetes mellitus	1.76 (1.01-3.05)	P=0.19	-	-	-
Hypertension	2.31 (1.42-3.75)	2.24 (1.38-3.63)	2.16 (1.32-3.54)	2.02 (1.24-3.31)	2.00 (1.22-3.29)
Hypercholester-olemia	P=0.43	P=0.59	-	-	-
Smoking	P=0.28	P=0.14	-	-	-
Heart failure	2.24 (1.29-3.89)	2.11 (1.22-3.67)	1.90 (1.09-3.32)	1.90 (1.09-3.31)	P=0.05
Stress test results					
Angina pectoris	P=0.77	-	P=0.47	P=0.65	P=0.54
ST-segment changes	P=0.48	-	P=0.31	P=0.91	P=0.95
Peak heart rate	P=0.41	-	P=0.31	P=0.44	P=0.34
Scan parameters					
Abnormal MPI	2.32 (1.38-3.91)	-	2.72 (1.59-4.66)	-	-
Fixed defect	P=0.13	-	-	P=0.05	-
Reversible defect	1.79 (1.10-2.93)	-	-	1.85 (1.12-3.04)	-
SSS*	1.11 (1.01-1.12)	-	-	-	1.09 (1.02-1.18)

Statistically significant predictors of outcome are presented as hazard ratio (confidence interval), of all other variables the P-value is presented. -, not included in the model. * per % myocardium increment.
MI = myocardial infarction. MPI = myocardial perfusion imaging. SSS = summed stress score.

In the ageing population, CAD is a major health problem and cardiovascular disease is still the leading cause of mortality in elderly patients.[17] As a result, elderly patients with known or suspected CAD are frequently encountered in a nuclear cardiology practice. Stress MPI is an important noninvasive technique for the evaluation of patients with known or suspected CAD. Elderly patients are frequently unable to perform an exercise test due to several comorbidities (e.g. obstructive lung disease, peripheral vascular disease). Dobutamine stress MPI is a feasible alternative for these patients and also for patients who have contraindications for vasodilator (dipyridamole or adenosine) stress testing.[3] The present study included 247 elderly patients unable to perform an exercise test. We found that dobutamine stress MPI had incremental long-term prognostic value additional to clinical variables and stress test results.

Several previous studies have evaluated the short or medium-term prognostic value of SPECT MPI in elderly patients with a follow-up duration ranging from 4.4 to 6.4 years. Steingart et al.[5] studied 578 patients aged 65 years or older (mean age 70.7±4.4 years) who underwent exercise MPI. A multivariable model revealed that age, male gender, limitation of exercise tolerance and the number of ischemic segments on MPI were significant predictors of death or MI. The authors concluded that an abnormal MPI provided prognostic information during the 4 year follow-up period. Valeti et al.[6] followed 247 elderly patients with a mean age of 77 years undergoing exercise thallium-201 MPI. A total of 42 (17%) patients had a history of CAD (history of MI) compared to 89 (36%) patients in the current study. Also, patients without a previous percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) were included, while in the current study 37% had a previous coronary revascularization. In that study of Valeti et al.[6], exercise MPI was accurate for risk stratification in elderly patients who were able to exercise during a median follow-up duration of 6.4 years.

A total of 3 studies have assessed the short to medium-term cardiovascular outcomes after pharmacological stress MPI. De Winter et al.[7] studied cardiovascular outcomes in a total of 294 patients (median age 78 years) that underwent exercise (n=103) or dipyridamole stress (n=191) ^{99m}Tc-tetrofosmin SPECT. During a median follow-up of 25.9 months 47 deaths occurred of whom 27 cardiac deaths. The summed rest score (SRS) was a significant predictor of all-cause mortality and cardiac mortality. The authors concluded that gated SPECT provided independent and incremental information above clinical and perfusion SPECT. Nagao et al.[9] studied the outcomes of 175 patients (aged 75–85 years) that underwent exercise (n=49) or vasodilator stress (n=126) ^{99m}Tc-sestamibi SPECT. A total of 64 patients (37%) had a previous MI or coronary revascularization compared to 73% in the current study. During a mean follow-up of 3.4 years, SPECT results were predictive of cardiovascular outcomes. The results of those studies are in line with the current study, in that elderly patients with a normal SPECT have a relative good prognosis compared to patients with an abnormal SPECT who have an increased risk of all-cause mortality and cardiac events. In those studies the maximum follow-up duration was limited to 6.4 years. Schinkel et al.[8] has described the 3.3 year cardiovascular outcomes of this cohort of 247 elderly patients. Dobutamine stress ^{99m}Tc-tetrofosmin SPECT provided incremental prognostic information for the prediction of total mortality and cardiac events. However, no data exists on the long-term prognostic value of pharmacologic stress MPI. The present study extends the observations drawn from these previous studies and demonstrates the long-term prognostic value of dobutamine stress MPI in elderly patients.

More recently, Kwon et al.[18] studied a Medicare cohort including 5994 patients (age >65years) who underwent exercise (n=1664) or adenosine stress (n=4280) MPI. During a median follow-up of 2.4 years, the ability to exercise and the number of METs achieved were predictive of outcome. Amongst patients who were able to perform an exercise test, MPI did not provide incremental significant risk stratification. Several factors may explain why the findings in the study of Kwon et al. differ from the current findings. First, the current study included only patients who were unable to perform an exercise test, which is a marker of an adverse outcome in itself. Second, this study included a substantial number of patients with known CAD (36% had a previous myocardial infarction, 18% had previous coronary angioplasty, and 19% had previous coronary bypass surgery). Third, this study had a long-term and nearly complete follow-up which included information from the patient, the general practitioner, civil registries, and review of hospital records. The all-cause mortality rate during the long-term follow-up in the current study was 68% versus 6% during the median follow-up of 2.4 years in the previous study of Kwon et al. All these factors could have influenced the outcomes.

SPECT MPI is routinely used in conjunction with both ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin as tracers. The latter is used in the current study. Multiple studies have reported the prognostic value of ^{99m}Tc-sestamibi during dobutamine[19, 20] or adenosine induced stress[21] in various patient subsets. In a previous study of our center, 473 patients were studied who underwent dobutamine stress ^{99m}Tc-sestamibi SPECT and were followed for a mean follow-up of 8[19] and 11 years.[20] A total of 44% of the patients had a previous MI and 35% had undergone previous revascularization. A total of 312 (66%) patients had abnormal MPI, defined as the presence of a fixed and/or reversible perfusion defect. The incremental prognostic value of dobutamine stress SPECT was maintained during a follow-up duration of 11 years. In the present long-term follow-up study, elderly patients with normal MPI had a maintained favorable event-free survival compared to patients with abnormal MPI. So, the present findings are consistent with these previous studies. Also, Hachamovitch et al.[21] studied 684 elderly patients (mean age 80.3±4.1 years) who underwent ^{99m}Tc-sestamibi SPECT MPI. Of the 684 patients, 26% had a previous MI and 30% had prior revascularization. During a mean follow-up of 6 years, cardiac mortality rates were significant lower in patients with normal MPI in contrast to patients with abnormal MPI. The findings of the current study extends the conclusions drawn from this study.

Study limitations

The current study has limitations. First, all elderly patients were unable to perform exercise testing reflecting a high-risk population. The results of these study may not be applicable to other elderly patients. Second, no attenuation or scatter correction was used for MPI. Application of attenuation and scatter correction may have further improved the accuracy of SPECT MPI.[22] Third, due to the elderly patient population studied, the current results may not be extrapolated to younger patients. Fourth, gated SPECT was not routinely used in our laboratory at the time that this study was performed. Previous data have demonstrated the superiority of gated SPECT to non-gated SPECT in outcome prediction. However, in the current study, we analyzed the prognostic value of non-gated SPECT. Finally, the examined patient population was relatively small. This could have influenced the outcome of the multivariable analysis.

CONCLUSIONS

Dobutamine- stress MPI provides incremental prognostic information for the prediction of all-cause mortality and cardiac events on the long-term outcome in elderly patients unable to perform exercise testing. Patients with a normal MPI have a favorable prognosis of long-term outcome, in contrast to patients with an abnormal study.

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Chapter 9

Eight-year prognostic value of QRS duration in patients with known or suspected coronary artery disease referred for myocardial perfusion imaging

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ABSTRACT

QRS duration is of prognostic relevance in patients with several underlying heart diseases. Short-term data also shows the prognostic value of QRS duration in lower-risk groups of patients. The aim of this study was to investigate the long-term prognostic value of QRS duration in patients with known or suspected coronary artery disease (CAD). The study cohort consisted of 512 patients (308 men, mean age 60±11 years) who underwent myocardial perfusion imaging (MPI) for the evaluation of suspected or known CAD. Follow-up data were collected to assess the prognostic value of QRS duration, alongside clinical characteristics and MPI results. Endpoints were cardiac death and cardiac death or non-fatal myocardial infarction (MI). During a mean follow-up of 8.6±5.2 years, 290 patients (60%) died, with 139 deaths (27%) attributable to cardiac causes. Non-fatal MI occurred in 28 patients (6%), and 127 patients (25%) underwent late coronary revascularization (>3mo). Patients with QRS duration <120ms had annualized cardiac death rates and cardiac death/non-fatal MI rates of 2.2% and 2.3%, respectively, compared to 4.1% and 4.4% in patients with QRS duration ≥120ms. Multivariate models identified QRS duration ≥120ms as an independent predictor of both endpoints, on top of clinical characteristics and MPI results.

In conclusion, QRS duration ≥120ms is an independent predictor of cardiac death and cardiac death/non-fatal MI, after adjustment for clinical characteristics and MPI results.

Key Words: Coronary artery disease; Prognosis; QRS duration.

INTRODUCTION

Surface 12-lead electrocardiography (ECG) is a valuable tool for diagnostics due to its low cost and simplicity. These features also make ECG an attractive option for cardiac risk stratification. Several studies have reported the prognostic value of QRS duration in patients with heart failure, left ventricular systolic dysfunction and acute coronary syndrome.[1-5] Recent studies have also aimed to assess the prognostic value of QRS duration in the general population and in groups of lower risk patients on a short term.[9,10] As long-term data in the latter group of patients is lacking, this study aims to assess the long-term prognostic value of QRS duration in patients with known or suspected coronary artery disease (CAD) referred for myocardial perfusion imaging (MPI) for the evaluation of myocardial ischemia.

METHODS

The study population consisted of 512 patients (308 men, 204 women, mean age 60±11 years) referred for MPI for evaluation of suspected or known CAD. This study was not subject to the Dutch Medical Research Involving Human Subjects Act. Therefore, approval from the local research ethics committee to conduct this prospective follow-up study was not required at the time of enrollment. Moreover, the study was conducted according to the Helsinki Declaration.[11] All patients consented participation in this study. An assessment of cardiac risk factors was done prior to the procedure. Hypertension was defined as a blood pressure ≥140/90 mmHg or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level of ≥140mg/dL or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol level ≥200mg/dL or treatment with lipid-lowering medication.

Twelve-lead surface electrocardiography was performed at rest, digitally stored, and analyzed by an experienced observer unaware of any other data, according to recommendations for the standardization and interpretation of the electrocardiogram.[12] QRS duration was calculated as the mean of 3 separate measurements using a dedicated computer system (Mortara Instruments, Bilthoven, The Netherlands). The dobutamine-atropine stress test was performed as described.[13] Dobutamine was injected intravenously up to a maximum dose of 40 μg/kg/min. If the test end point was not reached at a maximum dose of dobutamine, up to 1 mg of atropine was administered intravenously. Blood pressure, heart rate, and electrocardiography were monitored

continuously. Test endpoints were achievement of target heart rate (85% of maximum age-predicted heart rate), horizontal or downsloping ST-segment depression of >2 mm, ST-segment elevation of >1 mm in patients without previous myocardial infarction (MI), severe angina, systolic blood pressure fall of >40 mmHg, blood pressure of >240/120 mm Hg, or significant arrhythmia. Metoprolol was available to reverse the (side) effects of dobutamine or atropine if these did not revert spontaneously after termination of dobutamine infusion.

Approximately 1 min before the termination of the stress test, an intravenous dose of 370 MBq technetium-99m-tetrofosmin was administered. For resting studies, 370 MBq tetrofosmin were injected at least 24 h after the stress study. Image acquisition was performed with a triple-head gamma-camera system (Prism 3000 XP; Picker International, Cleveland, OH). 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. The interpretation of the MPI was performed semi-quantitatively by visual analysis assisted by analysis of the circumferential profiles. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of each patient's clinical data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in ≥2 contiguous segments or slices in the 47-segment model. A fixed perfusion defect was defined as a perfusion defect on stress images in ≥2 contiguous segments or slices, which persists on rest images in the 47-segment model. An abnormal study was considered in the presence of a fixed or reversible perfusion defect (or both).

Follow-up data were obtained in 2011. The mean follow-up period was 8.6±5.2 years, the median follow-up for all survivors was 13.4 years. Outcome data were obtained by a questionnaire, evaluation of hospital records, contacting the patient's general practitioner, and/or review of civil registries. The cause of death was retrieved at Statistics Netherlands (www.cbs.nl). The date of the last review or consultation was used to calculate the follow-up time. Outcome events were cardiac death and cardiac death or non-fatal MI. Cardiac death was defined as death caused by acute MI, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac death.

Values were expressed as mean ±SD or number (%) and compared using Student's t test or chi-square test. The probability of survival was calculated using the Kaplan-Meier

method, and survival curves were compared using log-rank test. Univariate and multivariate Cox proportional hazard regression models were used to assess the prognostic value of QRS duration in relation to the outcomes described above. All variables were forced to enter the model simultaneously. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval (CI). A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA).

Table 1. Baseline characteristics

Variable	All patients (n = 512)	QRS duration <120ms (n = 397)	QRS duration ≥120 ms (n = 115)	*p* value
Age (years)	60 ± 11	60 ± 11	62 ± 10	0.062
Men	308 (60%)	224 (56%)	84 (73%)	<0.005
Hypertension	232 (45%)	178 (45%)	54 (47%)	0.688
Smoker	137 (27%)	104 (26%)	33 (29%)	0.594
Hypercholesterolemia	175 (34%)	135 (34%)	40 (35%)	0.877
Diabetes mellitus	91 (18%)	71 (18%)	20 (17%)	0.903
Prior heart failure	88 (17%)	49 (12%)	39 (34%)	<0.001
Old myocardial infarction	152 (30%)	106 (27%)	46 (40%)	<0.05
Prior CABG	83 (16%)	56 (14%)	27 (23%)	<0.01
Prior PCI	92 (18%)	70 (18%)	22 (19%)	0.7
ACE inhibitor	149 (29%)	104 (26%)	45 (39%)	<0.01
Betablocker	204 (40%)	163 (41%)	41 (36%)	0.297
Calcium channel blocker	229 (45%)	170 (43%)	59 (51%)	0.04
Diuretic	126 (25%)	80 (20%)	46 (40%)	<0.001
Nitrate	159 (31%)	118 (30%)	41 (36%)	<0.01

ACE = angiotensin converting enzyme; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

RESULTS

Clinical characteristics are presented in Table 1. Electrocardiography at rest demonstrated a QRS duration ≥120ms in 115 patients (22%), of which 41 (36%) had a right bundle branch block, 19 (17%) had a left bundle branch block, 1 had Wolff-Parkinson-White syndrome (1%) and 54 (46%) had an unspecified intraventricular block. QRS duration ≥120ms was significantly more observed in men and in patients with a previous MI, congestive heart failure and an abnormal MPI result.

An abnormal MPI was observed in 297 patients (58%). This included fixed defects in 143 patients (28%) and reversible defects in 154 patients (30%). Of the 154 patients with reversible defects, 107 patients (21%) had partially reversible defects and 47 patients (9%) had completely reversible defects. During follow-up, 290 patients (57%) died, of which 139 deaths (27%) were attributed to cardiac causes. Non-fatal MI occurred in 28 patients (6%), and late coronary revascularization (>3 months) was performed on 127 patients (25%).

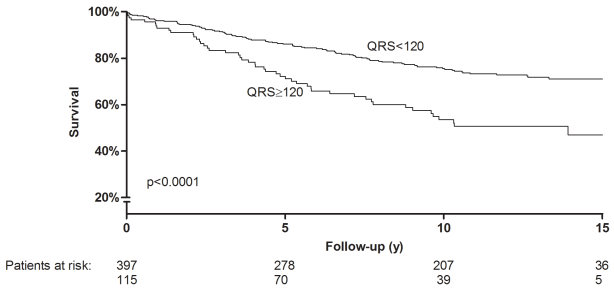

Figure 1. Kaplan-Meier survival curves for cardiac death according to QRS duration.

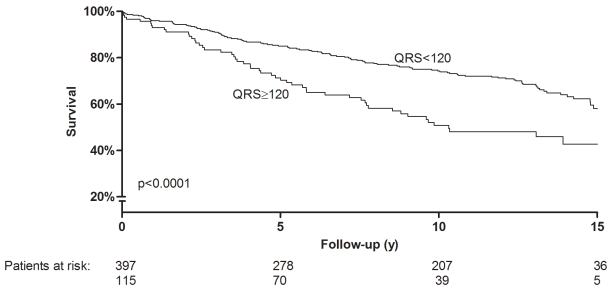

Figure 2. Kaplan-Meier survival curves for cardiac death or nonfatal MI according to QRS duration.

During the 8.6±5.2 year follow-up period, annualized cardiac death rates were 3.0% in patients with an abnormal MPI compared to 2.1% patients with normal MPI (p=0.0375). Cardiac death or non-fatal MI occurred at a rate of 3.2% in the abnormal MPI group compared to 2.3% in the normal MPI group (p=0.0185). Annualized cardiac death rates were 2.2% in patients with QRS duration <120ms and 4.1% in patients with QRS duration ≥120ms (p<0.0001). Cardiac death or non-fatal MI occurred at a rate of 2.3% in patients with QRS duration <120ms and 4.4% in patients with QRS duration ≥120ms (p<0.0001).

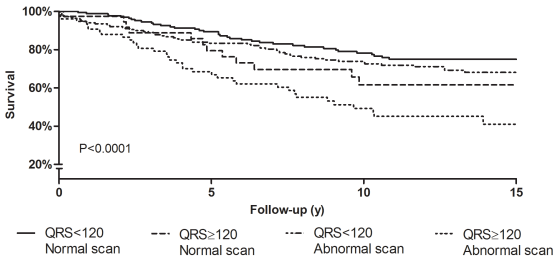

Figure 3. Kaplan-Meier survival curves for cardiac death according to QRS duration and MPI.

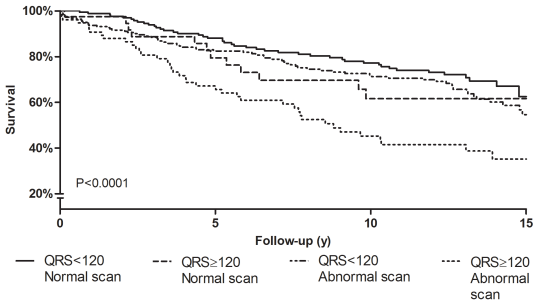

Figure 4. Kaplan-Meier curves for cardiac death or nonfatal MI according to QRS duration and MPI.

Kaplan-Meier survival curves for the endpoints cardiac death and cardiac death or non-fatal MI are presented in Figures 1 and 2. A significantly longer event-free survival for patients with QRS duration <120ms was seen for both endpoints. In Figures 3 and 4 survival is shown according to the combination of QRS duration and MPI results. QRS duration <120ms and a normal MPI was associated with a favorable prognosis and the combination of QRS duration ≥120ms and an abnormal MPI was associated with an adverse prognosis. An intermediate prognosis was observed in patients with normal QRS duration and an abnormal MPI, and in patients with QRS duration ≥120ms and normal MPI. This pattern was observed in both endpoints.

Univariate analysis results for each endpoint are shown in Tables 2 and 3. QRS duration ≥120ms was a strong predictor of cardiac death and cardiac death or non-fatal MI. An abnormal MPI was associated with an increased risk of cardiac death and cardiac death or non-fatal MI.

Table 2. Univariate and multivariate predictors of cardiac death

Variable	Univariate analysis	Model 1: Clinical variables	Model 2: Clinical variables and QRS duration	Model 3: Clinical variables, QRS duration, and MPI
Age (per year)	1.02 (1.01-1.04)	1.03 (1.01-1.04)	1.02 (1.01-1.04)	1.02 (1.01-1.04)
Male gender	1.80 (1.25-2.58)	1.94 (1.34-2.81)	1.81 (1.25-2.63)	1.77 (1.21-2.60)
Hypertension	1.63 (1.17-2.28)	1.68 (1.19-2.38)	1.71 (1.20-2.43)	1.75 (1.22-2.49)
Diabetes mellitus	1.96 (1.34-2.85)	1.86 (1.27-2.73)	1.93 (1.32-2.83)	1.87 (1.28-2.75)
Smoker	1.07 (0.74-1.56)	1.15 (0.77-1.70)	1.18 (0.80-1.76)	1.12 (0.75-1.67)
Hypercholesterolemia	0.91 (0.64-1.30)	0.82 (0.57-1.18)	0.81 (0.57-1.17)	0.78 (0.54-1.12)
QRS duration ≥120 ms	2.13 (1.50-3.02)	-	1.95 (1.36-2.78)	1.93 (1.35-2.76)
Abnormal MPI	1.45 (1.20-2.06)	-	-	1.24 (0.85-1.82)

Cox proportional hazard regression models were used to assess QRS duration as an independent predictor of cardiac death and cardiac death or non-fatal MI (Tables 2 and 3, respectively). Multivariate analysis was done separately for each endpoint according to 3 models. Clinical characteristics were entered into model 1. In model 2 clinical characteristics were entered together with QRS duration and model 3 combined clinical characteristics with QRS duration and abnormal MPI.

QRS duration ≥120ms was an independent predictor of cardiac death and cardiac death/MI and provides additional prognostic information over clinical variables and MPI. It was an especially strong predictor for cardiac death, even with the addition of MPI and clinical variables (HR 1.93, 95% CI [1.35-2.76]) (Table 2).

Table 3. Univariate and multivariate predictors of cardiac death or non-fatal myocardial infarction

Variable	Univariate analysis	Model 1: Clinical variables	Model 2: Clinical variables and QRS duration	Model 3: Clinical variables, QRS duration, and MPI
Age (per year)	1.03 (1.01-1.04)	1.03 (1.01-1.04)	1.03 (1.01-1.04)	1.02 (1.01-1.04)
Male gender	2.01 (1.43-2.82)	2.11 (1.50-2.96)	2.06 (1.46-2.92)	1.87 (1.31-2.67)
Hypertension	1.62 (1.19-2.21)	1.67 (1.22-2.29)	1.72 (1.66-2.40)	1.77 (1.27-2.45)
Diabetes mellitus	1.71 (1.19-2.45)	1.56 (1.09-2.24)	1.66 (1.16-2.39)	1.57 (1.09-2.26)
Smoker	0.98 (0.69-1.39)	1.04 (0.72-1.50)	1.07 (0.74-1.55)	1.02 (0.70-1.48)
Hypercholesterolemia	0.93 (0.68-1.29)	0.85 (0.61-1.18)	0.83 (0.59-1.16)	0.82 (0.59-1.15)
QRS duration ≥120 ms	1.94 (1.37-2.65)	-	1.69 (1.21-2.36)	1.68 (1.20-2.35)
Abnormal MPI	1.48 (1.07-2.05)	-		1.28 (0.90-1.82)

DISCUSSION

This study shows that QRS duration on surface electrocardiography is a strong predictor of long-term outcome of patients with known or suspected CAD. Patients with a QRS duration ≥120ms had an increased risk of cardiac death and the combined endpoint cardiac death/non-fatal MI. Kaplan-Meier survival curves showed that a QRS duration ≥120ms on surface electrocardiogram is associated with a significantly worse prognosis when compared to a QRS duration <120ms after a mean follow-up of 8.6±5.2 years for both endpoints. This association was still significant after adjustment for clinical variables and MPI results.

Previous studies have shown the prognostic significance of QRS duration in patients with cardiac disease, including heart failure,[1,2] left ventricular systolic dysfunction[3], acute coronary syndrome[4] and atrial fibrillation.[5] In the past years more evidence has come into existence addressing the prognostic significance of prolonged QRS duration in a relatively lower-risk group of patients, including patients referred for suspected CAD and the general population. Aro et al.[6] investigated prolonged QRS duration and found an increased risk of all-cause mortality, cardiac mortality and sudden arrhythmic death in 10.899 Finnish subjects after 30±11 years. Kurl et al.[7] found a 2.50-fold relative risk in subjects with QRS >110ms compared to subjects with QRS <96ms in 2049 men after a 19-year follow-up. Finally, a retrospective study conducted by Badheka et al.[8] found improved cardiovascular risk prediction when adding QRS duration to a model with traditional risk factors.

In a clinical setting, Schinkel et al.[9] demonstrated the predictive value of QRS duration for cardiac mortality (RR 1.8, 95% CI [1.2-2.7]) and cardiac death or non-fatal MI (RR 1.6, 95% CI [1.2-2.3]) in patients without known CAD referred for dobutamine stress echocardiography with a mean follow-up of 4.2±2.4 years. Elhendy et al.,[10] with a median follow-up of 3 years (maximum 8), have shown the prognostic significance of QRS prolongation as a predictor of mortality in a cohort of 4.033 patients with known or suspected CAD referred for exercise echocardiography, with QRS duration being incremental to clinical evaluation, exercise electrocardiography and echocardiography results. Our study adds to these results by showing the long-term prognostic significance of QRS duration for cardiac death and cardiac death or nonfatal MI.

The present study has some limitations. First, the study population consisted of both patients with suspected or known CAD and therefore our results cannot readily be extrapolated to a broader, asymptomatic low-risk population. Second, outcome data were obtained by a questionnaire, evaluation of hospital records, contacting the patient's

general practitioner, and/or review of civil registries. Data collection by a questionnaire has inherent limitations. Furthermore, inevitably the treating physicians of the patients in our study had access to our MPI results. It is possible and expected that physicians will opt for more intensive medical therapy and possibly coronary revascularization for patients with abnormal results. The prognosis of these patients will therefore be altered in their favor, possibly underestimating the prognostic value of QRS duration and MPI in these patients. In the period that the SPECT studies were performed, electrocardiogram gated acquisition was not routinely performed in our laboratory. Gated SPECT provides information on regional and global left ventricular function, which is an important predictor of prognosis. Future studies are needed to clarify the value of gated SPECT for the assessment of very long-term prognosis.

QRS duration is a simple, cheap and objective parameter and as such is a valuable tool in risk stratification. This is the first study with a long-term follow-up in patients with suspected or known CAD and extends the results of earlier studies.[9,10] The current findings suggest that both QRS duration and MPI results should be considered for optimal risk stratification. Future research is needed to develop a risk calculator for daily practice that incorporates both electrocardiographic and MPI data.

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Chapter 10

Dobutamine stress myocardial perfusion imaging: 8-year outcomes in patients with diabetes mellitus

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ABSTRACT

Aims. Many studies have examined the prognostic value of myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) for the prediction of short- to medium term outcomes. However, the long-term prognostic value of MPI in patients with diabetes mellitus remains unclear. Therefore, this study assessed the long-term prognostic value of MPI in a high-risk cohort of patients with diabetes mellitus .

Methods and results. A high-risk cohort of 207 patients with diabetes mellitus who were unable to undergo exercise testing underwent dobutamine stress MPI. Follow-up was successful in 206 patients; 12 patients were excluded due to early revascularization. The current data are based on the remaining 194 patients. Follow-up endpoints were all-cause mortality, cardiac mortality and nonfatal myocardial infarction. Kaplan-Meier survival curves were constructed and univariable and multivariable analyses were performed to identify predictors of long-term outcome. During a mean follow-up of 8.1±5.9 years, 134 (69%) patients died of which 68 (35%) died due to cardiac causes. Nonfatal myocardial infarction occurred in 24 patients (12%) and late (>60 days) coronary revascularization was performed in 61 (13%) patients. Survival analysis showed that MPI provided optimal risk stratification up to 4 years after testing. After that period, the outcome was comparable in patients with normal and abnormal MPI. Multivariable analyses showed that MPI provided incremental prognostic value up to 4 years after testing.

Conclusion. In high-risk patients with diabetes mellitus, dobutamine MPI provides incremental prognostic information in addition to clinical data for a 4-year period after testing.

INTRODUCTION

The worldwide prevalence of diabetes mellitus is increasing, concurrently with obesity and other comorbid conditions.[1] Despite significant advances in medical and invasive therapy, the leading cause of death in patients with diabetes mellitus remains coronary artery disease (CAD).[2] Myocardial perfusion imaging (MPI) is clinically useful for the evaluation of CAD in patients with diabetes mellitus. In patients with diabetes mellitus and suspected or known CAD, a strong evidence base has been accumulated that MPI provides diagnostic and prognostic information. Previous studies have shown that MPI provides incremental prognostic information in these patients for a short- to medium-term follow-up.[3–9] The follow-up period in these studies was on average 3.5 years. Currently, the long-term prognostic value of MPI in patients with diabetes mellitus is unclear. It is important to elucidate the long-term prognostic value of MPI in patients with diabetes mellitus because there are indications that over time a significant change in risk may occur, which may increase the annual cardiac event rate to 2% even in patients with a normal MPI.[10] Moreover, an accelerated progression of CAD may occur in patients with diabetes mellitus, which may influence the prognostic value of MPI. Diabetes mellitus is an important predictor of CAD progression.[11] Accordingly, this study assessed the long-term prognostic value of MPI in a high-risk cohort of patients with diabetes mellitus and limited exercise capacity.

METHODS

Patients selection

The study population consisted of a high-risk cohort of 207 consecutive patients with diabetes mellitus who were unable to undergo exercise testing and underwent dobutamine stress MPI. This study is a continuation of the study of Schinkel et al.[9] in which the same population was evaluated with a mean follow-up of 4 years. The test was requested for assessment of myocardial ischemia in all patients; 91 patients had known or suspected CAD, 63 had atypical angina, and 53 had typical angina. Diabetes was defined as a fasting blood glucose level of >140 mg/dL or the need for insulin or oral hypoglycemic agents. Follow-up was successful in 206 patients (99.5%). A total of 12 patients who had undergone coronary revascularization within 60 days of the test were excluded from the analysis. This exclusion was based on previously published data that indicated that

referral to coronary revascularization in the first 60 days after nuclear testing tends to be based on the results of the scan and that referral to revascularization >60 days after nuclear testing tends to be based on worsening of the patient's clinical status.[12] Data of the remaining 194 patients are described in this study. All patients gave informed consent before testing. The local medical ethics committee approved the study protocol. Before the test, a structured interview was performed and a clinical history was obtained, including assessment of cardiac risk factors. Hypertension was defined as blood pressure >140/90 mmHg or need for antihypertensive medication. Hypercholesterolemia was defined as total cholesterol level >6.4 mmol/L or need for lipid-lowering medication.

Stress test protocol

Dobutamine–atropine stress testing was performed according to a standard protocol.[13] Dobutamine was administered intravenously, starting at a dose of 10 µg/kg/min for 3 min, which was increased by 10 µg/kg/min every 3 min, up to a maximum dose of 40 µg/kg/min. If the test end point was not reached at a dobutamine dose of 40 µg/kg/min, atropine was administered intravenously (≤1 mg). Blood pressure and heart rate were monitored, and electrocardiography (ECG) was performed constantly. Test end points included the following:achievement of target heart rate (85% of maximum age- and sex 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,decrease in systolic blood pressure >40 mmHg, blood pressure >240/120 mmHg, severe angina, or significant cardiac arrhythmia. Metoprolol was available for administration to reverse the adverse effects of dobutamine/atropine.

SPECT MPI

Approximately 1 min before the termination of the dobutamine–atropine stress test, an intravenous dose of 370 MBq of technetium-99m (^{99m}Tc)-sestamibi (in 69 patients) or ^{99m}Tc-tetrofosmin (in 125 patients) was injected. For resting studies, 370 MBq of the same tracer was injected at least 24 h after the stress test. Image acquisition was performed with a commercially available single-photon emission computed tomography (SPECT) camera system (Orbiter camera; Siemens, Iselin, NJ; or Picker Prism 3000XP camera; Picker, Cleveland, OH). For each study, six oblique (short-axis) slices from the apex to the base and three sagittal (vertical long-axis) slices were defined. Each of the

six short-axis slices was divided into eight equal segments. The septal part of the two basal slices was excluded from analysis because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. Therefore, a total of 47 segments were identified (3 long axis and 44 short axis). The interpretation of the scan was semiquantitatively performed by visual analysis assisted by the circumferential profiles analysis. Stress and rest tomographic viewswere reviewed side by side by two experienced observers who were unaware of the patients' clinical data. In case of disagreement, a majority decision was achieved by a third observer.

A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in two contiguous segments or slices. A fixed perfusion defect was defined as a perfusion defect on stress images in two or more contiguous segments or slices that persisted on rest images. An abnormal study was considered in the presence of a fixed and/or reversible perfusion defect.

Patient follow-up

Collection of follow-up data was obtained by reviewing hospital records and/or by contacting the patient's general practitioner. The date of the last review or consultation was used to determine follow-up time. End points were all-cause mortality, cardiac mortality, and nonfatal myocardial infarction. Cardiac mortality was defined as a death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was included as cardiac mortality. Nonfatal myocardial infarction was described by elevated cardiac enzyme levels and typical changes on ECG. Hard cardiac events were defined as the occurrence of cardiac mortality or nonfatal myocardial infarction.

Statistical analysis

Values were expressed as mean value SD or number and were compared using Student's t-test or X^2 test. Univariable and multivariable Cox proportional hazard regression models were used to identify independent predictors of late cardiac events. 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 corresponding 95% confidence interval (CI). The incremental value of myocardial perfusion scintigraphy over the clinical variables in the prediction of cardiac events was determined according to two models. In Model I, the variable entered was the presence

of an abnormal scan; in Model II, the variables entered were fixed and reversible defect. The multivariable analysis was repeated per year of follow-up. Survival curves were performed using the Kaplan–Meier method, and survival curves were compared using the log-rank test. A P-value of <0.05 was considered statistically significant.

RESULTS

Demographics and stress test results

The clinical data of the 194 high-risk patients with diabetes mellitus are presented in Table 1. The Diamond and Forrester pretest probability of CAD was low in 39 (20%), intermediate in 94 (49%), and high in 61 patients (31%).

Table 1. Baseline characteristics

N = 194	Number (%)
Age (years)	61 ± 10
Men	116 (60)
Hypertension	110 (57)
Smoking	458 (25)
Hypercholesterolemia	64 (33)
Congestive heart failure	51 (26)
Prior myocardial infarction	82 (42)
Previous coronary artery bypass graft	32 (16)
Previous percutaneous coronary intervention	35 (18)
Beta-blockers	66 (34)
ACE inhibitors	83 (43)
Calcium channel blockers	102 (53)

Significant increases in heart rate (77±17–136±17 bpm, P<0.0001) and systolic blood pressure (144±26–158±33 mmHg, P <0.001) were achieved from rest to peak stress. The peak dobutamine dose was 10 µg/kg/min in 5 patients (3%), 20 µg/kg/min in 24 patients (12%), 30 µg/kg/min in 35 patients (18%), and 40 µg/kg/min in 130 patients (21%). Atropine was added in 78 patients (40%). Atropine was more frequently administered in patients using B-blocker therapy (41 of 66 patients, 62%) than in those not taking B-blockers (37 of 128, 29%, P<0.0001). Adverse effects during the test were ventricular

tachycardia (>10 beats) in 1 patient (0.5%), short ventricular tachycardia (<10 beats) in 7 patients (3.6%), atrial fibrillation in 2 patients (1%), severe hypotension (decrease in systolic blood pressure .40 mmHg) in 3 patients (1.5%), nausea in 11 patients (5.7%), and headache in 12 patients (6.2%). No patient experienced a myocardial infarction or fatal complication. Typical angina occurred in 53 patients (27%), whereas 54 patients (28%) exhibited ST-segment changes.

SPECT results and outcome

Abnormal MPI was detected in 125 (64%) patients. Perfusion abnormalities were reversible defects in 17 (9%) patients. Fixed defects were detected in 61 patients (31%) suggesting that they have had myocardial damage. Forty-seven patients (24%) had both fixed and reversible defects. During a mean follow-up of 8.1+5.9 years,134 (69%) patients died (all-cause mortality) of whom 68 (35%) died due to cardiac causes. Nonfatal myocardial infarction occurred in 24 patients (12%). Late (>60 days) coronary revascularization was performed in 61 (13%) patients.

The Kaplan–Meier survival curves are presented in Figure 1. The survival curves according to all-cause mortality demonstrate that up to 4 years after MPI, patients with a normal MPI had a better prognosis compared with patients with an abnormal MPI (Figure 1A). After 4 years of follow-up, the survival curves converge, indicating no significant difference in all-cause mortality for normal or abnormal MPI. Figure 1B and C shows the event-free survival curves for cardiac mortality and hard cardiac events, respectively. Both cumulative survival free of cardiac mortality (P=0.034) and hard cardiac events (P=0.036) show a significantly better prognosis in favor of a normal MPI. Conversely, patients with an abnormal MPI had a significant increased risk of cardiac mortality and hard cardiac events.

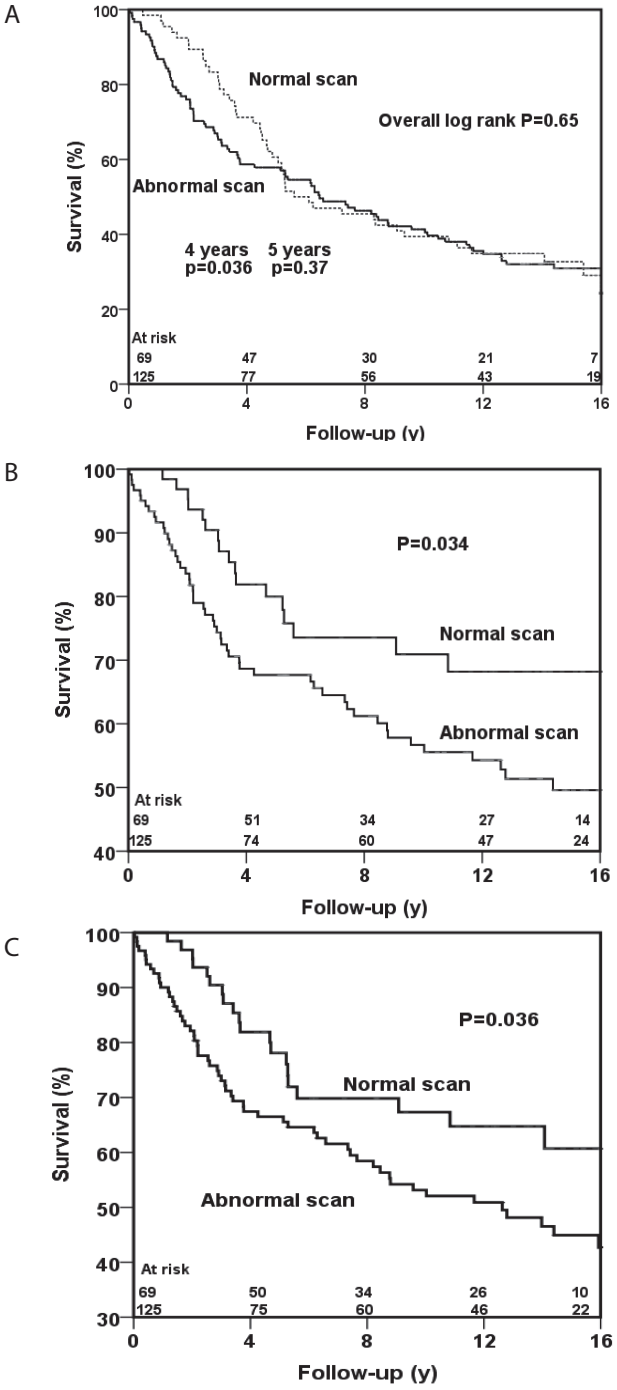

Figure 1. Kaplan-Meier survival curves with normal vs. abnormal MPI for all endpoints of interest: (A) all-cause mortality, (B) cardiac mortality, and (C) hard cardiac events. y=year.

Table 2. Univariable and multivariable predictors of cardiac mortality at 4-year follow-up

		Multivariable HR (CI)		
Variable	**Univariable HR (CI)**	**Clinical data**	**Model I**	**Model II**
Age[a]	1.03 (1.00–1.06)	1.04 (1.01-1.08)	1.06 (1.02-1.10)	1.06 (1.02-1.09)
Men	1.83 (1.09–3.09)	2.30 (1.27-4.20)	2.02 (1.04-3.91)	P=0.11
Typical angina pectoris	*P=0.72*	*P=0.71*	*P=0.96*	*P=0.92*
Hypertension	*P=0.76*	*P=0.78*	*P=0.61*	*P=0.27*
Hypercholesterolemia	*P=0.18*	*P=0.35*	*P=0.10*	1.90 (1.06-3.39)
Smoking	*P=0.17*	*P=0.47*	*P=0.38*	*P=0.19*
Scan parameters				
Abnormal scan	1.80 (1.04-3.12)	-	1.96 (1.10-3.88)	-
Reversible defect	1.72 (1.06-2.77)	-	-	2.14 (1.14-3.67)
Fixed defect	*P=0.31*	-	-	*P=0.20*

Statistically significant predictors of outcome are presented as hazard ratio (CI), of all other variables the P-value is presented. —, Not included in the model. [a]Per unit increment.

Predictors of long-term outcome

Multivariable analyses were performed for every year of follow-up to determine the maximum length of prognostic value of SPECT MPI. Tables 2 and 3 demonstrates the last year were the scan parameters had significant incremental value for the prediction of cardiac events. At a mean follow-up of 8.1 years, univariable analysis demonstrated that age, abnormal MPI, and reversible perfusion defect were predictors of cardiac mortality and hard cardiac events (Tables 2 and 3, respectively). In the multivariable analysis, the maximum length of prognostic value of SPECT MPI in diabetic patients was 4 years. After that follow-up duration, multivariable analysis demonstrated that SPECT MPI parameters failed to predict cardiac mortality (Table 2) and hard cardiac events (Table 3).

DISCUSSION

The current study assessed the long-term outcome after MPI in high-risk patients with diabetes mellitus and limited exercise capacity. The main finding of this study is that dobutamine stress MPI provides useful information for the prediction of outcome in patients with diabetes mellitus. Diabetic patients with a normal MPI

Table 3. Univariable and multivariable predictors of hard cardiac events at 4-year follow-up

		Multivariable HR (CI)		
Variable	**Univariable HR (CI)**	**Clinical data**	**Model I**	**Model II**
Age[a]	1.03 (1.00–1.06)	1.04 (1.01-1.07)	1.04 (1.01-1.07)	1.04 (1.01-1.08)
Men	1.73 (1.03–2.92)	1.92 (1.13-3.26)	P=0.06	P=0.07
Typical angina pectoris	*P=0.77*	*P=0.85*	*P=0.86*	*P=0.80*
Hypertension	*P=0.86*	*P=0.74*	*P=0.73*	*P=0.40*
Hypercholesterolemia	*P=0.26*	*P=0.49*	*P=0.11*	*P=0.09*
Smoking	*P=0.71*	*P=0.74*	*P=0.38*	*P=0.36*
Scan parameters				
Abnormal scan	1.91 (1.04-3.50)	-	1.83 (1.01-3.29)	-
Reversible defect	1.65 (1.02-2.67)	-	-	1.85 (1.09-3.13)
Fixed defect	*P=0.50*	-	-	*P=0.28*

Statistically significant predictors of outcome are presented as hazard ratio (CI), of all other variables the P-value is presented.

—, Not included in the model.

[a]Per unit increment.

have a significantly better prognosis compared with those with an abnormal study, up to 4 years after testing. The survival curves suggest that dobutamine MPI was predictive of outcome (for the end points cardiac mortality, and cardiac events) over the entire follow-up duration. However, the multivariate analysis demonstrated that dobutamine MPI was an independent predictor of outcome (all-cause mortality, cardiac mortality, and cardiac events) up to 4 years after the test. After this 4-year period, the predictive value of dobutamine stress MPI does not hold its independent predictive value.

This is the first study that has evaluated the long-term prognostic value of MPI in patients with diabetes mellitus. Several studies have established that MPI is a useful tool for short- and medium-term risk stratification of diabetic patients. The follow-up period in these previous studies was on average 3.5 years. Kang et al.[14] described 1271 patients with diabetes mellitus who underwent stress ^{99m}Tc- sestamibi MPI. During a mean follow-up of 23.7±7.7 months, patients with diabetes mellitus had higher cardiac event rates in comparison with patients without diabetes. The authors concluded that stress MPI was a valuable tool for risk stratification in diabetic patients. De Lorenzo et al.[3] demonstrated that an abnormal stress MPI significantly increased the risk of cardiac events in 108 diabetic patients during a follow-up of 36±18 months. Giri et al.[4] studied 929 diabetic patients undergoing stress MPI for a follow-up time of 2.5±1.5 years. Sig-

nificant more cardiac events occurred in the diabetic group (8.6%) compared with the nondiabetic cohort (4.5%; P<0.0001). Jeong et al.[5] studied 337 diabetic patients who were followed for 32±12 months. The gated SPECT data provided significant incremental prognostic information over that provided by historical, clinical, physiological variables and normal perfusion status in diabetic patients without known CAD. Acampa et al.[6] studied 436 asymptomatic patients with diabetes mellitus with a median follow-up of 50 months. Stress-induced ischemia by gated MPI influenced the temporal characteristic of the patient's risk. In 575 patients with diabetes mellitus, Bourque et al.[7] found that known CAD and MPI ischemia were independent predictors of cardiac events during a mean follow-up of 4.4 years. In ischemic patients, the rate of cardiac events was 5.7%/year compared with 2.6%/year in the total patient group. More recently, Acampa et al.[8] studied 828 patients of whom 260 with diabetes mellitus. During a median follow-up of 53 months after a normal stress MPI, diabetic patients were at significantly higher risk for cardiac events compared with nondiabetic patients. The current study differs from previous studies mainly because of the long-term mean followup time of 8.1 years. This study extends the results from previous studies, and it demonstrates that the prognostic value is maintained up to 4 years after MPI. Hence, the 'perishable date' of stress MPI for the prediction of outcome in patients with diabetes mellitus and limited exercise capacity is ~4 years.

There are several explanations why stress MPI has no incremental value for the prediction of outcome beyond 4 years after the test in patients with diabetes mellitus. In the current study, we describe a high-risk group of patients with diabetes mellitus and limited exercise capacity. The mean age of these patients was relatively high (61 years). A total of 82 patients (42%) have had a previous myocardial infarction. Moreover, 32 (16%) and 35 patients (18%) have had a previous coronary artery bypass graft and previous percutaneous coronary intervention, respectively. Overall, these factors indicate the high-risk status of the study population, which may have influenced the risk of cardiac events. Additionally, during follow-up, progression of CAD may have occurred and diabetes may have accelerated the natural progression of CAD.[15] Furthermore, the inability to perform an exercise test is a strong predictor of adverse outcome in itself.

A study of Hachamovitch et al.[10] showed that after a normal SPECT MPI a warranty period exists. The underlying clinical risk of diabetic patients may significantly influence the event rate after a normal SPECT scan. Recently, Acampa et al.[8] also suggest that the warranty period for a normal stress SPECT scan varies depending on patient clinical characteristics. The existence of hypertension, a previous myocardial infarction, and consequently myocardial damage can affect the risk on cardiac events. Depending on

the patient's clinical status, repeated testing is therefore recommended. To determine whether repeating SPECT MPI is indicated, the appropriateness criteria for cardiac imaging should be used.[16]

Pharmacologic stress MPI is a widely used technique for the evaluation of CAD. Adenosine and dipyridamole (coronary vasodilators) are the most used agents for stress testing and are superior in creating blood flow heterogeneity.[17,18] However, in patients who have contraindications for vasodilators, such as reactive airway disease or high-grade atrioventricular nodal block, dobutamine is the pharmacological stress agent of choice. Previous data showed that increased blood flow (hyperemia) induced by dobutamine–atropine stress testing is of equal magnitude to hyperemia induced by vasodilator stress agents.[19] Both sensitivity and specificity for diagnosing CAD are generally comparable among adenosine and dobutamine.[20] In a canine model, dobutamine attenuates the myocardial uptake of ^{99m}Tc-sestamibi and, as a result, underestimates the extent of significant coronary artery stenoses.[21,22] The radiotracers ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin have a nonlinear myocardial extraction at high flow rates. To date, however, ^{99m}Tc radiotracers in conjunction with MPI are of great value to assess prognosis of patients with known or suspected CAD.

The current study has limitations. First, during SPECT, no attenuation or scatter correction was used. Previous studies have shown that attenuation correction contributes to optimize further risk stratification[23,24]; application of attenuation or scatter correction could have improved the accuracy of the MPI studies. Second, the prognostic value of gated SPECT was not examined, due to the fact that at the time of data collection, gated SPECT was not routinely performed. Third, the study population consisted of 194 high-risk patients with diabetes mellitus with limited exercise capacity. The results of this study may not be applicable to patients with diabetes in general. Fourth, the examined patient population was relatively small.

In conclusion, in this study with a mean follow-up of 8.1±5.9 years, dobutamine stress MPI provided incremental information in addition to clinical and SPECT MPI results for the prediction of cardiac events of patients with diabetes mellitus up to 4 years after the test.

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Chapter 11

Long-term prognostic value of dobutamine stress echocardiography in diabetic patients with limited exercise capability: a 13-year follow-up study

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ABSTRACT

Objective. To determine the incremental prognostic value of dobutamine stress echocardiography (DSE) at 13-year follow-up (SD 3.2 years) for predicting mortality and cardiac events in diabetic patients.

Research Design and Methods. A total of 396 diabetic patients (mean age 61±11 years; 252 men [64%]) with limited exercise capacity who underwent DSE for evaluation of ischemia were studied. End points were all causes of mortality, cardiac death, and hard cardiac events (cardiac death and nonfatal myocardial infarction).

Results. During a mean follow-up of 13 years, 230 patients (58%) died (121 cardiac deaths), and 30 patients had nonfatal myocardial infarction. Cumulative survival in patients with an abnormal DSE at 5, 10, and 15 years was 68, 49, and 41%, respectively. In patients with a normal DSE, these respective numbers were 74, 57, and 44%. Multivariate analyses showed that DSE provided incremental value over clinical characteristics and stress test parameters for prediction of mortality and cardiac events. Survival analysis showed that DSE provided optimal risk stratification up to 7 years after initial testing; after that period, the risk of adverse outcome increased comparably in both normal and abnormal DSE patients.

Conclusions. DSE provided restricted predictive value of adverse outcome in patients with diabetes who were unable to performan adequate exercise stress test. DSE provided optimal risk stratification up to 7 years after initial testing. Repeated DSE at that time might add to its prognostic value.

INTRODUCTION

Coronary artery disease (CAD) is a major cause of mortality and morbidity in diabetic patients.[1]

To optimize therapeutic intervention, it is essential to identify patients at risk. Exercise stress testing is the most common stress modality used for the noninvasive evaluation of CAD. However, exercise tolerance in diabetic patients may be impaired, particularly because of the higher prevalence of peripheral vascular disease. Dobutamine stress echocardiography (DSE) is used to assess the severity of CAD in patients unable to perform an adequate exercise test. The safety, feasibility, and accuracy of DSE are comparable in diabetic and nondiabetic patients.[2] DSE has shown an incremental value in predicting death and hard cardiac events at short- and intermediateterm follow-up.[3–5] However, it is not known whether this incremental value can be maintained at long-term follow-up.

The goals of the current study with 13-year follow-up were to 1) assess very long-term outcome after DSE in patients with diabetes, 2) identify predictors of increased risk in patients with diabetes, and 3) define a low-risk period after normal DSE.

RESEARCH DESIGN AND METHODS

This retrospective study included 408 consecutive patients with diabetes who were unable to perform an adequate exercise test and who underwent DSE at the Thoraxcenter between January 1994 and January 2001. Diabetes was defined in the presence of fasting blood glucose ≥140mg/dL or requirement for insulin or oral hypoglycemic agents. A total of 12 patients were excluded because of inadequate echocardiographic images. The final population of this study consisted of 396 patients.

Clinical data including hypercholesterolemia, smoking, hypertension, a history of heart failure, a previous myocardial infarction (MI), and/or revascularization were collected at the time of DSE. Hypercholesterolemia was defined as total cholesterol >200mg/dL or use of cholesterol-lowering agents. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure >90 mmHg, or use of antihypertensive medication. Heart failure was defined in line with the New York Heart Association classification. For the clinical characteristics of the patients, we refer to the short-term study of this population done by Sozzi et al.[5] in 2003. Patients who underwent revascularization within 3 months after DSE were excluded. This exclusion was based on

previously published data indicating that referral to coronary revascularization within 3 months after testing tends to be based on the results of the test and that referral to revascularization>3 months after the test tends to be based on worsening of the patients clinical status.

DSE protocol

Left ventricular ejection fraction (LVEF) at rest was assessed using the modified biplane Simpson rule.[6] After baseline echocardiography, dobutamine was infused at a starting dose of 5 µg/kg/min for 3 min followed by 10 µg/kg/min for 3 min (low-dose stage). The dobutamine dose was increased by 10 µg/kg/min every 3 min up to a maximum dose of 40 µg/kg/min. Atropine (up to 1 mg) was administered intravenously at the end of the last stage if the target heart rate was not achieved. End points of the test were an achievement of the target heart rate (85% of the maximal heart rate predicted for age), the maximal dose of dobutamine and atropine, >2 mV downsloping ST-segment depression measured 80 ms from the J point compared with baseline, hypertension (blood pressure >240/120 mmHg), a decrease in systolic blood pressure of >40 mmHg, and significant arrhythmias.

Echocardiographic imaging and interpretation

Imaging was acquired at rest and continuously during the test and recovery. Images were recorded on videotapes and, in addition, the baseline, low-dose, peak-stress, and recovery images were recorded in a quad-screen format. The interpretation of images was performed by two independent observers blinded to the patients' clinical data. In case of disagreement, a majority decision was achieved by a third observer. In our laboratory, the inter- and intraobserver agreement for DSE assessments are 92 and 94%, respectively.[7] A 16-segment model was used for segmental analysis of LV function.[6] Wall Motion Score Index (WMSCI) was determined at rest and peak stress as the sum of the segmental scores of the 16 segments divided by 16. Each segment was scored using a 5-point Likert scale as follows: 1=normal, 2=mild hypokinesis, 3=severe hypokinesis, 4=akinesis, and 5=dyskinesis. Ischemia was defined as new or worsened wall motion abnormalities (WMAs) during stress, which was indicated by an increase of wall motion score ≥1 grade in ≥1 segment.[8] Ischemia was not considered to be present when akinetic segments at rest became dyskinetic during stress. DSE results were defined as abnormal if there was ischemia during stress[9] or fixed WMAs.[8]

Follow-up

Patients were contacted to retrieve followup information twice, in 2001 and in 2010. Prior to contacting them, the online municipal civil registry was used to determine the patients' present survival status. Survival status was retrieved in 100% of the patients. A mailed questionnaire was sent to all living patients. The response rate of the questionnaire was 85%. There were no significant differences between patients who responded to the survey and those who did not respond. This questionnaire was used together with medical records to obtain information about end points. The end points considered were all-cause mortality, cardiac death, and hard cardiac events (defined as nonfatal MI and cardiac death). Causes of death were obtained from the Central Bureau of Statistics Netherlands. Deaths were classified as either documented cardiac death or other. Nonfatal MI was confirmed by using clinical and electrocardiographic criteria and a typical rise and fall of cardiac markers.

Statistical analysis

Continuous variables were reported as mean±SD and compared with Student t test. Categorical variables were summarized as percentages; the X^2 test was used to compare groups. Cumulative survival was estimated by the Kaplan-Meier method, with comparisons between groups based on the log-rank test. Cox proportional hazards regression model was used to examine the additional value of DSE with the end points of interest at 7, 8, and 15 years after the test. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The incremental value of DSE information over clinical data was assessed in two modeling steps. First, clinical data only were selected to fit a multivariable model. These clinical data were then used as baseline risk factors, and DSE variables were added in a stepwise forward selection manner. The incremental value was determined by comparing the log likelihood X^2 values of both prediction models.

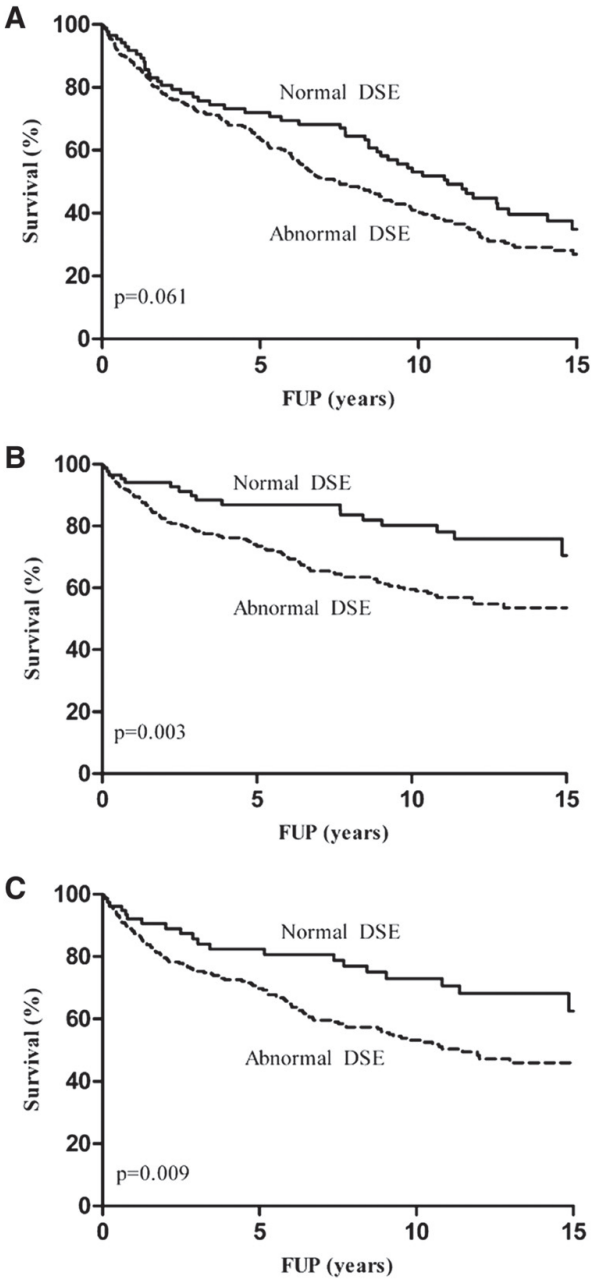

Figure 1. Kaplan-Meier survival curves with normal vs. abnormal DSE for all end points of interest. A: All-cause mortality: normal 88, 58, 41, and 12; abnormal 308, 164, 99, and 20 patients at risk at start, 5-, 10-, and 15-year follow-up (FUP), respectively. B: Cardiac death: normal 88, 58, 41, and 12; abnormal 308, 164, 99, and 20 patients at risk at start, 5-, 10-, and 15-year FUP, respectively. C: Hard cardiac events: normal 79, 48, 32, and 10; abnormal 296, 146, 82, and 20 patients at risk at start, 5-, 10-, and 15-year FUP, respectively.

RESULTS

Dobutamine-atropine induced a significant increase of heart rate (from 77±13 at rest to 132±16 bpm at peak dose, P<0.0001), whereas systolic blood pressure did not increase (137±27 at rest and 136±32 mmHg at peak stress). Atropine was administered in 179 patients (45%). Angina occurred in 89 patients (22%), and ST-segment depression occurred in 61 patients (15%). Reasons for termination of the test were achievement of the target heart rate in 320 patients (81%), angina in 42 patients (11%), ST-segment depression in 22 patients (5%), hypotension in 7 patients (2%), and ventricular arrhythmia in 5 patients (1%).

Resting WMAs were detected in 292 patients (74%), and 176 (60%) of these patients had a history of previous MI. Ischemia was detected in 141 patients (36%), and 125 (89%) of these patients had resting WMAs as well.

Outcome

During a mean follow-up of 13 years (SD 3.2), 230 patients (58%) died (121 cardiac deaths), 30 patients (8%) had a nonfatal MI, and 86 (22%) underwent myocardial revascularization. A total of 50 and 45, respectively, underwent percutaneous coronary intervention and coronary artery bypass procedures during follow-up, of whom 9 had both. Among the 141 patientswith ischemia by DSE, 62 underwent subsequent revascularization (72% of the total patients revascularized). The remaining patients with ischemia were treated medically.

Tabel 1. Independent predictors of all-cause mortality, cardiac death, and hard cardiac events using a two-step model.

	All-cause mortality		Cardiac death		Hard cardiac events	
	HR (95% CI)	X^2	HR (95% CI)	X^2	HR (95% CI)	X^2
Clinical						
Age	1.05 (1.03–1.06)		1.03 (1.01–1.05)		1.02 (1.00–1.04)	
Heart failure	2.08 (1.56–2.78)	67	2.62 (1.80–3.82)	55	2.41 (1.68–3.45)	41
Old MI	--		1.76 (1.21–2.58)		1.53 (1.07–2.19)	
Smoking	1.43 (1.08–1.88)		--		--	
Clinical + Imaging						
Peak WMSCI	1.74 (1.38–2.19)	93	1.93 (1.40–2.66)	77	1.74 (1.28–2.37)	55
LVEF	0.15 (0.06–0.40)	76	0.07 (0.02–0.30)	65	0.13 (0.04–0.48)	49

HR, hazard ratio. X^2, Chi-square. WMSCI, wall motion score index.

Clinical and DSE variables associatedwith an increased risk of all end points of interest in the multivariate model analysis are presented in Table 1.WMSCI at peakdose dobutamine and LVEF at rest added incremental value to the clinical parameters in predicting all-cause mortality (67 to 93 [P<0.0001] and 76 [P <0.0001],respectively). The additional value of DSE, however, did not increase any further after 7 years after the test for all end points of interest. Multivariate analysis showed that WMA at rest, new or worsened WMA, and these DSE parameters combined did not significantly improve the prediction model for adverse outcome.

The cumulative survival showed a better, although not significant, survival of normal DSE in comparison with abnormal DSE (74 vs. 68% at 5 years, 57 vs. 49% at 10 years, and 44 vs. 41% at 15 years; overall P=0.06) (Figure 1A). Figure 1B and 1C, respectively, shows the event-free survival curves for cardiac death and hard cardiac events with normal versus abnormal DSE. Both cumulative survival free of cardiac death (89 vs. 78% at 5 years, 84 vs. 69% at 10 years, and 81 vs. 66% at 15 years; overall P=0.003) and hard cardiac events (84 vs. 75%at 5 years, 81 vs. 65% at 10 years, and 77 vs. 63% at 15 years; overall P = 0.009) show a significantly better prognosis in favor of a normal DSE. The interaction between LVEF and peak WMSCI is shown in Figure 2.

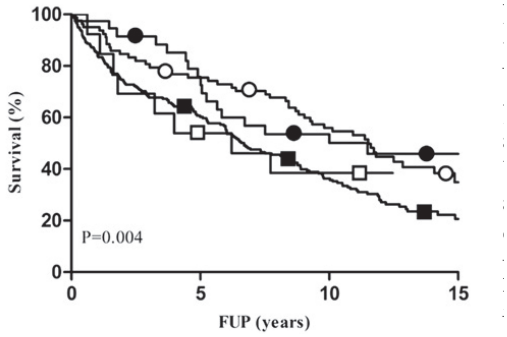

Figure 2. Kaplan-Meier survival curves demonstrating the interaction between peak WMSCI and LVEF. Group 1: ○, LVEF ≥50% and peak WMSCI = 1; 82, 58, 42, and 10 patients at risk at start, 5-, 10-, and 15-year follow-up (FUP), respectively. Group 2: □, LVEF<50% and peak WMSCI = 1; 13, 7, 5, and 0 patients at risk at start, 5-, 10-, and 15-year FUP, respectively. Group 3: ●, LVEF≥50% and peak WMSCI>1; 39, 24, 15, and 7 patients at risk at start, 5-, 10-, and 15-year FUP, respectively. Group 4: ■, LVEF<50% and peak WMSCI>1; 240, 120, 67, and 10 patients at risk at start, 5-, 10-, and 15-year FUP, respectively.

CONCLUSIONS

DSE is widely used for diagnosis and risk stratification, but the very long-term prognostic value of this test in patients with diabetes is not defined. Accurate long-term risk stratification of these patients is required to optimize patient management. Patients with normal DSE are considered at low risk of cardiac events; the annualized event rate is generally, <1% during the first years after testing.Accordingly, in these low-risk patients, further (invasive) diagnostic and therapeutic strategies and associated medical care costs can be avoided.

Still, over time, a significant change in risk may occur after a normal DSE. The underlying clinical risk of patients with diabetes and history of CAD may significantly influence the event rate after a normal DSE. These observations have lead to the perception that a "warranty period" exists after a normal DSE. In the currently available literature, mean follow-up after DSE was ~3 years. Very long-term outcome data after DSE are lacking and, consequently, the duration of the low-risk status after a normal test is not clear.

This study is a continuation of the 2003 study of Sozzi et al.[5] in which the same population of 396 patients with diabetes was evaluated, with a median followup of 3 years. The current study assesses the very long-term outcome after DSE in patients with diabetes and shows that DSE provides restricted predictive value of adverse outcome in patients with diabetes at very long mean follow-up of 13±3.2 years. The prognostic value of DSE was optimal till ~7 years after the initial test. DSE provided data in predicting all-cause mortality incremental to clinical parameters and increased the X^2 of the clinical and exercise electrocardiogram model from 67 to 93 ($P<0.0001$) at 15-year follow-up, but the additional value of DSE did not increase any further after 7 years after the test. This is in line with the Kaplan-Meier survival curves, which diverge until ~7 years. After that point, the lines start to run parallel. The most powerful echocardiographic predictor of outcome was peak WMSCI, with LVEF at rest coming up second. Multivariate analysis showed that peak WMSCI and LVEF were independent predictors of longterm outcome.

Kaplan-Meier survival analysis (Figure 2) showed that patients with LVEF ≥50% and peak WMSCI=1 had a favorable prognosis, whereas patients with LVEF <50% and peak WMSCI>1 had an adverse long-term prognosis. Patients with LVEF ≥50% and peak WMSCI>1 and those with LVEF <50% and peak WMSCI <1 had an intermediate prognosis. The survival curves continued to diverge up to ~7 years, implying that the incremental prognostic value of both LVEF and peak WMSCI was maintained up to 7 years after initial testing. These findings indicate that the prognosis in diabetic patients is related not

only to the extent of stress induced ischemia but also to LV function at rest. Similar DSE results were found for the end points cardiac death and hard cardiac events.

In 74% of the population, fixed WMA were found. It is likely that this high number has to do with the fact that our population consists of patients with impaired exercise capability, with a great portion of patients with a history of MI. Furthermore, it is well established that diabetes could result in myocardial dysfunction even in the absence of CAD. This could explain the high incidence of resting WMAs in this study.

We currently are not aware of any other study that has evaluated the prognostic value of DSE after such an extended follow-up time. Several studies prove that DSE is a useful tool for short- to medium-term risk stratification of diabetic patients. Bigi et al.[10] reported in 2001 that peak WMSCI was a significant predictor of hard cardiac events in a population of 259 diabetic patients at 2-year follow-up. D'Andrea et al.[11] concluded the same in 2003 in a population of 325 diabetic patients at a follow-up of 2.8 years. Both studies are in line with our long-term study. In 2006, Cortigiani et al.[12] compared the prognostic value of dipyridamole and DSE in 749 diabetic patients with 4.707 nondiabetic patients with known or suspected CAD during a median time of 2.6 years. In the diabetic population, restingWMSCI and ischemia at stress echo were the DSE variables with incremental value.

Chaowalit et al.[3] verified the prognostic significance of DSE in predicting mortality and cardiovascular morbidity during a mean period of 5.4 years in a large cohort (N=2,349) of patients with diabetes in 2006. Inmultivariate analyses, age, failure to achieve target heart rate, and the percentage of ischemic segments were important predictors of bothmortality and cardiovascular morbidity (nonfatal MI and late revascularization). Innocenti et al.[4] assessed the prognostic role of clinical, rest, and stress echocardiographic data in a group of 322 diabetic patients with known or suspected CAD during a mean follow-up duration of 3.3 years.[4] This study shows that presence of viability and severe ischemia during DSE was independently associated with higher occurrence of hard cardiac events.

The current study has limitations. The long-term prognostic value of the test is based on a population referred to DSE for clinical indications. Because of the clinical factors leading patients to be referred for DSE at the time of initial testing, they are likely to have had increased risk. This may limit application of the present findings to patients with diabetes in general. The results may not be necessarily applicable to patients with diabetes and without clinical indication for DSE. Therefore, the use of DSE for risk stratification of all patients with diabetes cannot be recommended.

Exercise or pharmacologic stress myocardial perfusion imaging has been recommended by the American Heart Association for evaluation of ischemic heart disease in diabetic patients.[13] However, DSE has the advantages of wider availability and lower cost, and it avoids radiation exposure to the patient. Appropriateness criteria have been developed to provide an estimate of the reasonableness of the use of DSE for several clinical scenarios. A detailed description of appropriate indications of DSE has been published recently[14], including detection of CAD/risk assessment in selected asymptomatic and symptomatic patients, preoperative evaluation before noncardiac surgery, risk assessment after acute coronary syndrome/postrevascularization, assessment of viability/ischemia, and stress study for hemodynamics.

In conclusion, in this study with a mean follow-up of 13±3.2 years, DSE provided restricted predictive value of adverse outcome in patients with diabetes who were unable to perform an adequate exercise stress test. The value of the test seems optimal till ~7 years after initial DSE. Repeating the test at that time might add to its diagnostic value.

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Chapter 12

Long-term (>10 year) prognostic value of dobutamine stress echocardiography in a high-risk cohort

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ABSTRACT

The prognostic value of dobutamine stress echocardiography (DSE) at >10-year follow-up is unknown. The aim of this study was to assess the very long-term prognostic value of DSE in a high-risk cohort of patients with known or suspected coronary artery disease. This prospective, single-center study included 3,381 patients who underwent DSE from January 1990 to January 2003. Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress, and during recovery. Follow-up events were collected and included overall mortality, cardiac death, nonfatal myocardial infarction, and revascularization. The incremental value of DSE in the prediction of selected end points was evaluated using multivariate Cox proportional hazard analysis. During a mean follow-up of 13±3.2 years (range 7.3 to 20.5 years), there were 1,725 deaths (51%), of which 1,128 (33%) were attributed to cardiac causes. Patients with an abnormal DSE had a higher mortality rate (44% vs 35% at 15-year follow-up, $p<0.001$) than those with a normal DSE. When comparing echocardiographic variables at rest to variables at maximum dose dobutamine, the chi-square of the test improved from 842 to 870 ($p<0.0001$) and from 684 to 740 ($p<0.0001$) for all-cause mortality and cardiac death, respectively. DSE provided incremental value in predicting all-cause mortality, cardiac death, and hard cardiac events. There seems, however, to be a "warranty period" of approximately 7 years, when the survival curves of a normal and abnormal DSE no longer diverge.

INTRODUCTION

Exercise electrocardiography is the most frequently used method for noninvasive evaluation of coronary artery disease (CAD). Still, a substantial number of patients have an impaired exercise capacity, because of a weak general physical condition, neuropathy, or peripheral vascular disease. Dobutamine stress echocardiography (DSE) has been reported as a safe[1] and effective noninvasive tool to provide diagnostic and prognostic information in various clinical scenarios.[2-7] Currently, it is not known whether the prognostic value of DSE in patients with limited exercise capacity is preserved at very long-term (>10 years) follow-up. The goals of this study were to assess the very long-term outcome after DSE in a high-risk group of consecutive patients and to evaluate whether DSE has incremental prognostic value over clinical variables and echocardiographic data at rest.

METHODS

This prospective study included 3,875 consecutive patients at high risk with known or suspected CAD, who were unable to perform an adequate exercise test. Indications for DSE were diagnosis of CAD (54%), preoperative evaluation before noncardiac surgery (34%), and risk stratification after myocardial infarction (MI, 12%). Of all patients who underwent DSE, 30% had a history of typical angina, and 13% had a history of atypical angina.[8] Data were collected from patients who underwent DSE from January 1990 to January 2003 at the Thoraxcenter, Rotterdam, the Netherlands. Follow-up data at shorter intervals and of specific subgroups of this study cohort have been previously published.[2,5,9] Thirty-nine patients were lost to follow-up, and 455 patients underwent early coronary revascularization in the first 60 days after DSE and were excluded from the analysis because referral for revascularization within this period is likely to be based on DSE results. The final population of this study consisted of 3,381 patients. This study was not subject to the Dutch Medical Research Involving Human Subjects Act. Therefore, approval from the local research ethics committee to conduct this prospective follow-up study was not required at the time of enrollment. The study was conducted according to the Declaration of Helsinki.[10] All patients consented participation in this study.

Clinical characteristics including hypertension, hypercholesterolemia, smoking, previous MI, a history of heart failure, and/or revascularization were recorded at the time of DSE in a computerized database. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive med-

ication. Hypercholesterolemia was defined as total cholesterol >200 mg/dl or the use of cholesterol-lowering agents. Heart failure was defined according to the New York Heart Association classification and based on established guidelines at the time of diagnosis.[11]

After baseline echocardiography, dobutamine was infused at a starting dose of 5 µg/kg/min for 3 minutes followed by 10 µg/kg/min for 3 minutes (low-dose stage). The dobutamine dose was increased by 10 µg/kg/min every 3 minutes up to a maximum dose of 40 µg/kg/min. Atropine (up to 1 mg) was administered intravenously at the end of the last stage if the target heart rate was not achieved. End points of the test were an achievement of the target heart rate (85% of the maximal heart rate predicted for age), the maximal dose of dobutamine and atropine, >2 mV downsloping ST-segment depression measured 80 ms from the J point compared with baseline, hypertension (blood pressure >240/120 mm Hg), a decrease in systolic blood pressure of >40 mm Hg, and significant arrhythmias.

Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress, and during recovery using standard views. Regional wall motion and systolic wall thickening were scored on a 5-point scale using a standard 16 segment left ventricular model. Ischemia was defined as new or worsened wall motion abnormalities (WMA) during stress indicated by an increase of wall motion score ≥1 grade in ≥1 segment. A biphasic response in an akinetic or severely hypokinetic segment was considered as an ischemic response. Ischemia was not considered present when akinetic segments at rest became dyskinetic during stress.[12] For each patient, a wall motion score index (WMSI) was calculated by dividing the sum of segment scores by the total number of interpreted segments. The test was considered abnormal if WMA were seen either at rest or during stress.

Follow-up

Outcome data were obtained by a questionnaire, evaluation of hospital records, contacting the patient's general practitioner, and/or review of civil registries. The cause of death was retrieved at Statistics Netherlands (www.cbs.nl). This permitted high accuracy for determination of survival status. Deaths were classified as either documented cardiac death or other. Before contacting the patient, the online municipal civil registry was used to determine the patient's present survival status. Survival status was retrieved in 99% of the patients. Questionnaires were sent to all patients alive. The response rate of this questionnaire was 83%. The date of response was used to calculate follow-up time. Follow-up events noted were overall mortality, hard cardiac events (non-fatal MI and cardiac death), and revascularization.

Statistical analysis

Continuous data are expressed as mean values ± SD. The Student t test was used to analyze continuous data, and the chi-square test was used for differences between proportions. The incremental value of DSE over the clinical variables in the prediction of selected end points was evaluated using multivariate Cox proportional hazard analysis (SPSS Software, version 21.0) including a model with baseline characteristics and clinical variables. Only variables that were significant in a univariate model were added to the multivariate model. Using a stepwise model, echocardiographic variables at rest were then added to the clinical model to investigate the increase in chi-square value of the model. Finally, the variables at peak-dose dobutamine were added to the model. The test was considered of additional value if there was a significant increase in chi-square value at the third step of the test. The echocardiographic variables that were added at rest and peak-dobutamine dose were heart rate, systolic and diastolic blood pressure, rate pressure product (defined as maximum heart rate times the maximum systolic blood pressure), WMSI, and WMA. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. To determine the warranty period of DSE, the Cox proportional hazard analysis for an abnormal DSE was repeated at 1, 2, 3, and so on years of follow-up. A p value <0.05 was considered statistically significant.

Table 1. Clinical characteristics.

Variable	N = 3381
Men	2275 (67%)
Age (years)	61.4 ± 12
Hypertension	1005 (30%)
Hypercholesterolemia	770 (23%)
Smoking	988 (29%)
Diabetes mellitus	378 (11%)
Heart failure	454 (13%)
Coronary artery disease	1525 (13%)
Beta-blockers	1116 (33%)
Calcium-channel blockers	816 (24%)
Angiotensin-converting-enzyme blockers	845 (25%)
Diuretics	477 (14%)
Nitrates	1031 (31%)

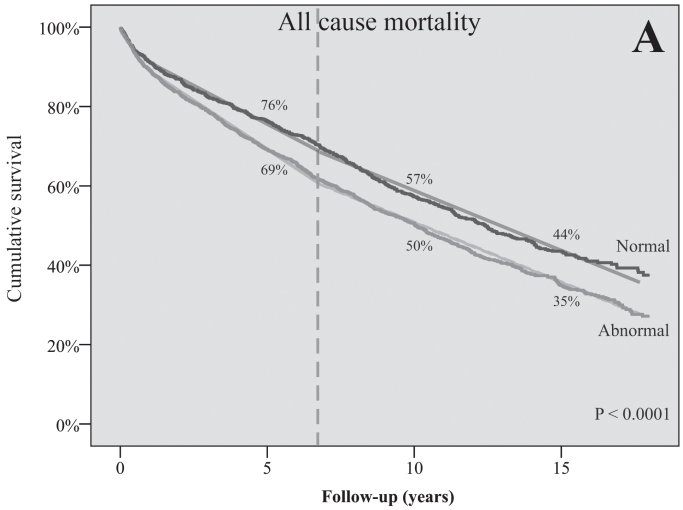
RESULTS

Mean age at time of DSE was 61±12 years. There were 2,275 men (67%) and 1,106 women (33%). Forty-five percent of the patients had known CAD. Clinical characteristics are presented in Table 1. The test was terminated for achievement of the target heart rate in 89% of the patients, maximal dobutamine/atropine dose in 3%, ST-segment changes in 3%, arrhythmias in 1%, severe angina in 1%, abnormal blood pressure in 1%, and other symptoms in 2%. Five hundred sixty eight (17%) patients had typical angina during dobutamine stress.

DSE was normal in 1,170 of the patients (35%). Ischemia on DSE was detected in 1,610 patients (48%); of which 1,441 (90%) had WMA at rest. Six hundred one (18%) patients had WMA at rest alone. During a mean follow-up of 13±3.2 years (range 7.3 to 20.5 years), there were 1,725 deaths (51%), of which 1,128 (33% of total study cohort) were attributed to cardiac causes. Two hundred ninety-seven patients (8.8%) had a nonfatal MI, and 793 patients were revascularized (23.5%) at during follow-up. The annualized mortality rate of patients who underwent revascularization after an ischemic event was comparable to the group who did not undergo percutaneous coronary intervention (3.9% vs 4.2%, respectively).

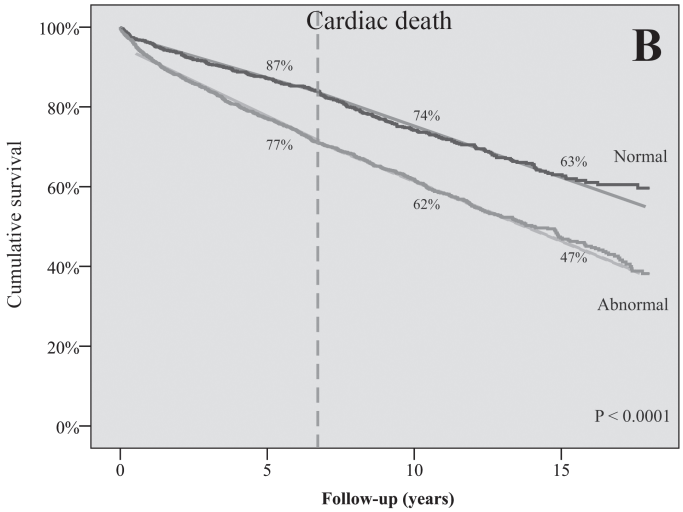
Cumulative survival curves (Figure 1) showed a significantly better survival of patients with normal DSE in comparison with abnormal DSE (76% vs 69% at 5 years, 57% vs 50% at 10 years, and 44% vs 35% at 15 years; overall $p<0.001$). Figure 1 illustrates that also for the end points cardiac death (87% vs 77% at 5 years, 74% vs 62% at 10 years, and 63% vs 47% at 15 years; overall $p<0.001$) and hard cardiac events (82% vs 69% at 5 years, 65% vs 51% at 10 years, and 52% vs 34% at 15 years; overall $p<0.001$), the population with a normal DSE had significant lower chance of adverse events.

Univariate and multivariate predictors associated with an increased risk of all end points of interest are presented in Tables 2 and 3. Echocardiographic variables at peak-dose dobutamine significantly increased the value of the test for all end points. When comparing echocardiographic variables at rest to variables at maximum dose dobutamine, the chi-square of the test improved from 842 to 870 ($p<0.0001$) and from 684 to 740 ($p<0.0001$) for all-cause mortality and cardiac death, respectively. WMSI during stress predicted both all-cause mortality and cardiac death. At 5 years of follow-up, the hazard ratio of having an abnormal DSE reached a maximum of 1.37 and started to decrease after 7 years of follow-up.



At risk:

Time (y)	*0*	*5*	*10*	*15*
Normal	1,170	801	464	195
Abnormal	2,211	1,378	754	179



At risk:

Time (y)	*0*	*5*	*10*	*15*
Normal	1,170	801	464	195
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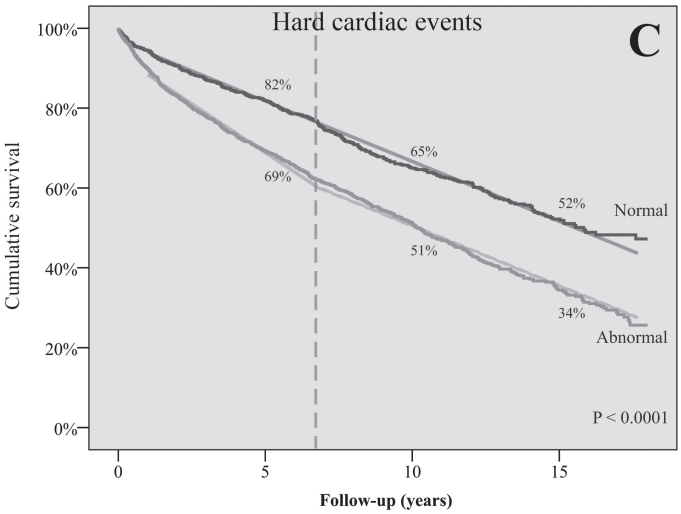

At risk:

Time (y)	*0*	*5*	*10*	*15*
Normal	1,054	669	363	145
Abnormal	2,024	1,123	568	117

Figure 1. Kaplan-Meier survival curves for all-cause mortality (A), cardiac death (B), and hard cardiac events (C) in patients with normal (dark gray) versus abnormal (light gray) DSE. The dummy lines illustrate that the curves start to run parallel at approximately 7 years (dashed line).

DISCUSSION

DSE is a commonly used tool to predict short to medium-term outcome of patients with limited exercise capacity. In this high-risk patient cohort, DSE has incremental value at very long-term follow-up for predicting all end points of interest in a consecutive population with known or suspected CAD. DSE added prognostic value to clinical variables and stress test data in predicting all-cause mortality, cardiac death, and hard cardiac events. Heart rate, WMSI, and new or worsened WMA during peak-dose dobutamine were significant predictors depending on the end points of interest (Tables 2 and 3). Kaplan-Meier curves confirmed the previously described findings because outcome for all end points of interest was in favor of a normal DSE in comparison with an abnormal DSE at 18 years after initial testing ($p<0.001$).

Although the Kaplan-Meier curves showed a significant improved outcome in favor of a normal DSE for all end points, it is of interest to see that the curve of all-cause mortality (Figure 1) diverges up to approximately 7 years after DSE. At this point, the test seems to stop to further discriminate between abnormal and normal DSE and both lines

Table 2. Independent predictors of all-cause mortality.

	Univariate	I: Clinical	II: I + DSE at rest	III: II + DSE at peak
Variable		**HR (CI)**	**HR (CI)**	**HR (CI)**
Male gender	1.45 (1.31-1.62)	1.39 (1.25-1.55)	1.39 (1.25-1.55)	1.38 (1.23-1.54)
Age	1.06 (1.05-1.06)	1.06 (1.05-1.06)	1.06 (1.06-1.07)	1.06 (1.06-1.07)
Coronary artery disease	n.s.	-	-	-
Heart failure	1.91 (1.68-2.17)	1.59 (1.38-1.82)	1.36 (1.18-1.58)	1.40 (1.21-1.62)
Diabetes mellitus	1.44 (1.25-1.65)	1.49 (1.30-1.72)	1.41 (1.22-1.62)	1.40 (1.21-1.61)
Hypertension	n.s.	-	-	-
Hypercholesterolaemia	0.71 (0.62-0.80)	0.74 (0.65-0.84)	0.68 (0.60-0.77)	0.69 (0.60-0.78)
Smoking	1.24 (1.12-1.37)	1.42 (1.28-1.57)	1.42 (1.28-1.58)	1.42 (1.28-1.58)
Beta-blockers	0.81 (0.73-0.89)	0.86 (0.77-0.96)	n.s.	-
Calcium-channel blockers	n.s.	-	-	-
Angio-converting enzyme inhibitors	1.29 (1.16-1.43)	n.s.	-	-
Diuretics	1.73 (1.53-1.97)	1.33 (1.15-1.53)	1.23 (1.07-1.42)	1.23 (1.07-1.42)
Digoxin	2.24 (1.88-2.68)	1.36 (1.12-1.65)	n.s.	-
Nitrates	n.s.	-	-	-
Heart rate rest	1.11 (1.07-1.15)	-	1.13 (1.09-1.18)	n.s.
Systolic blood pressure rest	1.05 (1.03-1.07)	-	n.s.	-
Diastolic blood pressure rest	n.s.	-	-	-
Rate pressure product rest	1.01 (1.00-1.01)	-	n.s.	-
Wall motion score index rest	1.48 (1.38-1.59)	-	1.32 (1.22-1.44)	-
Rest wall motion abnormalities	1.29 (1.17-1.42)	-	n.s.	-
Heart rate peak	0.97 (0.95-0.99)	-	-	n.s.
Systolic blood pressure peak	0.97 (0.95-0.99)	-	-	n.s.
Diastolic blood pressure peak	0.95 (0.92-0.98)	-	-	n.s.
Rate pressure product peak	1.00 (1.00-1.00)	-	-	n.s.
Wall motion score index peak	1.54 (1.43-1.67)	-	-	1.35 (1.23-1.48)
Peak wall motion abnormalities	1.37 (1.25-1.51)	-	-	n.s.
Any wall motion abnormalities	1.27 (1.15-1.41)	-	-	n.s.
X^2-test		**842**	**870**	**870**
P-value		**-**	**P<0.0001**	**P<0.0001**

n.s. = not significant, - = variable not included.

Table 3. Independent predictors of cardiac death.

Variable	Univariate	I: Clinical HR (CI)	II: I + DSE at rest HR (CI)	III: II + DSE at peak HR (CI)
Male gender	1.56 (1.36-1.78)	1.46 (1.27-1.67)	1.40 (1.22-1.61)	1.38 (1.20-1.59)
Age	1.07 (1.05-1.05)	1.06 (1.06-1.07)	1.06 (1.06-1.07)	1.06 (1.05-1.07)
Coronary artery disease	1.33 (1.18-1.50)	n.s.	-	-
Heart failure	2.47 (2.14-2.86)	2.00 (1.70-2.35)	1.60 (1.36-1.89)	1.65 (1.40-1.94)
Diabetes mellitus	1.40 (1.17-1.67)	1.42 (1.19-1.70)	1.32 (1.11-1.58)	1.30 (1.09-1.56)
Hypertension	n.s.	-	-	-
Hypercholesterolaemia	0.78 (0.67-0.90)	0.80 (0.69-0.94)	0.72 (0.62-0.84)	0.73 (0.63-0.86)
Smoking	1.36 (1.20-1.54)	1.54 (1.36-1.74)	1.54 (1.35-1.74)	1.53 (1.35-1.73)
Beta-blockers	0.81 (0.71-0.92)	0.86 (0.75-0.98)	n.s.	-
Calcium-channel blockers	n.s.	-	-	-
Angio-converting enzyme inhibitors	1.48 (1.30-1.68)	n.s.	-	-
Diuretics	1.95 (1.67-2.26)	1.34 (1.12-1.59)	n.s.	-
Digoxin	2.68 (2.18-3.28)	1.46 (1.17-1.83)	1.36 (1.09-1.70)	1.33 (1.06-1.66)
Nitrates	1.32 (1.16-1.49)	n.s.	-	-
Heart rate rest	1.12 (1.06-1.17)	-	1.13 (1.08-1.18)	1.14 (1.09-1.19)
Systolic blood pressure rest	1.03 (1.01-1.06)	-	n.s.	-
Diastolic blood pressure rest	n.s.	-	-	-
Rate pressure product rest	1.01 (1.00-1.01)	-	n.s.	-
Wall motion score index rest	1.78 (1.64-1.94)	-	1.54 (1.39-1.69)	n.s.
Rest wall motion abnormalities	1.70 (1.50-1.93)	-	n.s.	-
Heart rate peak	0.96 (0.94-0.99)	-	-	n.s.
Systolic blood pressure peak	0.95 (0.93-0.97)	-	-	n.s.
Diastolic blood pressure peak	0.93 (0.89-0.96)	-	-	n.s.
Rate pressure product peak	1.00 (0.99-1.00)	-	-	n.s.
Wall motion score index peak	1.93 (1.77-2.12)	-	-	1.63 (1.47-1.81)
Peak wall motion abnormalities	1.76 (1.57-1.99)	-	-	n.s.
Any wall motion abnormalities	1.70 (1.49-1.94)	-	-	n.s.
X^2-test		**684**	**734**	**740**
P-value		**-**	**P<0.0001**	**P<0.0001**

n.s. = not significant, - = variable not included.

start to run parallel. This effect is less pronounced in the Kaplan-Meier curves of cardiac death and hard cardiac events (Figure 1), but it suggests a certain "warranty period" of a DSE. This in line with what we observed in the diabetic subcohort of this population,[5] where a similar phenomenon was observed at 7 years.

The prognostic significance of DSE at short- to medium-term follow-up has been demonstrated in several studies.[13-17] Currently, there are no studies evaluating the very long-term prognostic role of DSE. In a meta-analysis, Shaw et al[18] investigated the prognostic role of dipyridamole and DSE in preoperative screening before vascular surgery. The meta-analysis included 15 studies, of which 5 studies (n=445) were based on studies on DSE. The analysis demonstrated that echocardiographic WMA were predictive of adverse perioperative outcomes. Their analysis supports pharmacologic stress imaging as a tool for preoperative screening in patients at intermediate risk. These previous studies provide useful information about the clinical importance of DSE, but the very long-term prognostic value of a DSE remains unclear. This study provides unique information on the very long-term prognostic value of the test in a consecutive population of subjects with known or suspected CAD. It demonstrates the clinical importance of DSE results for assessment of very long-term outcome.

The event rate in this present study is high (51% of the patients died during follow-up). There are multiple factors that may explain the relatively high event rate in this study. First, this cohort is a high-risk group, the mean age was 61 years and 45% had known CAD, whereas 65% of the patients had an abnormal DSE. Second, all patients underwent DSE because of limited exercise capacity. The inability to perform an adequate exercise test is an indicator of adverse outcome in itself. Third, the follow-up of this cohort was nearly complete. Finally, this study has followup period of >10 years, which is significantly longer than previous studies.

Although this study included a high-risk population, Table 1 demonstrates that patients seemed undertreated according to current standards. Inclusion of patients in this study started as early as 1990, a time at which medical treatment was suboptimal compared with current standards, as has been demonstrated in the EUROASPIRE (EUROpean Action on Secondary and Primary prevention through Intervention to Reduce Events) registry.[19] Referral to coronary revascularization (23.5%) was also relatively low given the 48% of the patients with detected ischemia. However, previous studies have demonstrated that the timing of revascularization requires careful consideration. Patients with no or mild symptoms and little ischemia can safely be treated with medical treatment alone. Furthermore, the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial[21] has demonstrated that clinical outcome in

patients with stable angina does not significantly differ between patients who receive an initial therapy of coronary revascularization and optimal medical therapy compared to patients with optimal medical therapy alone.

The American College of Cardiology recommends pharmacologic stress with either nuclear myocardial infusion imaging or echocardiography for risk assessment in patients with stable ischemic heart disease who are either unable to exercise to an adequate workload regardless of interpretability of electrocardiogram, patients with left bundle branch block on electrocardiogram regardless of ability to exercise to an adequate workload or patients who are being considered for revascularization of known coronary stenosis of unclear physiological significance.[22] The appropriateness criteria for stress echocardiography formulated by the American College Cardiology illustrate these recommendations and add several clinical scenarios in which stress echocardiography is the preferred technique or can be considered.[23] The present study demonstrates that DSE is a valuable test in predicting all-cause mortality, cardiac death, and hard cardiac events, even at very long-term follow-up. The long-lasting follow-up of this study is unique and reinforces the finding from shorter follow-up studies that stress echo is a powerful prognostic test. There seems to be a "warranty period" of approximately 7 years after which a DSE start to lose its ability to further discriminate between a normal and abnormal DSE.

This study has some limitations. First, because of the clinical factors leading patients to be referred for DSE at the time of initial testing, they are likely to have had increased risk for adverse events with a worse prognosis than a general population. This may limit application of the present findings to patients suspected for CAD in general. Furthermore, left ventricular ejection fraction was not available in all patients because it was only measured on indication and could therefore not be used in the analysis.

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Chapter 13

Cardiac stress imaging for the prediction of very long-term outcomes: dobutamine stress echocardiography or dobutamine ^{99m}Tc-sestamibi SPECT?

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ABSTRACT

Background. Both dobutamine stress echocardiography (DSE) and myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) are frequently used for cardiac risk stratification. The long-term relative prognostic value of these modalities has not been studied. Therefore, this study evaluated the long-term prognostic value of DSE compared to MPI in patients unable to perform exercise testing.

Methods. This prospective, single center study included 301 patients (mean age 59±12 years, 56% men) unable to perform exercise tests who underwent DSE and dobutamine stress ^{99m}Tc-sestamibi MPI. End-points during follow-up were all-cause mortality, cardiac mortality and nonfatal myocardial infarction (MI). Univariable and multivariable Cox proportional hazards regression models were used to identify independent predictors of outcome. The probability of survival was calculated using the Kaplan-Meier method.

Results. A total of 182 patients (60%) had an abnormal DSE and 198 (66%) patients had an abnormal MPI. The agreement between DSE and MPI was 82% (κ=0.62). During a median follow-up of 14 years (range 5-18) , 172 deaths (57%) occurred, of which 72 (24 %) were due to cardiac causes. Nonfatal MI occurred in 46 patients (15%). The multivariable analysis demonstrated that an abnormal DSE was a significant predictor of cardiac mortality (HR 2.35, 95% CI [1.17-4.73]) and hard cardiac events (HR 2.11, 95% CI [1.25-3.57]). Also, an abnormal MPI result was a significant predictor of cardiac mortality (HR 3.03, 95% CI [1.33-6.95]) and hard cardiac events (HR 2.06, 95% CI [1.12-3.79]).

Conclusions. DSE and MPI are comparable in predicting long-term cardiac mortality and hard cardiac events in patients unable to perform exercise testing.

Key Words: DSE, myocardial perfusion imaging, SPECT, long-term prognostic value, cardiac events.

ABBREVIATIONS

CAD	Coronary artery disease
C-index	Concordance index
DSE	Dobutamine stress echocardiography
ECG	Electrocardiography
LVEF	Left ventricular ejection fraction
MBq	Megabecquerel
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
SPECT	Single-photon emission computed tomography
^{99m}Tc	Technetium-99m

INTRODUCTION

Coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide. As such, noninvasive imaging techniques are important to diagnose and risk stratify patients with CAD.[1] In patients who cannot exercise, due to conditions such as degenerative joint disease and peripheral vascular disease, pharmacologic stress testing is an appropriate alternative. Both dobutamine stress echocardiography (DSE) and stress myocardial perfusion imaging (MPI) are widely used for the evaluation of stress-induced myocardial ischemia, and provide significant prognostic information.[2-7] Currently, information on the long-term relative prognostic value of DSE compared to MPI is lacking. Therefore, this study evaluated the long-term prognostic value of DSE compared to MPI in patients unable to perform exercise testing.

METHODS

Study population

The study population consisted of 354 consecutive patients. This study is a continuation of the previously reported study in which the same patient population was evaluated with a mean follow-up of 7.3 years.[3] All patients underwent simultaneous dobutamine stress echocardiography and dobutamine stress ^{99m}Tc-sestamibi SPECT for the evalua-

tion of suspected or known CAD. Follow-up was successful in 351 (99%) patients. Fifty patients underwent early coronary revascularization <60 days after MPI and were excluded from analysis. This exclusion was based on previously published data indicating that referral to coronary revascularization in the first 60 days after testing tends to be based on the results of the test. Referral to revascularization >60 days after testing tends to be based on the worsening of the patient's clinical status.[8] All patients gave informed consent before testing and the local ethics committee approved the study protocol. Patients were enrolled between January 1991 and January 1995. The test in these patients with known or suspected CAD was requested for evaluation of ischemia. Before the stress test, a structured interview was achieved, including assessment of cardiac risk factors. Hypertension was defined as blood pressure ≥140/90 mmHg or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level >140 mg/dL or use of insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol ≥6.4 mmol/L or treatment with lipid-lowering medication.

Dobutamine stress testing protocol

The dobutamine stress testing was performed using a standard protocol as described previously.[3] Dobutamine was injected intravenously, starting at a dose of 10 µg/kg/min for 3 minutes and increasing by 10 µg/kg/min to a maximum dose of 40 µg/kg/min. If the test end point was not reached at a maximum dose of dobutamine, up to 1 mg of atropine was administered intravenously. During stress testing, blood pressure, heart rate and electrocardiography were continuously monitored. Test endpoints were achievement of target heart rate (85% of maximum age and sex-predicted heart rate), horizontal or downsloping ST segment depression of more than 2 mm, ST-segment elevation of more than 1 mm, severe angina, systolic blood pressure decrease >40 mmHg, blood pressure > 240/110 mmHg or clinically important cardiac arrhythmias. An intravenous beta-blocker was used to reverse the effects of dobutamine/atropine.

^{99m}Tc-sestamibi SPECT MPI

An intravenous dose of 370 MBq of ^{99m}Tc-sestamibi was administered approximately 1 minute before the termination of the stress test. For resting studies, 370 MBq of ^{99m}Tc-sestamibi was injected ≥ 24 hours after the stress study. Image acquisition was achieved with a Gammasonics single-head camera (Siemens, Iselin, NJ) without attenuation or scatter correction, using a low-energy all-purpose collimator. In all cases, transaxial

tomograms were reconstructed; for each study, six short-axis and three sagittal long-axis slices were analysed. To compare the rest and stress studies, each of the short-axis slides was divided into eight equal segments. The septal part of the two basal slices was excluded from analysis because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. The apical region was assessed from the three sagittal cross-sections. A total of 47 segments per patient were analysed. Data interpretation was performed visually and semiquantitatively. Circumferential profile analysis was used to assist visual analysis of images.

Stress and rest tomographic views were reviewed side-by-side by two experienced observers who were unaware of clinical data and echocardiograms, using a 5-point scoring system (1 = normal, 2 = slightly reduced, 3 = moderately reduced, 4 = severely reduced, 5 = absent uptake). Ischemia was defined as a perfusion defect on stress images that partially or completely resolved at rest in at least two contiguous segments. A region was classified as infarcted in the case of a perfusion defect on stress images in two or more contiguous segments, which persisted on rest images. An abnormal scan was considered in the presence of a fixed or reversible perfusion defect. To overcome misalignment between the myocardial perfusion data and the echocardiographic data, an identical six-segment model was used for both techniques. The 16 echocardiographic and 47 scintigraphic segments were regrouped into six major myocardial regions (anterior, septum anterior, septum inferior, inferoposterior, lateral and apical).

Dobutamine stress echocardiography

Two dimensional echocardiograms were acquired at rest, during dobutamine stress testing, and during recovery. Two experienced observers, unaware of any other data, scored the echocardiograms using a standard 16-segment model. Regional wall motion and systolic wall thickening were scored on a 5-point scale (1=normal, 2= mild hypokinesia, 3 = severe hypokinesia, 4 = akinesia, 5 = dyskinesia). Ischemia was defined as new or worsened wall motion abnormalities during stress, indicated by an increase in wall motion score of ≥ 1grade in one or more segments. Ischemia was not considered to be present when akinetic segments at rest became dyskinetic during stress. Dobutamine stress echocardiographic results were defined as abnormal if there was ischemia during stress or fixed wall motion abnormalities. Echocardiographic segments were grouped into six major segments for comparison with SPECT.[9] Tests that were stopped prematurely in the absence of perfusion or wall motion abnormalities were considered negative.

Follow-up

Clinical outcome data were obtained in 2012 by contacting the patient, the patients' general practitioners, civil registries and reviewing hospital records. The date of the last review or consultation was used to calculate follow-up time. The endpoints were all-cause mortality, cardiac mortality and nonfatal myocardial infarction (MI). Cardiac mortality was defined as death caused by MI, cardiac arrhythmias, refractory heart failure, or sudden death occurring without another explanation. The combined endpoint of cardiac mortality and nonfatal MI was considered as hard cardiac events. MI was defined according to the Joint European Society of Cardiology/American College of Cardiology Committee criteria.[10] Diagnosis of an acute, evolving, or recent MI was fulfilled either by a typical rise and gradual fall (troponin) or more rapid rise and fall (creatinine kinase–MB) of biochemical markers of myocardial necrosis with at least one of the following criteria: ischemic symptoms, development of pathological Q waves on the electrocardiogram, electrocardiogram changes indicative of myocardial ischemia (ST-segment elevation or depression), or coronary artery intervention; or by pathological findings of an acute MI.

Statistical analysis

Values were expressed as means (±SD) or number, and compared using the Student t test or chi-squared test. Agreement between DSE and MPI was assessed by κ statistics. Univariable and multivariable Cox proportional hazard models were used to identify variables that were independently predictive of late cardiac events. The risk of a variable was expressed as hazard ratios with corresponding 95% confidence intervals. Clinical data, stress test variables, and non-invasive imaging data were incorporated into the analysis. The multivariable analysis was performed by first considering the clinical data, and next the combination of clinical and stress test variables. In the final models, the stress echocardiographic or ^{99m}Tc-sestamibi SPECT data were added. The discriminative ability of the Cox regression models was determined by calculating the concordance-(C)-index. Models are typically considered reasonable when the C-index > 0.7.[11] The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS 22 (IBM Corp., Armonk, NY, USA).

Table 1. Clinical characteristics.

Variable (number and %)	Total	Cardiac mortality	No cardiac mortality	*p-value*	Cardiac events	No cardiac events	*p-value*
	N=301	N=72	N=229		N=118	N=183	
Clinical data							
Age>70 years	55 (18)	22 (31)	33 (14)	0.65	23 (19)	32 (17)	0.38
Male gender	168 (56)	50 (69)	118 (52)	0.01	79 (67)	89 (49)	0.002
Previous MI	149 (50)	51 (71)	98 (43)	<0.001	79 (34)	70 (38)	<0.001
Hypertension	132 (44)	34 (47)	98 (43)	0.49	54 (46)	78 (43)	0.45
Hypercholesterolemia	76 (25)	23 (32)	53 (23)	0.21	34 (29)	42 (23)	0.27
Smoking	79 (26)	26 (36)	53 (23)	0.03	34 (29)	45 (25)	0.42
Heart failure	57 (19)	26 (36)	31 (14)	<0.001	30 (25)	27 (15)	0.003
Diabetes mellitus	43 (14)	14 (19)	29 (13)	0.16	19 (16)	24 (13)	0.55
Stress test results							
Typical angina	72 (24)	16 (22)	56 (24)	0.69	33 (28)	39 (21)	0.21
ST-segment changes	85 (28)	31 (43)	54 (24)	0.001	47 (21)	38 (21)	0.001
Abnormal DSE	182 (60)	59 (82)	123 (54)	<0.001	92 (78)	90 (49)	<0.001
Abnormal MPI	198 (66)	62 (86)	136 (59)	<0.001	97 (82)	101 (55)	<0.001

*MI = myocardial infarction. DSE = dobutamine stress echocardiography. MPI = myocardial perfusion imaging

RESULTS

Patient demographics and stress test results

The clinical characteristics are presented in Table 1. The mean age of the 301 patients was 59±12 years, and 56% were men. A total of 149 patients (50%) had a previous MI. During the dobutamine-atropine stress test, heart rate increased from a mean (±SD) of 69 ± 13 beats per minute to 136 ± 17 beats per minute (P<0.0001) and systolic blood pressure increased from 136 ± 23 mm Hg to 147 ± 30 mm Hg (P<0.001). Atropine, which was added in 129 patients (43%), was more frequently administered in patients taking beta-blockers (67% (84/125]) than in those who were not (26% (45/176], P<0.0001). Side effects during stress testing included non-sustained ventricular tachycardia in 13 patients (4%), atrial fibrillation in 4 patients (1%), severe hypotension in 2 patients (0.7%), nausea in 15 patients (5%), and headache in 15 patients (5%). No patient experienced a MI or fatal complication. The test was terminated because of side effects in 17 patients (6%).

Imaging results and follow-up

Abnormal DSE was detected in 182 (60%) patients, whereas 198 (66%) patients had an abnormal MPI. The agreement between DSE and MPI was 82% ($\kappa = 0.62$). When considered the 152 patients without previous MI the agreement between DSE and MPI was 81% ($\kappa = 0.60$). The agreement between DSE and MPI was 86% ($\kappa = 0.36$) when only ischemia was considered. Normal DSE and abnormal MPI was observed in 35 patients, whereas 19 patients had a normal MPI and an abnormal DSE. During a median follow-up of 14 years (range 5-18), 172 deaths (57%) occurred, of which 72 (24 %) were due to cardiac causes. Nonfatal MI occurred in 46 patients (15%).

Clinical data and outcome

Univariable predictors of both endpoints (cardiac mortality and hard cardiac events) were age, male gender, previous MI, heart failure and ST-segment changes (Table 1). When analyzed as a dichotomous variable age was not a significant predictor. Smoking was also a significant predictor of cardiac mortality. Both an abnormal DSE and an abnormal MPI were strongly associated with both endpoints.

Survival analysis and predictors of long-term outcome

Annualized event rates for cardiac mortality for patients with normal DSE was significantly lower (0.8%) than for those with abnormal DSE (2.8%, $p< 0.001$). According to hard cardiac events, annualized event rates for normal DSE were 1.5% compared to 3.8% in abnormal DSE ($p< 0.001$). Equally, the annualized event rates for cardiac mortality for patients with normal MPI was significantly lower than for those with abnormal MPI (0.6% versus 2.8%, $p < 0.001$). The annualized rates for hard cardiac events were 1.3% in normal MPI and 3.7% in abnormal MPI ($p< 0.001$).

Kaplan-Meier survival curves are presented in Figures 1, 2 and 3. The survival curves show that a normal DSE and a normal MPI were associated with relatively low risk for all-cause mortality, cardiac mortality and hard cardiac events. Conversely, patients with

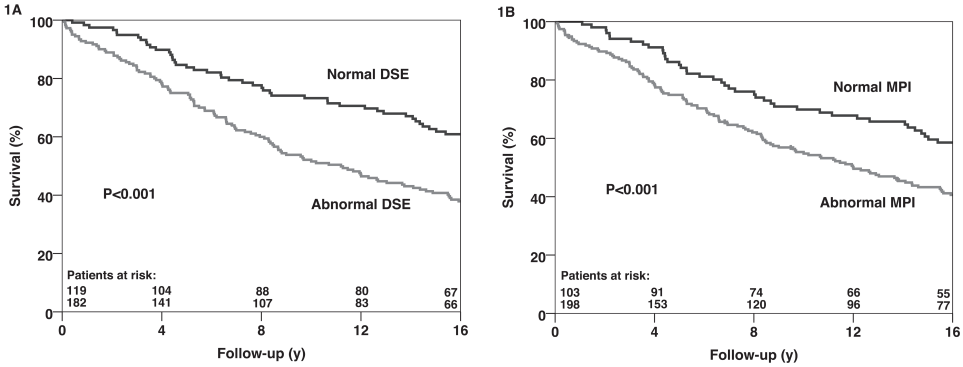

Figure 1. Kaplan-Meier survival curves for all-cause mortality using DSE (1A) and MPI (1B).

y=years. MPI = myocardial perfusion imaging. DSE = dobutamine stress echocardiography.

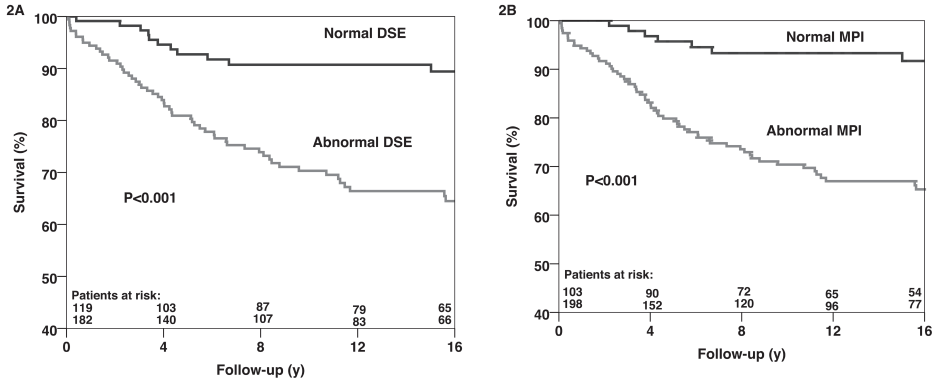

Figure 2. Kaplan-Meier survival curves for cardiac mortality using DSE (2A) and MPI (2B).

y=years. MPI = myocardial perfusion imaging. DSE = dobutamine stress echocardiography.

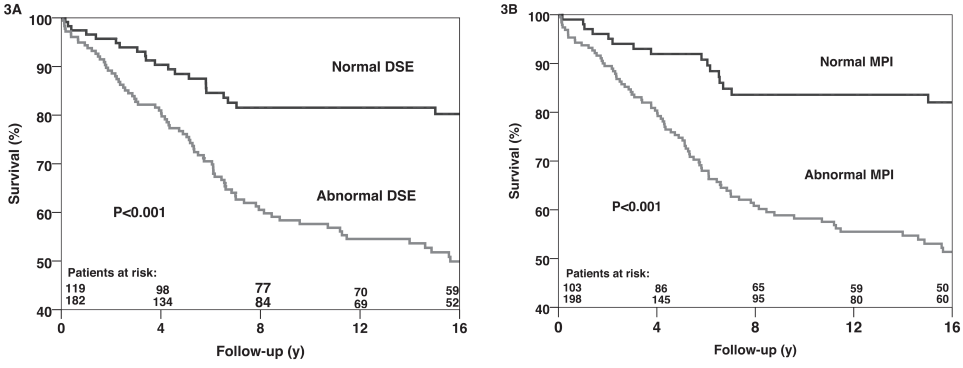

Figure 3. Kaplan-Meier survival curves for hard cardiac events using DSE (3A) and MPI (3B).

y=years. MPI = myocardial perfusion imaging. DSE = dobutamine stress echocardiography.

an abnormal test result had a significantly increased risk of all-cause mortality (Figure 1), cardiac mortality (Figure 2) and hard cardiac events (Figure 3). The survival curves continued to diverge during the long-term follow-up period, which indicated a maintained prognostic value of both imaging modalities.

Multivariable analysis demonstrated that age, previous MI, smoking and heart failure were independent predictors of cardiac mortality (Table 2). Previous MI and heart failure were independent predictors of hard cardiac events (Table 2). Age was of borderline significance. A multivariable model also revealed that both an abnormal DSE and an abnormal MPI had an incremental prognostic value over clinical variables and stress test parameters. For the prediction of cardiac mortality, the C-index for clinical and clinical and stress test data was 0.73 and 0.76 respectively. The C-index was 0.76 when DSE or MPI was added. For the prediction of hard cardiac events, the C-index for clinical and clinical and stress test data was 0.70 and 0.71 respectively and 0.71 when DSE or MPI were added.

DISCUSSION

The present study is the first to assess the prognostic value of DSE compared to MPI for long-term outcome. During a median follow-up of 14 years, 172 deaths occurred, of which 72 were due to cardiac causes. Nonfatal MI occurred in 46 patients. The survival curves continued to diverge during the follow-up period, indicating a maintained prognostic value of both DSE and MPI. Both patients with a normal DSE and a normal MPI had a relatively favourable long-term prognosis in contrast to patients with an abnormal imaging result. A multivariable model revealed that both an abnormal DSE and an abnormal MPI had an incremental prognostic value over clinical variables and stress test parameters. Ischemia on DSE but not ischemia on MPI was predictive of outcome. Both modalities were comparable in identifying patients with low or high risk of cardiac events during long-term follow-up.

Non-invasive imaging techniques are central in diagnosing patients with known of suspected CAD. Both DSE and MPI play important roles in this regard, in particular in patients with an intermediate likelihood of CAD[12], and show similar accuracy in the diagnosis of CAD.[5, 6] Data on the long-term prognostic implications of these imaging techniques are lacking.[13]

Table 2. Multivariable predictors of cardiac mortality and hard cardiac events.

	Cardiac mortality				Hard cardiac events			
Variable	Clinical data	Clinical data + stress test	Clinical data + stress test + SPECT	Clinical data + stress test + ECHO	Clinical data	Clinical data + stress test	Clinical data + stress test + SPECT	Clinical data + stress test + ECHO
Clinical data								
Age*	1.04 (1.01-1.06)	1.04 (1.02-1.06)	1.04 (1.02-1.07)	1.04 (1.02-1.06)	p=0.05	1.02 (1.01-1.04)	1.02 (1.00-1.04)	1.02 (1.00-1.04)
Men	p=0.25	p=0.36	p=0.36	p=0.30	p=0.10	p=0.08	p=0.15	p=0.09
Previous MI**	2.32 (1.34-4.01)	2.16 (1.24-3.75)	p=0.09	p=0.06	2.25 (1.47-3.45)	2.06 (1.33-3.17)	1.69 (1.06-2.68)	p=0.05
Hypertension	p=0.29	p=0.29	p=0.80	p=0.90	p=0.37	p=0.18	p=0.24	p=0.73
Hypercholesterolemia	p=0.23	p=0.23	p=0.14	p=0.17	p=0.94	p=0.72	p=0.73	p=0.48
Smoking	1.88 (1.14-3.10)	1.78 (1.08-2.94)	1.78 (1.08-2.95)	1.89 (1.14-3.12)	p=0.67	p=0.54	p=0.82	p=0.42
Heart failure	2.52 (1.52-4.18)	2.39 (1.43-3.97)	2.29 (1.38-3.82)	2.31 (1.38-3.88)	1.77 (1.14-2.76)	1.63 (1.04-2.54)	p=0.08	1.62 (1.03-2.55)
Diabetes mellitus	p=0.28	p=0.41	p=0.24	p=0.27	p=0.87	p=0.93	p=0.86	p=0.71
Stress test variables								
Typical angina	-	p=0.25	p=0.39	p=0.33	-	p=0.83	p=0.82	p=0.54
ST-segment changes	-	1.93 (1.18-3.14)	1.69 (1.03-2.77)	1.78 (1.08-2.93)	-	1.85 (1.23-2.77)	1.67 (1.11-2.52)	1.61 (1.05-2.45)
Abnormal MPI	-	-	3.03 (1.33-6.95)	-	-	-	2.06 (1.12-3.79)	-
Abnormal DSE	-	-	-	2.35 (1.17-4.73)	-	-	-	2.11 (1.25-3.57)
C-index	0.73	0.76	0.76	0.76	0.70	0.71	0.71	0.71

*per 10% increase

**MI = myocardial infarction. MPI = myocardial perfusion imaging. SPECT = single-photon emission computed tomography

Values are expressed as Cox proportional hazard ratio (HR) and 95% confidence interval (CI).

A few previous studies have compared the prognostic value between DSE and MPI with a mean follow-up time of less than 8 years.[2, 3 ,5-7, 14, 15] Geleijnse et al.[2] studied 220 patients with chest pain undergoing DSE and simultaneous ^{99m}Tc-sestamibi SPECT. 24 patients experienced hard cardiac events. During a follow-up of 31±15 months, event rates after both stress modalities were similar. They concluded that DSE and MPI provided comparable prognostic information. Olmos et al.[14] reported a study of 248 patients who underwent exercise echocardiography and thallium-201 SPECT. During a mean follow-up of 3.7 ± 2.0 years, 8 nonfatal infarctions and 7 cardiac deaths occurred. They reported that exercise echocardiography and thallium-201 SPECT provide comparable prognostic information for cardiac death and cardiac events. In 146 patients with previous MI, Acampa et al.[15] compared the prognostic value of DSE and SPECT MPI. During a mean follow-up of 44±19 months, 20 cardiac events occurred. Ischemia at MPI, but not at echocardiography, was a significant predictor of cardiac events. Previously, we reported the 7-year follow-up in these 301 patients. In that study, patients with normal DSE and MPI maintained a relatively low event rate compared to patients with an abnormal DSE and MPI. Compared to these previous studies, our study included 301 patients who were followed for a median time of 14 years. The present study extends the observations from these previous studies and demonstrates that the long-term prognostic value of DSE is similar to that of stress MPI.

A meta-analysis reported higher annualized cardiac events for patients with normal pharmacological SPECT (1.78%) compared to patients with normal exercise SPECT (0.65%).[16] Several reasons has been attributed for these difference; patients who underwent pharmacological stress SPECT are older, have more co-morbidities and has an increased number of risk factors for CAD. In the current study, we found an annualized hard cardiac event rate of 1.3% for normal dobutamine stress MPI. From a clinical perspective, patients unable to perform exercise tests who have a normal MPI have a good prognosis and could be spared invasive evaluation of the coronary arteries. Based on the current findings, both a normal DSE and a normal stress MPI identified low- and high-risk patient groups. As a consequence, both stress modalities could be used interchangeably in identifying low-risk patient group.

Both DSE and MPI have developed rapidly over the past years and have emerged as a valuable tool for diagnosis and prognosis of CAD. These imaging methods have inherent differences: SPECT probes myocardial hypoperfusion, whereas DSE probes systolic dysfunction.[13] According to the ischemic cascade, a series of biochemical reactions that occurs after inadequate myocardial blood supply, perfusion abnormalities precede sys-

tolic dysfunction.[13] This may influence the sensitivity and specificity of MPI and DSE for the evaluation of myocardial ischemia. DSE is less sensitive in detecting CAD for mild disease, but more specific for the overall patient group. Stress SPECT has a higher diagnostic accuracy in patients with multivessel CAD.[17] A recent multicenter study[18] compared commonly used imaging techniques and found that both MPI and stress echocardiography had good diagnostic accuracy for CAD (area under the curve 0.74 and 0.70 respectively). Our findings show that there are comparable implications in risk-stratifying patients, using either modality. Which of these modalities is most suitable still depends on the patients clinical status, availability and local expertise and costs.

This study has some limitations. First, the prognostic value of gated SPECT was not examined, due to the fact that at the time of data collection gated SPECT was not routinely performed in our center. As a result left ventricular ejection fraction (LVEF) was not available. Also, LVEF was not routinely examined during DSE. Information about LVEF could have improved the current analysis. Second, attenuation or scatter correction during stress SPECT was not routinely performed. Previous studies have shown that attenuation correction contribute to optimize further risk stratification.[19, 20] Third, the patient population was relatively small. This could have influenced the results.

New knowledge gained

Dobutamine stress echocardiography and dobutamine stress ^{99m}Tc-sestamibi SPECT are comparable in predicting long-term (>14 years) cardiac mortality and hard cardiac events in high risk patients (patients unable to perform exercise testing). From a clinical view, both techniques can be used interchangeably to classify patients as low or high risk of cardiac events.

CONCLUSIONS

In this study DSE and MPI provide comparable prognostic information for the prediction of cardiac mortality and hard (cardiac mortality and nonfatal MI) cardiac events in patients unable to perform exercise testing. Both techniques can be used interchangeably to classify patients as low or high risk of cardiac events.

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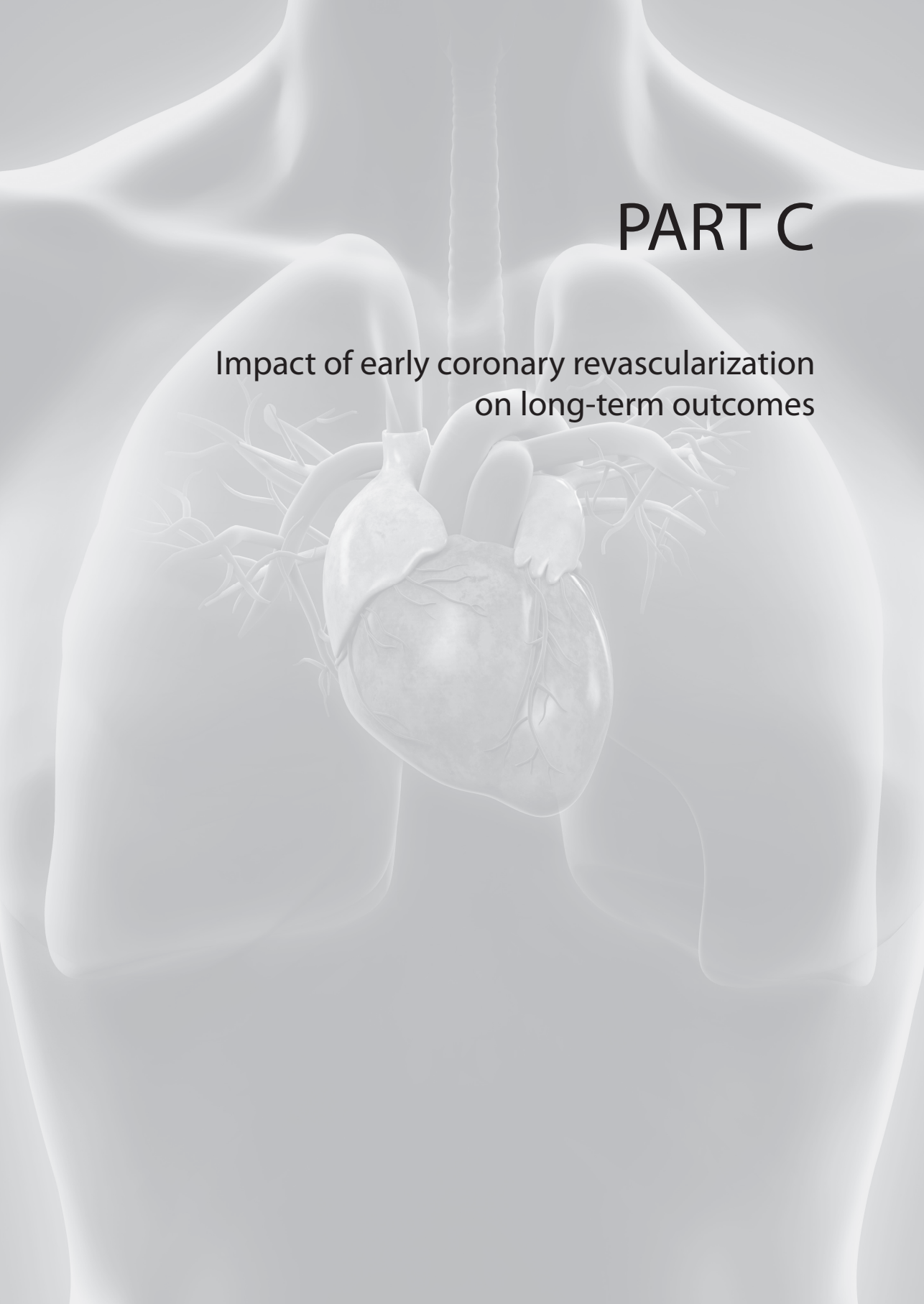

PART C

Impact of early coronary revascularization on long-term outcomes

Chapter 14

Impact of early coronary revascularization on long-term outcomes in patients with myocardial ischemia on dobutamine stress echocardiography

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ABSTRACT

The role of early coronary revascularization in the management of stable coronary artery disease (CAD) remains controversial. The aim of this study was to evaluate the impact of early coronary revascularization on long-term outcomes (>10 years) after an ischemic DSE in patients with known or suspected CAD. Patients without stress-induced ischemia on DSE and patients who underwent late coronary revascularization (>90 days after DSE) were excluded. The final study cohort consisted of 905 patients. A DSE with a peak wall motion score index (WMSI) of 1.1 to 1.7 was considered mild to moderately abnormal (n=460), and >1.7 was markedly abnormal (n=445). Endpoints were all-cause mortality and cardiac mortality. The impact of early coronary revascularization on outcomes was assessed using Kaplan Meier survival analysis and Cox's proportional hazard regression models. Early coronary revascularization was performed in 222 patients (PCI in 113 [51%] and CABG in 109 patients [49%]). During a median follow-up time of 10 years (range 8-15), 474 deaths (52%) occurred, of which were 241 (51%) due to cardiac causes. Kaplan-Meier survival curves showed that both in patients with a markedly abnormal DSE and a mild to moderately abnormal DSE, early revascularization was associated with better long-term outcomes. Multivariable analyses revealed that early revascularization had a beneficial effect on all-cause mortality (HR 0.60, 95% CI 0.46-0.79) and cardiac mortality (HR 0.49, 95% CI 0.34-0.72). In conclusion, early coronary revascularization has a beneficial impact on long-term outcomes in patients with myocardial ischemia on DSE. Early coronary revascularization was associated with better outcomes not only in patients with a markedly abnormal DSE but also in those with a mild to moderately abnormal DSE.

Key Words: Early Revascularization; Long-term; Ischemia; DSE.

INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of mortality worldwide.[1] Medical therapy and revascularization (either percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) are both valuable treatment options of patients with stable CAD.[2,3] Major advances in medical therapy and invasive coronary procedures have contributed to improved outcomes. In patients with acute coronary syndrome, it has been shown that coronary revascularization substantially reduces mortality.[4] However, the role of early coronary revascularization in the management of stable CAD remains controversial. The COURAGE trial, among patients with stable ischemic heart disease, demonstrated no difference in long-term mortality rates with medical therapy and PCI compared to medical therapy alone.[5] Information on the impact of coronary revascularization on long-term outcome in patients with myocardial ischemia at dobutamine stress echocardiography (DSE) is scarce. The follow-up period in previous studies was on average 3 years.[6,7] Accordingly, the objectives of the present study were twofold:
1 to evaluate the impact of early coronary revascularization on long-term (>10 years) mortality after an ischemic DSE and
2 to evaluate whether the amount of ischemia determines the prognostic benefit of revascularization.

METHODS

The study population consisted of 3922 consecutive patients with known or suspected CAD who underwent DSE between January 1990 and January 2003. Only patients with stress-induced ischemia on DSE were included (n=1191). Early coronary revascularization was defined as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) ≤90 days after DSE. Patients who underwent late revascularization (defined as >90 days after DSE) were excluded (n=286). The reason for this exclusion was based on the primary goal of the current study, i.e. to evaluate the impact of early revascularization (≤90 days after DSE). The decision to revascularization was made on clinical grounds. The final study cohort consisted of 905 patients. The test was requested for diagnostic reasons in 517 (57%) patients, for preoperative cardiac risk assessment in 211 (23%), or for evaluation of viable myocardium in 177 (20%) with left ventricular dysfunction. Clinical data were collected at the time of DSE. Hypercholesterolemia was defined as total cholesterol >200mg/dL or use of lipid-lowering medications. Hyperten-

sion was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication. Diabetes was defined in the presence of fasting blood glucose ≥140 mg/dL or requirement for insulin or oral hypoglycemic agents. Heart failure was defined according to the New York Heart Association classification.[8] This study was not subject to the Dutch Medical Research Involving Human Subjects Act. Therefore, approval from the local research ethics committee to conduct this prospective follow-up study was not required at the time of enrollment. The study was conducted according to the Helsinki Declaration.[9] All patients consented participation in this study.

After baseline echocardiography, dobutamine was infused at a starting dose of 5 µg/kg per minute for 3 min, followed by 10 µg/kg/min for 3 min (low-dose stage). The dobutamine dose was increased by 10 µg/kg/min every 3 min, up to a maximum dose of 40 µg/kg/min. Atropine (up to 1 mg) was administered intravenously at the end of the last stage if the target heart rate was not achieved. End points of the test were an achievement of the target heart rate (85% of the maximal heart rate predicted for age), the maximal dose of dobutamine and atropine, >2 mV downsloping ST-segment depression measured 80 ms from the J point compared with baseline, hypertension (blood pressure >240/120 mmHg), a decrease in systolic blood pressure of >40 mmHg, and significant arrhythmias. Typical angina during dobutamine stress testing was defined as substernal chest discomfort provoked by dobutamine stress and relieved by withdrawing dobutamine.

Echocardiographic images (two dimensional, using standard views) were acquired at rest and continuously during the test and recovery. The interpretation of images was performed by two independent blinded observers. In case of disagreement a third observer also interpreted the images. In our laboratory, the inter- and intraobserver agreement for DSE assessments are 92 and 94%, respectively.[10] Regional wall motion and systolic wall thickening were scored using a standard 16-segment left ventricular model. Each segment was scored using a 5-point scale as follows: 1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, 5 = dyskinesis. Ischemia was defined as new or worsened wall motion abnormalities during stress, which is indicated by an increase of ≥ 1 grade in ≥ 1 segment of the wall motion score. A biphasic response in an akinetic or severely hypokinetic segment was considered as an ischemic response. When akinetic segments at rest became dyskinetic during stress, this was not considered as ischemia.[11] DSE results were defined as abnormal if there was ischemia during stress or fixed wall motion abnormalities. The wall motion score index (WMSI) was calculated by dividing the sum of segment scores by 16. The WMSI was obtained at rest and

at peak stress. A DSE with a peak WMSI of 1.1 to 1.7 was considered mild to moderately abnormal, and >1.7 was markedly abnormal.[12]

Outcome data were obtained by a questionnaire, evaluation of hospital records, contacting the patient's general practitioner, and/or review of civil registries. The online municipal civil registry was used to determine the patient's present survival status. The date of response was used to calculate follow-up time. The endpoints considered were all-cause mortality and cardiac mortality. Causes of death were obtained from the Central Bureau of Statistics (CBS) Netherlands. A death caused by acute MI, significant arrhythmias, refractory heart failure, or sudden death without other explanation, was defined as cardiac mortality.

Table 1. Clinical characteristics.

Value	All (N=905)	Early revascularization (N=222)	No early revascularization (N=683)	*P-value*
Age (years ± SD)	61.4±11.9	60.0±9.6	61.9±12.6	0.41
Men	688 (76%)	177 (80%)	511 (75%)	0.14
Smoker	300 (33%)	81 (36%)	219 (32%)	0.22
Hypertension	260 (29%)	61 (27%)	199 (29%)	0.64
Hypercholesterolemia	283 (31%)	100 (45%)	183 (27%)	<0.001
Heart failure	198 (22%)	76 (34%)	122 (18%)	<0.001
Diabetes mellitus	117 (13%)	28 (13%)	89 (13%)	0.87
Previous revascularization	73 (8%)	5 (2%)	68 (9%)	<0.001
Previous MI	519 (57%)	166 (75%)	353 (52%)	<0.001
Medications				
ACE-inhibitors	303 (33%)	95 (43%)	208 (30%)	<0.001
ß-blockers	381 (42%)	121 (55%)	260 (82%)	<0.001
Calcium-channel blockers	294 (32%)	98 (44%)	196 (29%)	<0.001
Diuretics	170 (19%)	51 (23%)	119 (17%)	0.07
Nitrates	397 (44%)	148 (67%)	249 (36%)	<0.001
Echocardiographic results				
Rest WMSI	1.68±0.60	1.76±0.55	1.65±0.61	0.01
Peak WMSI	1.79±0.55	1.94±0.52	1.74±0.54	<0.001
Peak WMSI >1.7	445 (49%)	138 (31%)	307 (69%)	<0.001

Values are expressed as means ± SD or numbers (%). MI = myocardial infarction. WMSI = wall motion score index.

Continuous data were presented as mean± SD and were compared using the Student t test. Categorical data were presented as percentages and were compared using the chi-square test. Correlation between continuous variables was estimated with Pearson's correlation coefficient. Survival curves were generated using the Kaplan-Meier method to assess the probability of (event-free) survival and were compared using the log-rank test. The impact of early coronary revascularization on survival was investigated using univariable and multivariable Cox's proportional hazard regression models. The multivariable model was performed using known prognostic factors, including clinical characteristics and DSE results. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. P <0.05 was considered statistically significant. All analyses were performed with ÌBM SPSS statistical software version 22.

RESULTS

The clinical characteristics of the 905 patients with myocardial ischemia on DSE are presented in Table 1. The mean age was 61 years and the majority of the patients were men (76%). During the dobutamine stress test, heart rate increased from a mean of 70±13 beats per minute to 128±19 beats per minute (P<0.001), whereas overall systolic blood pressure did not significantly change (132±25 mmHg at rest and 132±29 mmHg at stress). During dobutamine stress testing, 295 patients (33%) experienced typical angina, and ST-segment changes occurred in 293 patients (32%).

All patients had myocardial ischemia on DSE. A total of 445 patients (49%) had a peak WMSI>1.7. Patients with a peak WMSI >1.7 had more cardiac mortality compared to patients with a peak WMSI ≤1.7 (30% versus 23%, respectively, p=0.013). Early coronary revascularization was performed in 222 patients (25%); a total of 113 patients underwent PCI (51%) and 109 patients underwent CABG (49%); a total of 3 patients (1%) underwent both PCI and CABG. The mean interval between DSE and early revascularization was 37±6 days. The remaining 683 patients with myocardial ischemia were treated medically. Patient groups were comparable according to age, male gender, smoking, hypertension, diabetes mellitus and the use of diuretics, digoxin and platelet inhibitors. Patients who underwent early revascularization more frequently had a history of cardiac disease (previous MI and heart failure) and less frequently had a previous revascularization. Mean rest WMSI and mean peak WMSI were 1.68 ±0.60 and 1.79±0.50, respectively. Both rest WMSI and peak WMSI were significantly higher in patients who underwent early revascularization (Table 1). This probably has contributed to the reason for intervention.

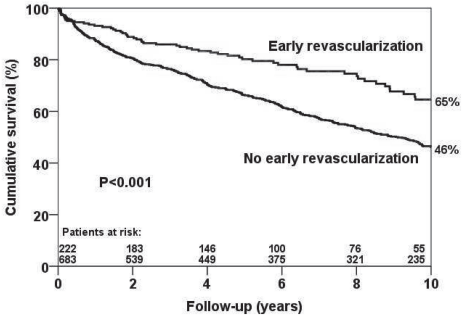

Figure 1. Kaplan-Meier curves for all-cause mortality according to strata of early coronary revascularization.

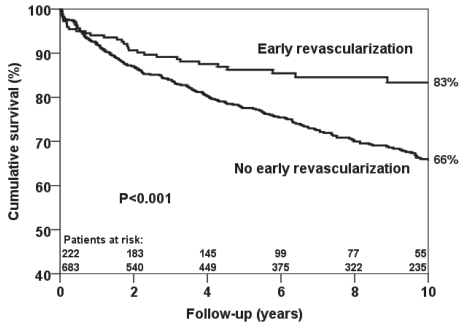

Figure 2. Kaplan-Meier curves for cardiac mortality according to strata of early coronary revascularization.

During a median follow-up time of 10 years (range 8-15), 474 deaths (52%) occurred, of which were 241 (51%) due to cardiac causes. Kaplan-Meier survival curves showed that patients with myocardial ischemia on DSE who underwent early revascularization had a lower risk for all-cause mortality (event-free survival: 80 vs 65% at 5 years, 65 vs 46% at 10 years; overall p<0.001, Figure 1) and cardiac mortality (event-free survival: 86 vs 77% at 5 years, 83 vs 66% at 10 years; overall p<0.001, Figure 2). Figures 3 and 4 demonstrates the event-free survival for all-cause mortality and cardiac mortality respectively according to strata of revascularization and peak WMSI. In the 445 patients with markedly abnormal DSE results, early revascularization was associated with better long-term outcomes compared to patients without early revascularization (all-cause mortality [Figure 3] and cardiac mortality [Figure 4] both p<0.001). Also, in the 460 patients with mild to moderately abnormal DSE results, early revascularization was associated with better long-term outcomes compared to patients without early revascularization (all-cause mortality, p<0.008, Figure 3; cardiac mortality, p<0.001, Figure 4).

Univariable associations of long-term outcome are presented in Table 2 and 3. Univariable predictors of all-cause mortality were age, male gender, hypertension, hypercholesterolemia, history of heart failure, prior revascularization, rest and peak WMSI (Table 2). Univariable predictors of cardiac mortality were age, male gender, hypercholesterolemia, history of heart failure, previous revascularization, previous MI and rest and peak WMSI (Table 3). The univariable analysis demonstrated that early revascularization was inversely related to both endpoints of interest.

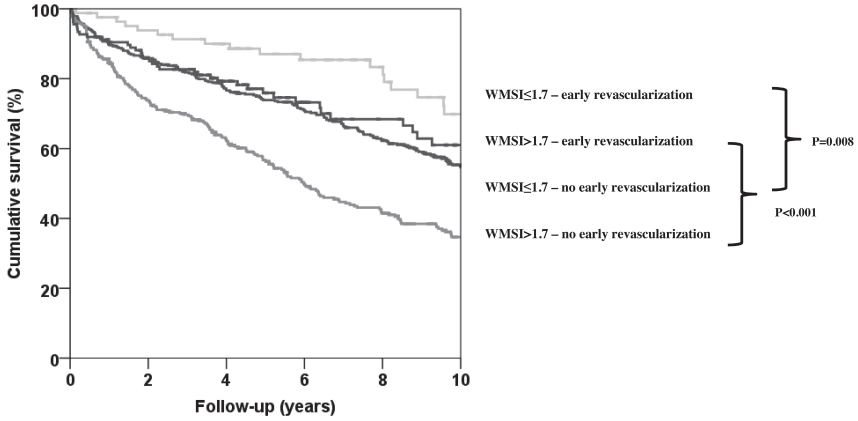

Figure 3. Kaplan-Meier curves for all-cause mortality according to strata of wall motion score index (WMSI) and early coronary revascularization.

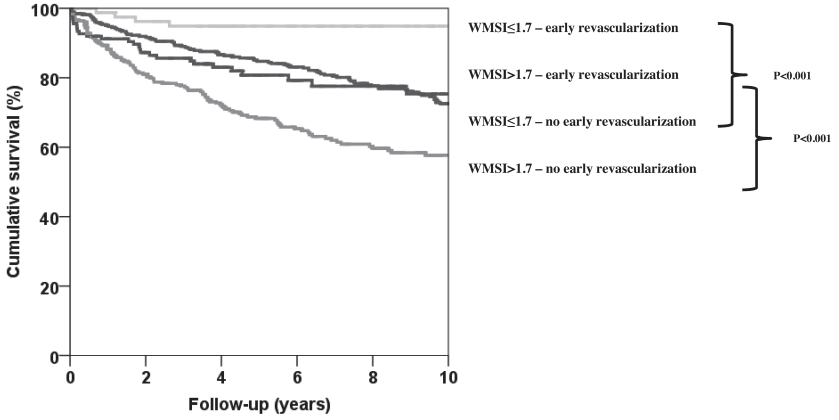

Figure 4. Kaplan-Meier curves for cardiac mortality according to strata of wall motion score index (WMSI) and early coronary revascularization.

Multivariable predictors of clinical data, DSE results and early revascularization are shown in Table 2 and 3. Age, hypertension, hypercholesterolemia, smoking, history of heart failure, previous revascularization were associated with both all-cause mortality (Table 2) and cardiac mortality (Table 3). A multivariable Cox regression model revealed that revascularization had a beneficial effect on all-cause mortality (HR 0.60, 95% CI 0.46-0.79) and cardiac mortality (HR 0.49, 95% CI 0.34-0.72).

Table 2. Univariable and multivariable predictors of all-cause mortality

Variable	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Age*	1.05	1.04-1.06	1.05	1.04-1.06
Men	1.31	1.06-1.63	1.24	0.98-1.56
Hypertension	1.33	1.10-1.61	1.46	1.18-1.79
Diabetes mellitus	0.92	0.76-1.29	1.06	0.80-1.40
Hypercholesterolemia	0.67	0.54-0.84	0.69	0.55-0.88
Smoking	1.19	0.99-1.43	1.48	1.21-1.82
Heart failure	1.46	1.18-1.81	1.30	1.02-1.66
Previous revascularization	0.44	0.25-0.77	0.42	0.23-0.76
Previous MI	1.10	0.92-1.32	0.94	0.77-1.16
Rest WMSI	1.51	1.29-1.75	1.31	0.90-1.89
Peak WMSI	1.53	1.29-1.80	1.34	0.90-2.01
Early revascularization	0.64	0.50-0.83	0.60	0.46-0.79

*per unit increment. MI = myocardial infarction. WMSI = wall motion score index.

Table 3. Univariable and multivariable predictors of cardiac mortality

Variable	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Age*	1.06	1.05-1.07	1.06	1.04-1.07
Men	1.46	1.06-1.99	1.29	0.93-1.79
Hypertension	1.13	0.86-1.49	1.33	1.00-1.77
Diabetes mellitus	0.95	0.65-1.38	1.04	0.71-1.52
Hypercholesterolemia	0.62	0.45-0.84	0.65	0.47-0.90
Smoking	1.29	1.00-1.67	1.55	1.18-2.03
Heart failure	1.80	1.35-2.38	1.50	1.10-2.04
Previous revascularization	0.32	0.13-0.78	0.26	0.10-0.64
Previous MI	1.46	1.12-1.90	1.27	0.96-1.68
Rest WMSI	1.67	1.36-2.04	1.13	0.69-1.88
Peak WMSI	1.74	1.39-2.18	1.65	0.96-2.84
Early revascularization	0.54	0.38-0.78	0.49	0.34-0.72

*per unit increment. MI = myocardial infarction. WMSI = wall motion score index.

DISCUSSION

In this study, the impact of early coronary revascularization (≤90days) on long-term outcomes was assessed in 905 patients with myocardial ischemia. During a median follow-up duration of 10 (range 8-15 years), 474 patients died of which 241 deaths were due to cardiac causes. Kaplan-Meier survival curves showed that early revascularization (PCI or CABG) after an ischemic DSE had a beneficial effect on all-cause mortality and cardiac mortality. This benefit was apparent during the entire follow-up period, with survival curves diverging up to 10 years. Both in patients with a mild to moderately abnormal DSE (peak WMSI≤1.7) and in patients with a markedly abnormal DSE (peak WMSI>1.7), early revascularization was associated with better long-term outcomes. When adjusting for clinical characteristics and DSE results, as the multivariable analysis demonstrates, early revascularization had a beneficial effect on all-cause mortality (40% reduction) and cardiac mortality (51% reduction) during long-term follow-up.

In the present study, patients with markedly abnormal DSE (peak WMSI>1.7) had benefit from early revascularization. This is in line with previous data[13] indicating that a certain amount of ischemia has to be present for revascularization to be beneficial.[14] Also, contrary to previous studies[15], patients with a mild to moderately abnormal DSE (peak WMSI≤1.7) who underwent early revascularization had lower mortality compared to patients without early revascularization.

To date, CAD is the leading cause of mortality worldwide. Patients with ischemic heart disease may be treated with either medical therapy alone or combined with revascularization (PCI or CABG). In patients with CAD, it has been shown that left ventricle dysfunction may be reversible after coronary revascularization.[16, 17] Two randomized trials were undertaken to study the potential benefit of coronary revascularization compared to medical therapy in patients with stable CAD. The COURAGE trial[2] included 2287 patients who had objective evidence of myocardial ischemia and significant coronary artery disease and studied PCI as the revascularization procedure. Both patients in the PCI group and patients in the medical-therapy group had a preserved left ventricular ejection fraction (mean LVEF 60.8 versus 60.9%, respectively). During a median follow-up of 4.6 years, the authors concluded that there was no benefit of PCI on death and MI. More recently, during the long-term follow-up of up to 15 years in these patients, the authors did not find a benefit of survival of PCI in 1211 patients with stable ischemic heart disease, objective evidence of ischemia, and significant coronary artery disease.[5] Additionally, in the BARI-2D trial 2368 diabetic patients with evidence of ischemia, or symptoms of angina in the presence of angiographic defined CAD, were studied with

either PCI or CABG.[18] Both revascularization techniques showed no benefit on survival. From a clinical perspective, both mentioned trials have important implications; patients with the characteristics of the included patients of these trials needs intensive medical therapy and lifestyle intervention. In the present study, the impact of early coronary revascularization of patients with myocardial ischemia on DSE was evaluated. The current study differs from these previous trials demonstrating that survival was significantly different between patients with revascularization and those without during long-term follow-up. Jeremias et al.[19] performed a meta-analysis and demonstrated that both PCI and CABG were associated with improved survival in patients with nonacute CAD. The findings of the current study (describing also patients with nonacute CAD) are in line with this meta-analysis. There are several explanations why early revascularization in the present patient cohort had a beneficial effect on long-term outcomes. In the current study, we describe a high-risk group of patients who were unable to perform an exercise test. Previous mentioned trials enrolled low-risk patients in contrast to the current study. Also, 57% of the 905 patients (versus 38%) had previous myocardial infarction and 198 (22%) patients (versus 4.7%) had known heart failure compared to the COURAGE trial; this also may have caused beneficial effect of early coronary revascularization in this patient cohort.

Despite major developments of PCI , advanced techniques of CABG and improvements in medication, the optimal therapy in patients with CAD remains controversial. The guidelines of the European Society of Cardiology (ESC) indicates revascularization in case of a large area of ischemia [defined as >10% of the left ventricle].[3] The American guidelines recommend CABG in preference to PCI to improve survival in patients with multivessel CAD.[20] In both guidelines, special considerations are made for diabetic patients; revascularization should be considered for diabetic patients whose symptoms compromise their quality of life. Also, diabetic patients with stable CAD and an acceptable surgical risk, CABG is recommended over PCI. The current study included 117 patients (13%) with diabetes mellitus. Clearly multiple factors influence the decision to perform coronary revascularization. including symptoms, presence of myocardial ischemia, coronary anatomy, and comorbid conditions. Moreover, daily clinical practice requires the need of balancing between invasive CABG and less invasive PCI. The ISCHEMIA trial (including > 8000 patients with at least moderate ischemia on an ischemia test) aims to demonstrate whether patients will benefit from a treatment of cardiac catheterization, revascularization, and medical therapy or a treatment of medical therapy alone with cardiac catheterization specially for those who fail medical therapy.[21]

Patients with stable coronary artery disease (CAD) and myocardial ischemia who undergo no or delayed revascularization are at increased risk of adverse events. This may have several reasons. First, chronic myocardial ischemia may result in hibernating or scarred myocardium and an impairment of LV function.[17] Second, patients with myocardial ischemia are at increased risk of developing ventricular arrhythmias, especially those with a severely impaired LV function.[22] Third, natural progression of CAD may result in adverse events, including myocardial infarction.

Patients in the present study were unable to perform exercise testing, because of comorbid conditions. DSE may be a valuable alternative method for the evaluation of myocardial ischemia in these patients. DSE has been established as a relatively safe stress modality.[23] Noncardiac side effects (nausea, headache, chills, urgency and anxiety) are usually well tolerated, without the need for test termination. The most common cardiovascular side effects are angina, hypotension and cardiac arrhythmias.[23] Life-threatening complications are rare, and in patients at increased risk for these complications (those with impaired LV function and/or a previous infarction), close monitoring is required also during the recovery phase, and any possible cardiovascular or neurological symptoms should be addressed immediately. The risk-benefit ratio of DSE should always be evaluated carefully.

This study has some limitations. First, the decision to revascularize was made on clinical grounds. The decision to perform early coronary revascularization may have been influenced by multiple factors like age, life expectancy and comorbid conditions. These factors may also have influenced long-term outcomes. Second, at time of data collection, contrast-enhanced stress echocardiography was not routinely performed. The use of an ultrasound contrast agent could further increase the accuracy and simultaneous evaluation of myocardial function and perfusion.[24] Medications that reduce mortality in patients with CAD include β-blockers, angiotensin-converting enzyme inhibitors and statins. At time of data collection, however, these medications were underused, probably because the beneficial effect of these medications was not yet fully understood.[25] Finally, at the time of data collection, left ventricular ejection fraction (LVEF) was not routinely performed in our center. Information about LVEF could have improved the present analysis.

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Chapter 15

Ischemia burden on stress SPECT MPI predicts long-term outcomes after revascularization in stable coronary artery disease

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ABSTRACT

Background. Coronary revascularization may be beneficial when added to medical therapy in selected patients with stable coronary artery disease (CAD). It is not entirely clear whether ischemia burden on stress single-photon emission computed tomography (SPECT) effectively identifies patients who have a long-term benefit from coronary revascularization.

Methods and Results. The study population consisted of 719 patients with ischemia (defined as the presence of a reversible or partially reversible perfusion defect) on stress SPECT. Follow-up was complete in 702 (98%) patients. Early coronary revascularization was defined as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) ≤90 days after SPECT. Patients who underwent late revascularization (>90 days after SPECT) were excluded (n=164). The final study population consisted of 538 patients who underwent exercise (n=220) or dobutamine (n=318) stress SPECT. The extent of myocardial ischemia on stress SPECT was defined by the number of segments with reversible perfusion defects. Kaplan-Meier curves and Cox proportional hazard models were performed to assess the impact of ischemia burden and early coronary revascularization on all-cause mortality and cardiac mortality. Of the 538 patients (73% men, mean age 59.8±11 years) 348 patients (65%) had low ischemia burden (defined as <3 ischemic segments) and 190 patients (35%) had moderate to high ischemia burden (defined as ≥3 ischemic segments). A total of 76 (14%) patients underwent early revascularization. During a median follow-up of 12 years (range 4-17), 283 (53%) patients died of whom 125 (44%) due to cardiac causes. Kaplan-Meier survival curves showed that patients with myocardial ischemia on stress SPECT who underwent early revascularization had a lower risk for all-cause mortality and cardiac mortality. This was mainly caused by patients with moderate to high ischemia burden on SPECT. Multivariable analyses showed that early revascularization was beneficial on all-cause mortality (HR 0.47, 95% CI 0.31-0.72) and cardiac mortality (HR 0.51, 95% CI 0.28-0.93).

Conclusions. Patients with myocardial ischemia on stress SPECT who underwent early revascularization had a lower all-cause mortality and cardiac mortality during long-term follow-up as compared to patients who received pharmacological therapy alone. This difference in long-term outcomes was mainly caused by the survival benefit of early revascularization in the patients with moderate to high ischemia burden.

Key Words: Early revascularization, Long-term, Ischemia, SPECT.

INTRODUCTION

Advances in pharmacotherapy have substantially improved the symptoms and long-term outcomes of patients with stable coronary artery disease (CAD) over the last decades. A subset of these patients may also benefit from coronary revascularization. The survival benefit of coronary revascularization is related to the amount of myocardial ischemia. Stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is a reliable tool to assess the ischemia burden, and may be used to identify coronary revascularization candidates.[1] Patients with CAD and ischemia on stress SPECT have higher risk of all-cause mortality and myocardial infarction (MI) compared to patients without ischemia.[2] Previous data showed that coronary revascularization may be beneficial over medical therapy in patients with moderate to severe ischemia.[3] Randomized trials showed that early revascularization showed no improvement in all-cause mortality or myocardial infarction (MI) compared to optimal medical therapy.[4,5] However, nuclear substudies of these randomized trials are conflicting.[6,7] Moreover, long-term information after early coronary revascularization in patients with ischemia on stress SPECT is lacking. Therefore, the primary aim of this study was to evaluate the impact of early coronary revascularization on long-term outcomes in patients with myocardial ischemia on stress SPECT. The second goal was whether the ischemia burden on stress SPECT determines the prognostic benefit of revascularization.

METHODS

Study Design

The study population consisted of 719 patients with ischemia (defined as the presence of a reversible or partially reversible perfusion defect) on stress SPECT performed between November 1990 and May 2002. Follow-up was complete in 702 (98%) patients. Early coronary revascularization was defined as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) ≤90 days after SPECT MPI. Patients who underwent late revascularization (defined as >90 days after SPECT MPI) were excluded (n=164). Thus, the data presented are based on 538 patients. Patients underwent exercise bicycle (n=220) or dobutamine (n=318) stress SPECT. The type of stress test was selected based on the patient's ability to exercise. Before the stress test, a structured clinical interview and cardiac risk factors were acquired. A blood pressure ≥140/90 mm

Hg, or treatment with antihypertensive medication was considered as hypertension. A fasting glucose level ≥7.8 mmol/L or the need for insulin or oral hypoglycemic agents was considered as diabetes mellitus. A total cholesterol ≥6.4 mmol/L, or treatment with lipid-lowering medication was considered as hypercholesterolemia. Heart failure was defined according to the New York Heart Association classification.[8] This study was not subject to the Dutch Medical Research Involving Human Subjects Act. Therefore, approval from the local research ethics committee to conduct this prospective follow-up study was not required at the time of enrollment. The study was conducted according to the Helsinki Declaration.[9] All patients consented participation in this study.

Stress Test Protocol

Symptom-limited, upright, bicycle ergometry with stepwise increments of 20 W every minute was performed. Three electrocardiographic leads were continuously monitored. Cuff blood pressure measurements and 12-lead electrocardiograms were recorded at rest and every minute during exercise and recovery. In patients who were unable to perform exercise tests, dobutamine stress testing was performed as previously reported.[10] Dobutamine was administered intravenously, starting at a dose of 5 µg/kg/minutes for 3 minutes, then 10 µg /kg/minutes for 3 minutes, increasing by 10 µg /kg/minutes every 3 minutes up to a maximum dose of 40 µg /kg/minutes. If the test endpoint was not reached at a dobutamine dose of 40 µg /kg/minutes, atropine (up to 2 mg) was given intravenously. Blood pressure, heart rate, and electrocardiography were monitored continuously. Test endpoints were achievement of target heart rate (85% of maximum age and gender-predicted heart rate), horizontal or downsloping ST segment depression >2 mm at an interval of 80 ms after the J point, ST-segment elevation >1 mm in patients who had no previous myocardial infarction, severe angina, systolic blood pressure decrease >40 mm Hg, blood pressure >240/120 mm Hg, or significant cardiac arrhythmias.

SPECT Imaging

An intravenous dose of 370 MBq of ^{99m}Tc-tetrofosmin (n=234) or ^{99m}Tc-sestamibi (n=304) was injected approximately 1 minute before the cessation of exercise. In rest studies, 370 MBq of tetrofosmin or sestamibi was administered at least 24 hours after the stress test. Myocardial images were acquired with a triple-head gamma-camera system (Picker Prism 3000 XP, Cleveland, Ohio, USA). The interpretation of the SPECT was semiquantitatively performed by visual analysis and aided by circumferential profiles analysis. Stress and rest tomographic views were reviewed side by side by an experienced observer

who was blind to the patients' clinical information. A reversible perfusion defect was defined as a perfusion defect on the exercise images that partially or completely resolved at rest. A fixed perfusion defect was defined as a perfusion defect on exercise images, which persists on rest images. To assess the severity of perfusion abnormalities, the left ventricular myocardium was divided into 6 segments: anterior, inferior, septal anterior, septal posterior, posterolateral, and apical. Each of the 6 major left ventricular segments was scored using a 4-point scoring method (0 = normal, 1 = slightly reduced, 2 = moderately reduced, and 3 = severely reduced or absent uptake). The extent of myocardial ischemia on stress SPECT was defined by the number of segments with reversible or partially reversible perfusion defects. Low ischemia burden was defined as the presence of reversible perfusion abnormalities in <3 segments, whereas moderate to high ischemia burden was defined as ≥3 ischemic segments on SPECT.[7]

Follow-up

Outcome data were obtained by a questionnaire, evaluation of hospital records, contacting the patient's general practitioner, and/or review of civil registries. The online municipal civil registry was used to determine the patient's present survival status. The date of response was used to calculate follow-up time. The endpoints considered were all-cause mortality and cardiac mortality. Causes of death were obtained from the Central Bureau of Statistics Netherlands (www.cbs.nl). A death caused by acute MI, significant arrhythmias, refractory heart failure, or sudden death without other explanation, was defined as cardiac mortality.

Statistical Analysis

Statistical analysis was performed using SPSS version 22 (IBM, Armonk, New York). Continuous data are expressed as mean ± SD and percentages are rounded. Continuous variables were compared with Student's t test for unpaired samples. Differences between proportions were compared with the chi-squared test. Kaplan-Meier survival curves were performed and were compared using the log-rank test. The impact of early coronary revascularization on survival was investigated using univariable and multivariable Cox's proportional hazard regression models. The multivariable model was performed using known prognostic factors, including cardiac risk factors and stress SPECT results. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (95% CI). $P < .05$ was considered statistically significant.

Table 1. Clinical characteristics of 538 patients with reversible perfusion defects

Value (%)	All (N=538)	Early revascularization (N=76)	No early revascularization (N=462)	*P-value*
Age	59.8±11	59.8±9	59.8±11	0.96
Male gender	395 (73)	64 (84)	331 (72)	0.02
BMI	26.8±4.4	26.9±3.4	26.9±4.5	0.99
Cardiac risk factors				
Smoking	158 (29)	23 (30)	135 (29)	0.85
Hypertension	215 (40)	28 (37)	187 (40)	0.55
Hypercholesterolemia	188 (35)	31 (41)	157 (34)	0.25
Heart failure	82 (15)	9 (12)	73 (16)	0.37
Diabetes mellitus	84 (16)	11 (14)	73 (16)	0.77
Previous revascularization	161 (30)	34 (45)	127 (27)	0.002
Previous MI	223 (41)	37 (49)	186 (40)	0.17
Medications				
ACE-inhibitors	156 (29)	22 (38)	134 (29)	0.99
Beta blockers	243 (45)	53 (70)	191 (41)	<0.001
Calcium-channel blockers	209 (39)	43 (57)	166 (36)	<0.001
Diuretics	116 (22)	10 (13)	106 (23)	0.06
Nitrates	188 (35)	32 (42)	156 (34)	0.16
Stress type				
Exercise bicycle	220 (41)	42 (55)	178 (39)	0.01
Dobutamine	318 (59)	34 (45)	284 (61)	0.01
SPECT parameters				
Number of abnormal segments	2.2±1.5	2.5±1.2	2.1±1.1	0.005
Low ischemia burden*	348 (65)	38 (50)	310 (67)	0.004
Moderate to high ischemia burden*	190 (35)	38 (50)	152 (33)	0.004

Values are expressed as means ± SD or numbers (%). BMI = body mass index. MI = myocardial infarction.
ACE = angiotensin-converting-enzyme. SPECT = single-photon emission computed tomography.
*Low ischemia burden = 1 or 2 abnormal segments. Moderate to high ischemia burden = ≥3 abnormal segments.

RESULTS

Patient characteristics

The 538 patients with myocardial ischemia on stress SPECT are characterized in Table 1. Mean age and mean body mass index (BMI) were 59.8±11 years and 26.8±4.4 respectively. A total of 395 (73%) patients were men. Regarding stress testing, 220 patients (41%) underwent exercise bicycle stress and 318 patients (59%) underwent dobutamine stress. During the stress test, there was a significant increase in heart rate (73±15 –134± 29 bpm, P<0.001) and systolic blood pressure (138±22 – 164±33 mmHg, P<0.001) from rest to peak stress. Typical angina occurred in 150 patients (28%), whereas 176 patients (33%) exhibited ST-segment changes.

All patients had myocardial ischemia (defined as reversible or partially reversible perfusion defect) on stress SPECT. Fixed defects were observed in 81 (15%) patients. Both fixed and reversible defects were present in 344 (64%) patients. A total of 348 patients (65%) had low ischemia burden and 190 patients (35%) had moderate to high ischemia burden. A total of 76 (14%) patients underwent early revascularization (≤90 days after the stress SPECT); PCI was performed in 53 (70%) patients and CABG was performed in 27 (36%) patients. A total of 4 patients (5%) underwent both PCI and CABG. The remaining 462 patients with myocardial ischemia on stress SPECT were treated only with pharmacologic therapy. Among the 76 patients who underwent early revascularization, mean number of abnormal segments was 2.5±1.2 compared to 2.1±1.1 in patients

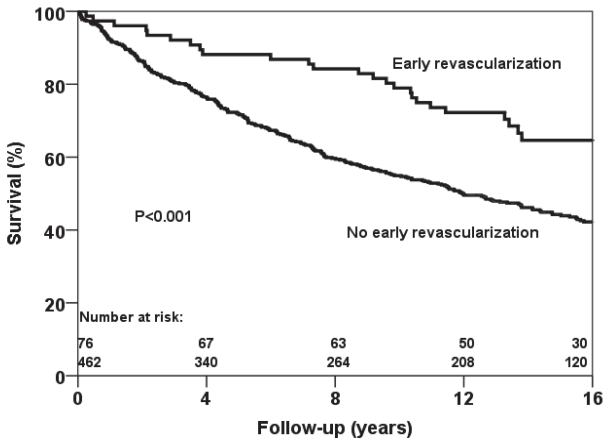

Figure 1. Kaplan-Meier curves for all-cause mortality according to strata of early coronary revascularization.

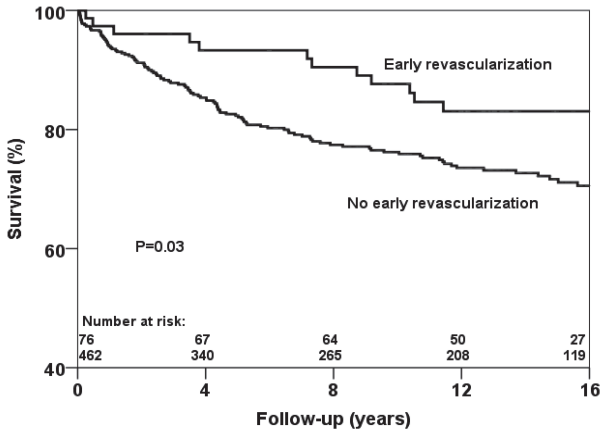

Figure 2. Kaplan Meier curves for cardiac mortality according to strata of early coronary revascularization.

without early revascularization (p=0.005). Patient groups were comparable according to age, BMI, smoking, hypertension, hypercholesterolemia, heart failure, diabetes mellitus and previous MI. Comparison of the patient groups shows that the patients who underwent early coronary revascularization were more frequent men, had more prior revascularization and had more moderate to high ischemia burden. These factors may have contributed to referring for early coronary revascularization.

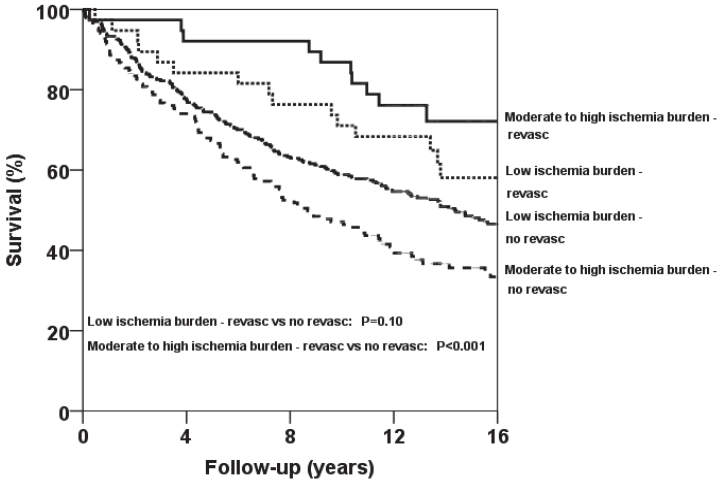

Figure 3. Kaplan-Meier curves for all-cause mortality according to strata of the extent of ischemia (low ischemia burden versus moderate to high ischemia burden) and early coronary revascularization (revasc versus no revasc).

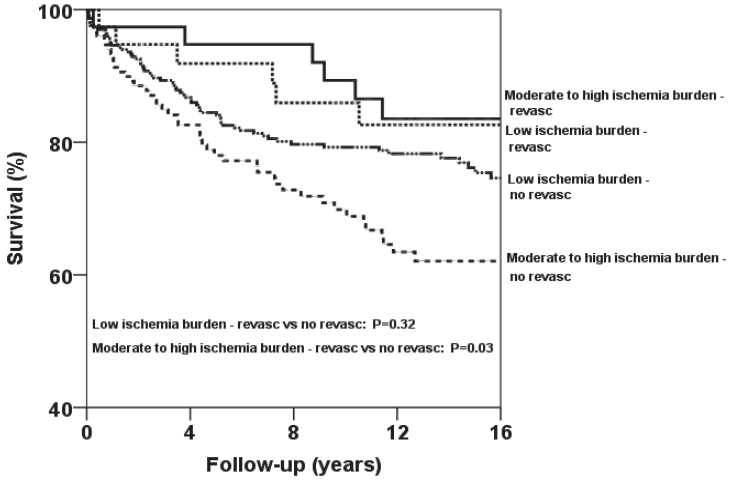

Figure 4. Kaplan-Meier curves for cardiac mortality according to strata of the extent of ischemia (low ischemia burden versus moderate to high ischemia burden) and early coronary revascularization (revasc versus no revasc).

Long-term outcomes

During a median follow-up of 12 years (range 4-17), a total of 283 (53%) patients died (all-cause mortality) of whom 125 (44%) were due to cardiac causes. Kaplan-Meier survival curves are demonstrated in Figures 1-5. Survival curves showed that patients with myocardial ischemia on stress SPECT who underwent early revascularization had a lower risk for all-cause mortality (event-free survival: 88 vs 72% at 5 years, 79 vs 55% at 10 years, 65 vs 44% at 15 years; overall $p<0.001$, Figure 1) and cardiac mortality (event-free survival: 93 vs 82% at 5 years, 88 vs 76% at 10 years, 83 vs 72% at 15 years; overall $p=0.03$, Figure 2). As Figures 3 and 4 shows, this lower risk was not caused by the 348 patients with low ischemia burden (all-cause mortality, $p=0.10$, Figure 3, and cardiac mortality, $p=0.32$, Figure 4). In contrast, in the 190 patients with moderate to high ischemia burden early revascularization was associated with better long-term outcomes compared to patients without early revascularization (all-cause mortality, $p<0.001$, Figure 3; cardiac mortality, $p=0.03$, Figure 4).

Patients who were able to perform exercise bicycle testing had a better prognosis as compared with the patients who underwent dobutamine stress testing. In patients who underwent early revascularization, all-cause mortality was significantly higher in the dobutamine group than in the exercise group (Figure 5).

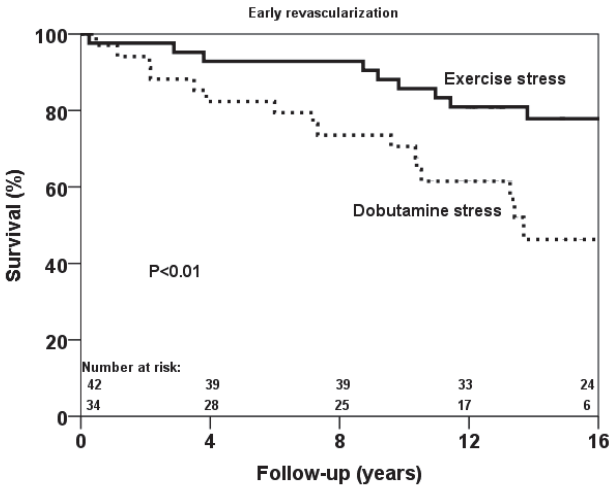

Figure 5. Kaplan-Meier survival curves for the endpoint of all-cause mortality in patients who underwent early revascularization stratified to stress type (exercise test versus dobutamine stress test).

Univariable and multivariable predictors of outcome

Univariable and multivariable predictors of long-term outcome are presented in Table 2 and 3. Univariable predictors of all-cause mortality were age, male gender, hypertension, diabetes mellitus, hypercholesterolemia, heart failure, prior MI, and number of abnormal segments on SPECT (Table 2). Univariable predictors of cardiac mortality were age, hypertension, diabetes mellitus, heart failure, previous MI and number of abnormal segments on SPECT (Table 3). The univariable analysis also demonstrated that early revascularization was inversely related to both endpoints of interest.

The results of the multivariable analysis are shown in Table 2 and 3. Age, male gender, hypertension, diabetes mellitus, hypercholesterolemia, smoking, heart failure were associated with all-cause mortality (Table 2). Multivariable predictors of cardiac mortality were age, diabetes mellitus and heart failure (Table 3).The multivariable Cox regression model revealed that early revascularization had a beneficial effect on both all-cause mortality (HR 0.47, 95% CI 0.31-0.72) and cardiac mortality (HR 0.51, 95% CI 0.28-0.93).

Table 2. Univariable and multivariable predictors of all-cause mortality

Variable	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Age*	1.06	1.04-1.07	1.07	1.05-1.08
Male gender	1.34	1.09-1.77	1.63	1.21-2.20
Hypertension	1.57	1.24-1.98	1.32	1.03-1.70
Diabetes mellitus	2.47	1.87-3.27	2.48	1.83-3.36
Hypercholesterolemia	0.67	0.52-0.87	0.72	0.56-0.94
Smoking	1.04	0.80-1.34	1.59	1.21-2.09
Heart failure	2.34	1.79-3.18	1.59	1.17-2.17
Previous revascularization	1.08	0.84-1.38	1.11	0.84-1.45
Previous MI	1.46	1.15-1.84	1.15	0.88-1.49
# Abnormal segments on SPECT	1.13	1.02-1.24	1.06	0.95-1.18
Early revascularization	0.46	0.30-0.69	0.47	0.31-0.72

*per unit increment. #number. MI = myocardial infarction. SPECT = single-photon emission computed tomography.

Table 3. Univariable and multivariable predictors of cardiac mortality

Variable	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Age*	1.06	1.04-1.07	1.06	1.04-1.08
Male gender	1.29	085-1.97	1.52	0.97-2.38
Hypertension	1.60	1.12-1.27	1.23	0.84-1.79
Diabetes mellitus	3.14	2.13-4.62	3.03	1.98-4.64
Hypercholesterolemia	0.70	0.48-1.03	0.76	0.52-1.14
Smoking	0.96	0.65-1.42	1.47	0.97-2.23
Heart failure	2.99	2.01-4.45	1.88	1.22-2.90
Previous revascularization	1.19	0.82-1.73	1.19	0.80-1.77
Previous MI	1.69	1.19-2.41	1.28	0.86-1.89
# Abnormal segments on SPECT	1.20	1.04-1.39	1.09	0.93-1.28
Early revascularization	0.52	0.29-0.95	0.51	0.28-0.93

*per unit increment. #number. MI = myocardial infarction. SPECT = single-photon emission computed tomography.

DISCUSSION

The present study evaluated the impact of early revascularization (≤90 days after stress SPECT) on long-term outcome in patients with myocardial ischemia on stress SPECT. Of the 538 patients, 30% of patients had previous revascularization and 41% had previous MI. During a median follow-up of 12 years, a total of 283 (53%) patients died (all-cause mortality) of whom 125 (44%) were due to cardiac causes. Kaplan-Meier survival curves showed that early revascularization (either PCI or CABG) after an ischemic stress SPECT was beneficial on both all-cause mortality and cardiac mortality. In patients with low ischemia burden on stress SPECT (defined as <3 ischemic segments) early revascularization was not associated with better long-term outcomes whereas in patients with moderate to severe ischemia burden (defined as ≥3 ischemic segments) early revascularization was associated with better long-term outcomes. The multivariable model demonstrated that early revascularization was associated with a 53% reduction in all-cause mortality and a 49% reduction in cardiac mortality. Regarding the type of stress test, patients with early revascularization who performed a dobutamine stress test had higher all-cause mortality compared to patients who performed exercise bicycle stress testing. This finding is in accordance with a previous report from our center.[11] The inability to perform exercise testing is a negative prognostic marker in patients with CAD. In recent years there has been a considerable interest concerning treatment strategies in patients with stable CAD resulting in a wealth of published literature. Both revascularization (PCI and/or CABG) and optimal medical therapy are treatment options in these patients. SPECT MPI play a central role in this regard. To date, information on long-term outcomes after revascularization in relation to the ischemia burden on stress SPECT is relatively scarce. Previous studies have examined the short-term to medium-term outcomes after revascularization in patients with ischemia on SPECT. Hachamovitch et al.[3] studied >10.000 patients without previous MI and without previous revascularization who underwent stress SPECT. The study population was divided in patients who were treated medically and patients who underwent early revascularization and was followed during a mean follow-up of 1.9 years. In patients with moderate to severe ischemia (>10% myocardial ischemia) revascularization was associated with improved survival in comparison to medical therapy. Sorajja et al.[12] evaluated 826 asymptomatic diabetic patients without known CAD who underwent exercise, adenosine or dobutamine stress SPECT. SPECT images were classified as low-, intermediate-, and high-risk. A total of 261 patients (32%) had a high-risk SPECT (defined as a summed stress score ≤47, based on:

the lower the score the higher the radioisotope uptake). During a mean follow-up of 5.7±3.3 years CABG was associated with better survival in patients with moderate to severe ischemia. The current study differs from these previous studies for several reasons. First, the current study evaluated a high-risk patient group (30% had previous revascularization and 41% had previous MI versus 0% in the studies of Hachamovitch et al. and Sorajja et al. Second, this study showed higher event rates. This may be explained by the high prevalence of cardiac history indicating a higher risk status in contrast to these previous studies. Also, during the current long-term follow-up natural progression of CAD may have occurred. Third, the mean follow-up duration in these previous studies was 1.9 and 5.7 years. In the present long-term follow-up study median follow-up duration was 12 years. To our knowledge, this is the first study that has examined the impact of early revascularization in relation the amount of ischemia in patients with stable CAD for long-term (>10 years) outcome. This study extends the conclusions drawn from these previous studies in that early revascularization in patients with moderate to high ischemia burden is beneficial during long-term outcome. The current findings are also in line with previous data which indicates that a certain amount of ischemia has to be present for revascularization to be beneficial.[13]

In a nuclear substudy of the COURAGE trial[6] a total of 314 patients were enrolled who underwent either exercise or vasodilator stress ^{99m}Tc-sestamibi SPECT. Moderate to severe ischemia on SPECT was defined as ≥10% myocardium. The authors found that the magnitude of residual ischemia was proportional to the risk of all-cause mortality. However, as the authors noted, these findings are based on underpowered data due to the small proportion of enrolled patients.[6] More recently, a second nuclear substudy of the COURAGE trial was performed.[7] Of the 1381 patients who underwent SPECT, 699 patients were treated medically and 682 patients received medical treatment and PCI. Patients were followed for a median follow-up of 4.6 years. The extent of ischemia was not associated with adverse events; the event rates in both mild ischemia and moderate-severe ischemia were similar according to treatment options (medical treatment or medical treatment combined with PCI). In the current long-term follow-up study early revascularization was associated with lower all-cause mortality and cardiac mortality.

This study has several limitations. First, the decision to perform coronary revascularization was made by the treating physician, this could have influenced the current results. Further randomized controlled trials are needed to further study the impact of ischemia burden and early revascularization on long-term outcomes. Second, at time of data collection, medications were underused in view of the current treatment guide-

lines, maybe because the beneficial effect of these medications was not yet fully understood.[15] Third, there were some imbalances in baseline characteristics (more patients in the early revascularization group were men and had previous revascularization). This could have influenced the outcome.

CONCLUSION

Patients with myocardial ischemia on stress SPECT who underwent early revascularization had a lower all-cause mortality and cardiac mortality during long-term follow-up as compared to patients who received pharmacological therapy alone. This difference in long-term outcomes was mainly caused by the survival benefit of early revascularization in the patients with a moderate to high ischemia burden. In patients with low ischemia burden early coronary revascularization had no beneficial impact on long-term outcomes as compared to a treatment strategy based on pharmacological therapy alone.

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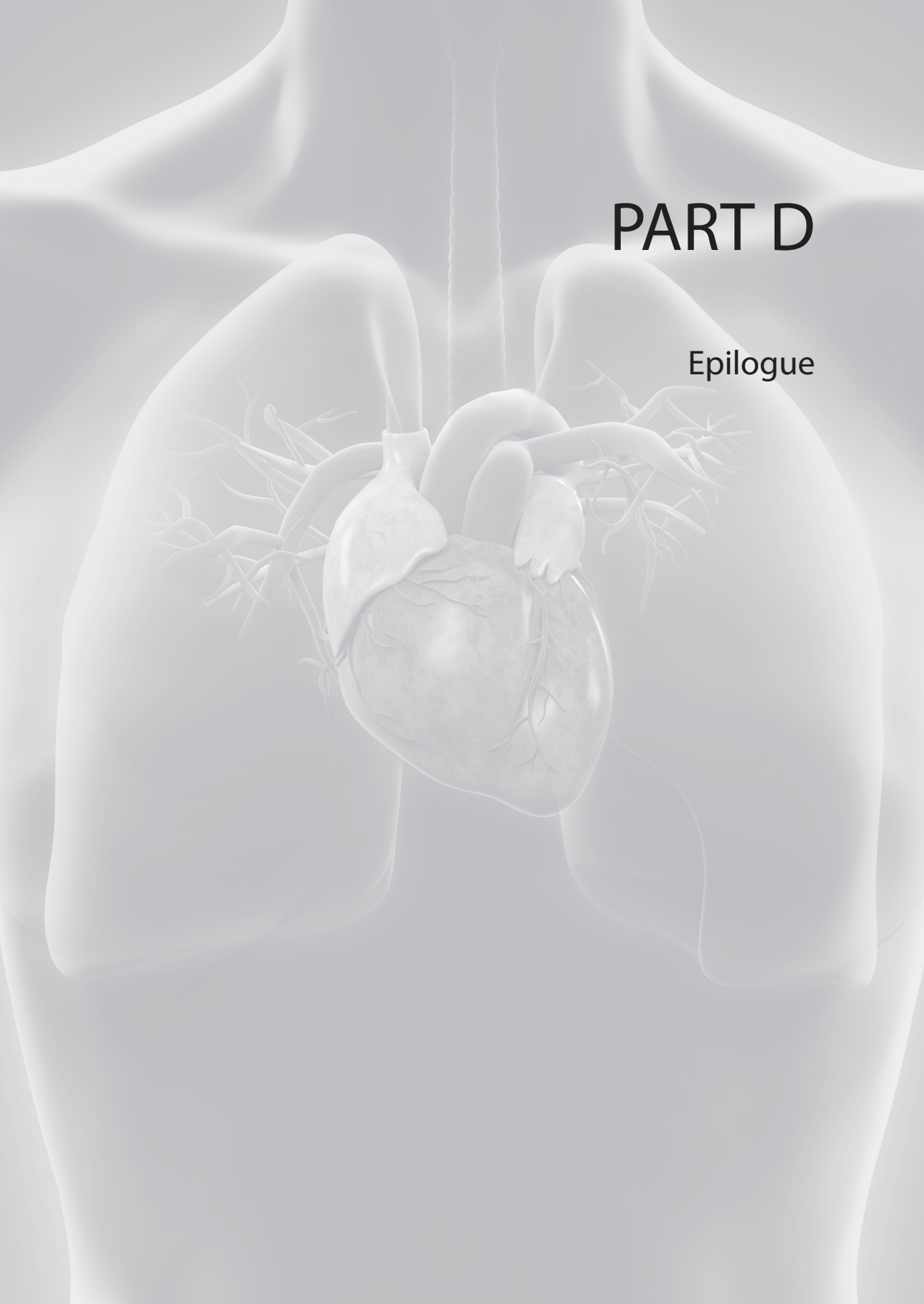

PART D

Epilogue

Chapter 16

General discussion and summary

Hendrik J. Boiten

Since the 70s of the last century both myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT, introduced in 1970) and dobutamine stress echocardiography (DSE, introduced in 1979) have played an important role in the diagnosis of coronary artery disease (CAD).[1,2] In the last decades, stress imaging has not only been used for diagnosing CAD, it also has emerged as a noninvasive tool providing risk stratification and prognostic information. Risk stratification is based on the concept that patients with normal stress test results could be spared invasive angiographic assessment, because a normal test result defines patients at low-risk (typically <1% per year of follow-up) for cardiac events.[4] On the other hand, patients with abnormal stress test results are candidates for invasive coronary angiography and intervention because they have a greater risk of cardiac events. However, risk after a normal stress test result varies along with the temporal characteristics of the patients, for example the presence of known CAD, use of pharmacologic stress and the presence of diabetes mellitus.[5] This so called warranty period is defined as the duration of time whereby the patient's risk alters significantly from that observed during the early portion of follow-up. Figure 1 shows the cumulative survival curves of patients with normal versus abnormal DSE. The vertical line illustrate that the curves diverge until 7 years. After that point, the curves start to run parallel indicating a 'warranty period' of 7 years.

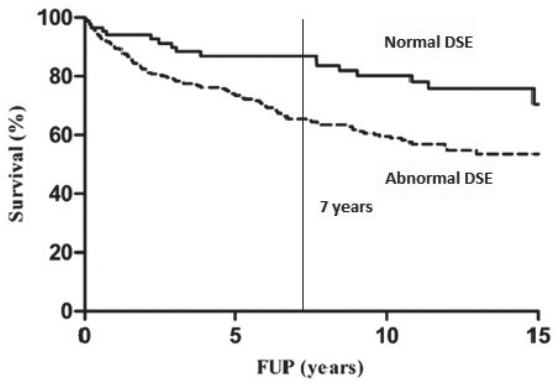

Figure 1. Survival curves of patients with normal versus abnormal DSE. The vertical line illustrate that the curves start to run parallel at approximately 7 years.

Multiple studies, to date, have demonstrated the prognostic value of DSE and stress SPECT MPI in several patient populations, including obese patients[6], elderly patients[7], diabetic patients[8,9] and patients with limited exercise capacity.[10,11] In the currently avail-

able literature patients were followed for short – and medium term follow-up. Data on the (very) long-term outcome after noninvasive cardiac stress imaging are lacking.
This thesis focused on the long-term prognostic value of cardiac stress imaging, more precisely on DSE and SPECT MPI in patients with known or suspected CAD. The prognostic value of both imaging modalities was studied in various patient groups, which are commonly encountered in with daily practice. The studies that forms this thesis can be divided in three main topics:

A) Duration of low risk after a normal cardiac exercise stress test,
B) Prediction of long-term outcome in patients considered at increased risk of adverse events,
C) Impact of early coronary revascularization on long-term outcomes.

PART A: Duration of low risk after a normal cardiac exercise stress test

A normal stress SPECT MPI is associated with a low risk of cardiac events irrespective of other features including known CAD. In a pooled analysis of 19 studies including a total of 39.173 patients the hard cardiac event rate was 0.6% per year for patients with a normal SPECT MPI.[12] However, even in the presence of a normal SPECT MPI a temporal risk occurs which increases the cardiac event rate to 2%.[5] The duration of the low-risk period after a normal SPECT MPI is not clear. In **Chapter 2** of this thesis the long-term outcome is described of 233 patients who underwent bicycle ^{99m}Tc-sestamibi SPECT MPI and had normal myocardial perfusion at exercise and at stress. We found relatively low cardiac event rates during the long-term follow-up of 15 years, particularly in the first 5 years. Age, male gender and diabetes mellitus were predictors of cardiac events in patients with known or suspected CAD. Follow-up should be more intense in these patients.

Exercise electrocardiography (ECG) and exercise SPECT MPI are well established methods for the evaluation of patients with known or suspected CAD. The long-term impact of SPECT MPI in patients with a normal exercise ECG test is not known. In **Chapter 3** it is shown that approximately 50% of patients with normal exercise ECG tests had an abnormal SPECT MPI. A total of 20% of patients had reversible perfusion defects indicating myocardial ischemia. Current guidelines recommend exercise ECG testing for evaluation of known or suspected CAD.[13] Our data show that even in patients with normal exercise ECG, improved risk stratification can be obtained using SPECT MPI.

PART B: Prediction of long-term outcome in patients considered at increased risk of adverse events

The short- to medium-term prognostic value of both DSE and SPECT MPI has been firmly established and both techniques can be used to identify low-risk and high-risk patient groups.[4] This is important for guiding therapy (medical therapy, revascularization) and better patient outcomes. **Part B** of this thesis contains studies evaluating the long-term prognostic value of cardiac stress imaging in patients considered at increased risk of cardiac events. In **Chapter 4**, in a large patient cohort of 638 patients of whom 46% had known CAD, the results showed that exercise SPECT MPI has an incremental prognostic value over clinical and exercise test parameters during a long-term follow-up period of 11 years. Furthermore, patients with an abnormal SPECT MPI have a significantly increased risk of cardiac events compared to patients with a normal SPECT MPI. The long-term prognostic value of SPECT MPI in high-risk patients (obese patients, heart transplant recipients, diabetic patients, patients unable to perform a stress test) may be impaired due to the underlying cardiovascular risk. Accordingly, in **Chapter 5** the results of the long-term outcome after stress SPECT MPI are presented in a total of 267 obese patients. Up to a 6-year period after testing, stress ^{99m}Tc-tetrofosmin SPECT MPI does hold its value for the prediction of all-cause mortality and cardiac events in these patients. After 6 years repeated testing may be considered in obese patients depending on the patient's symptoms and clinical status.

The guidelines of the International Society for Heart and Lung Transplantation (ISHLT) state that SPECT MPI may be useful for diagnosing cardiac allograft vasculopathy (CAV) in heart transplant recipients.[14] CAV limits the long-term success of heart transplantation. The long-term prognostic role of noninvasive SPECT MPI in heart transplant recipients remains unclear. In a total of 166 heart transplant recipients, it is demonstrated in **Chapter 6** that this technique provides valuable prognostic information. Heart transplant recipients with a normal stress ^{99m}Tc-tetrofosmin SPECT MPI have a significantly better prognosis as compared with those with an abnormal study, up to 5 years after initial testing.

SPECT MPI after submaximal exercise stress may underestimate the extent of ischaemia. Therefore, patients unable or limited to exercise should be risk stratified using SPECT MPI or echocardiography coupled with pharmacologic stress. Both vasodilators (adenosine, dipyridamole) and dobutamine are feasible stressors. The latter is used in studies described in this thesis. In **Chapter 7** the 11-year prognostic value of dobutamine stress SPECT MPI is assessed using ^{99m}Tc-sestamibi as a tracer in 473 patients with

limited exercise capacity. A total of 61% of the patients died (all-cause mortality) giving an annualized event rate of 5.6%/year. The incremental prognostic value of dobutamine stress SPECT MPI over clinical data was maintained during the very long-term follow-up period. An abnormal SPECT MPI was associated with an increased risk of major adverse cardiac events (hazard ratio 1.53, CI 1.02-2.30) incremental to age, male gender, cardiac risk factors and stress test results. Subsequently, in **Chapter 8**, the long-term outcome after dobutamine stress ^{99m}Tc-tetrofosmin SPECT MPI is described in 247 elderly patients (>65 years, mean age 71 years) unable to perform an exercise test. During the median follow-up of 14 years, not only the presence of an abnormal SPECT MPI, but also the extent and severity of the perfusion defect (as expressed as the summed stress score) provided optimal risk stratification.

Due to its low cost and simplicity, surface 12-lead electrocardiography (ECG) is a valuable diagnostic tool. These features also make ECG an attractive option for cardiac risk stratification. Recent studies have established the prognostic value of QRS duration at ECG in the general population and in groups of lower risk patients on a short term. In **Chapter 9**, the long-term (8 year) prognostic value of QRS duration is evaluated in 512 patients with known or suspected CAD referred for SPECT MPI for the evaluation of myocardial ischemia. QRS duration ≥120ms was a strong predictor of cardiac mortality (hazard ratio 1.95, CI 1.36-2.78) and cardiac mortality or non-fatal MI (hazard ratio 1.69, CI 1.21-2.36) even after adjustment for clinical variables and SPECT MPI results. An abnormal MPI is associated with an increased risk of cardiac mortality and cardiac mortality or non-fatal MI.

The worldwide prevalence of diabetes mellitus is increasing and CAD is a major cause of mortality and morbidity is these patients.[15] In diabetic patients, both SPECT MPI and DSE have shown an incremental value in predicting all-cause mortality and hard cardiac events at short- and intermediate term follow-up. However, it is not known whether this incremental value is maintained at long-term follow-up. We therefore assessed the long-term outcome after SPECT MPI (8 years) and DSE (13 years) in diabetic patients with limited exercise capacity in **Chapter 10** and **Chapter 11** respectively. Up to 4-years after testing, there was a significantly better prognosis of patients with a normal SPECT MPI compared to those with an abnormal study, described in **Chapter 10**. The Cox proportional hazard regression model showed that an abnormal SPECT MPI, and a reversible perfusion defect were predictors of cardiac mortality and hard cardiac events. Comparably, as described in **Chapter 11**, the prognostic value of DSE was optimal up to approximately 7 years after the initial test. The most powerful echocardiographic predictor of outcome was peak wall motion score index (pWMSI), with

left ventricular ejection fraction (LVEF) at rest coming up second. Multivariate analysis showed that pWMSI and LVEF were independent predictors of long-term outcome. We also found that patients with LVEF≥50% and peak WMSI=1 had a favorable prognosis, whereas patients with LVEF<50% and pWMSI>1 had an adverse long-term prognosis. Patients with LVEF≥50% and pWMSI>1 and those with LVEF<50% and peak WMSI<1 had an intermediate prognosis. Importantly, the prognosis in diabetic patients is related not only to the extent of stress induced ischemia but also to LV function at rest. Overall, patients with diabetes mellitus with limited exercise capacity indicate a high-risk patient group. This characteristic may have influenced the risk of cardiac events, thereby limiting the long-term prognostic value of SPECT MPI and DSE. So, a warranty period exists of both SPECT MPI and DSE in patients with diabetes.

Currently, it is not known whether the prognostic value of DSE in these patients is preserved at very long-term (>10 years) follow-up. In **Chapter 12** the very long-term outcome after DSE in a large (n=3381) high-risk patient group is investigated. Forty-five percent of the patients had known CAD. During a mean follow-up of 13 years there were 1.725 deaths (51%), of which 1.128 (33% of total study cohort) were attributed to cardiac causes. Patients with a normal DSE had a significantly better survival in comparison with patients with an abnormal DSE (44% vs 35% at 15 years; p<0.001). WMSI during stress predicted both all-cause mortality and cardiac mortality. Interestingly, the survival curve of all-cause mortality diverges up to approximately 7 years after DSE indicating that the test seems not to have further discriminating value after this time period. This in line with the observations described in **Chapter 11**.

The research described in **Chapter 13** reported on the comparison between DSE and dobutamine ^{99m}Tc-sestamibi SPECT MPI. We studied 301 patients with known or suspected CAD who underwent both noninvasive imaging modalities. During a mean follow-up of 14 years, 172 (57%) deaths and 118 (39%) cardiac events occurred. Age, previous MI and the presence of heart failure were the major determinants of long-term prognosis. Multivariable analysis revealed that both an abnormal DSE and an abnormal SPECT MPI (agreement was 82%, kappa=0.62) had an incremental prognostic value over clinical and stress test variables. Both techniques can be used interchangeably to classify patients as low or high-risk of subsequent cardiac events.

PART C: Impact of early coronary revascularization on long-term outcomes

In patients with acute coronary syndrome, it has been shown that coronary revascularization substantially reduces mortality.[16] Patients with stable CAD can be treated by

medical therapy or coronary revascularization. The ESC guidelines on the management of stable CAD recommends percutaneous coronary intervention (PCI) in patients with single-vessel disease or in patients in which coronary artery bypass graft surgery (CABG) may be contra-indicated (e.g. prior CABG, severe lung disease). In patients with recurrent in-stent restenosis or multivessel disease with left anterior descending artery (LAD) involvement CABG is the preferred revascularization method. However, the jury is still out concerning the impact of early coronary revascularization in patients with stable CAD.[17] Information on the impact of coronary revascularization on long-term outcome in patients with myocardial ischemia at DSE or SPECT MPI is lacking. **Chapter 14** evaluated the impact of early coronary revascularization on long-term mortality in patients with stress-induced ischemia at DSE. Early coronary revascularization was defined as PCI or CABG ≤90 days after DSE. During a median follow-up of 10 years, 52% of the 905 patients died, of which 51% due to cardiac causes. Our findings show that early revascularization (PCI or CABG) after an ischemic DSE had a beneficial effect on all-cause mortality and cardiac mortality, adjusted for clinical characteristics and DSE results. Importantly, both in patients with a mild to moderately abnormal DSE (peak WMSI≤1.7) and in patients with a markedly abnormal DSE (peak WMSI>1.7), early revascularization was associated with better long-term outcomes. The multivariable model showed that early revascularization had a beneficial effect on all-cause mortality (hazard ratio 0.60, 95% CI 0.46-0.79) and cardiac mortality (hazard ratio 0.49, 95% CI 0.34-0.72) during long-term follow-up.

Stress SPECT MPI is a reliable tool to assess the ischemia burden, and may be used to identify coronary revascularization candidates.[18] In **Chapter 15** we further examined the impact of early coronary revascularization on long-term outcomes in 538 patients with myocardial ischemia on exercise bicycle or dobutamine stress SPECT MPI (defined as the presence of a reversible or partially reversible perfusion defect). A low ischemia burden was defined as the presence of reversible perfusion abnormalities in <3 segments, whereas a moderate to high ischemia burden was defined as ≥3 ischemic segments on SPECT MPI. During a median follow-up of 12 years, it was shown that patients with myocardial ischemia on stress SPECT MPI who underwent early revascularization (n=76) had a lower all-cause mortality (hazard ratio 0.47, 95% CI 0.31-0.72) and cardiac mortality (hazard ratio 0.51, 95% CI 0.28-0.93) as compared to patients who received pharmacological therapy alone. This difference in long-term outcomes was mainly caused by the survival benefit of early revascularization in the patients with moderate to high ischemia burden.

Clinical implications

The unique contribution of the current thesis is based on the (very) long-term prognostic value of cardiac stress imaging. The studies performed in this thesis have several potential implications for daily clinical practice.

First, clinicians should be aware that patients with a normal exercise SPECT MPI have a favorable prognosis even at long-term (15-year) follow-up. Consequently, in these patients a watchful waiting approach is justified and unnecessary invasive coronary angiography could be avoided.

Second, several clinical (e.g. age, male gender, diabetes, history of CAD) and exercise test parameters (peak exercise heart rate, ST segment changes) can identify patients with increased risk of cardiac events who have normal exercise SPECT MPI and follow-up should be closer in these patients.

Third, approximately 20% of patients with known or suspected CAD and normal exercise electrocardiographic testing have completely or partially reversible myocardial perfusion defects. SPECT MPI provides additional information for the prediction of long-term cardiovascular outcomes in these patients.

Fourth, the results of this thesis confirms and extends numerous previous studies regarding the short- and medium-term value of DSE and SPECT MPI for risk-stratifying patients with low – or high risk at cardiac events. Results of both imaging modalities demonstrates the clinical importance for assessment of very long-term outcome in the way that these test have a valid role in assisting clinicians in determining therapy to reduce the likelihood of cardiac events. This applies for obese patients, heart transplant recipients, patients with limited exercise capacity, elderly patients, and patients with diabetes mellitus. However, depending on the characteristics of the patients a warranty period exists. Less intensive management and eliminating the need for follow-up testing would be expected in patients considered at low risk for cardiac events.

Fifth, the prognosis in diabetic patients is related not only to the extent of stress induced ischemia (pWMSI>1 indicates an adverse long-term prognosis) but also to the function of the left ventricle (LV) at rest (LVEF<50% indicates an adverse long-term prognosis).

Sixth, DSE and SPECT MPI still have comparable prognostic value even when a follow-up period is extremely long. Prognostic accuracy is superior for both noninvasive imaging modalities as compared with clinical variables alone.

Finally, while waiting for the ongoing randomized results of the ISCHEMIA trial[19] the decision to revascularize will depend on a thorough risk assessment and the patient's

symptoms.[18] Also, as this thesis demonstrates, the extent of ischaemia, as assessed by DSE and/or stress SPECT MPI, can be used in guiding therapy.

Future challenges

With the ageing of the population more patients are referred for diagnostic and prognostic work-up. Noninvasive imaging techniques therefore, will continue to grow with advances in pharmacologic stressors and imaging agents. Landmarks leading to the current applications of SPECT MPI include the introduction of ^{99m}Technetium based tracers and the use of attenuation correction.[20] New ultrafast SPECT cameras have evolved resulting in high-quality perfusion imaging. Moreover, half the dose of a radionuclide tracer can be used.[21] More recently, other imaging techniques, including CT coronary angiography, cardiac magnetic resonance imaging (cMRI) and positron emission tomography (PET) have emerged as alternative methods for evaluating myocardial perfusion.[22,23] This list of novel techniques reflects the need for continuing innovation by clinicians involved in the treatment of CAD. With the introduction of gated SPECT combined evaluation of myocardial perfusion and left ventricular function can be performed. Future studies are needed to clarify the value of gated SPECT for the evaluation of long-term prognosis.

Furthermore, examples of recently developed radiopharmaceuticals for SPECT MPI and PET are ^{18}F-flurpiridaz, ^{13}N-ammonia, $H_2{}^{15}O$, ^{82}Rubidium, and ^{123}I-meta-iodo-benzylguanidine (mIBG).[24] Also, new combination modalities are used to improve the detection of CAD more quantitatively, including CCTA/SPECT MPI, PET-CT and SPECT-CT. These so-called hybrid imaging techniques combine physiologic and anatomic information in order to reduce tracer use and costs. Due to advances in technology of SPECT MPI, which simultaneously occur with the introduction of PET imaging, more studies are needed to compare these techniques.

Other challenges for cardiac stress imaging are based on the procedural limitations of cardiac stress imaging: the length of the tests and the radiation exposure to the patients. The average SPECT MPI study exposes the patients to 12-15 mSV [20], while stress echocardiography is free of radiation. Regarding the future of stress echocardiography, contrast echocardiography, myocardial Doppler imaging and 3D-echocardiography are promising relatively new techniques. To date however, due to the lack of a standardized technique, stress echocardiography and stress SPECT MPI are still the most commonly used and widely available techniques in the evaluation and management of patients with known or suspected CAD.

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Chapter 17

Nederlandse samenvatting

Inleiding

Ondanks betere diagnostiek en behandeling blijven coronaire hartziekten (ziekten van de kransslagaders) de belangrijkste doodsoorzaak in veel Westerse landen. Door vergrijzing worden er meer patiënten verwezen voor het diagnosticeren en inschatten van de prognose van coronaire hartziekten. Voor het op niet-invasieve wijze in beeld brengen van coronaire hartziekten kan men gebruikmaken van myocardscintigrafie en echografie. Door een patiënt zich te laten inspannen op een loopband of met een fiets (een stress test) kunnen veranderingen van de hartspier uitgelokt worden die duiden op zuurstofgebrek van de hartspier (ischemie). Myocard perfusie scintigrafie middels single-photon emission computed tomography (SPECT) meet de doorstroming (perfusie) van het hartspierweefsel (myocard) in rust en tijdens inspanning. Stress echocardiografie visualiseert wandbewegingsstoornissen van het hart. SPECT en dobutamine stress echocardiografie (DSE) worden gebruikt om myocardischemie op te sporen tijdens of na inspanning. Bij patiënten die om welke reden dan ook geen inspanning kunnen leveren, kan medicatie worden toegediend om stress van het hart na te bootsen. Veelgebruikte medicijnen voor dit doel zijn dipyridamol, adenosine en dobutamine.

Cardiaal stress onderzoek

Cardiaal stress onderzoek speelt een belangrijke rol bij het stellen van de diagnose en de bepaling van de prognose van coronaire hartziekten. Patiënten met een normaal stress onderzoek hebben een laag risico (<1% per jaar) op cardiale dood of een hartinfarct; een invasief coronair angiogram kan daarom worden vermeden. Echter, patiënten met een afwijkend stress onderzoek hebben een verhoogd risico op overlijden en het krijgen van een hartinfarct. Bij deze patiënten kan de prognose worden verbeterd door een coronairangiogram te verrichten en vervolgens, afhankelijk van de bevindingen, een percutane coronaire interventie (dotterbehandeling meestal met stent-implantatie) of coronaire bypass operatie te doen.

Het risico van de patiënt op overlijden of een hartinfarct kan na een normaal stress onderzoek in de loop van de tijd toenemen, bijvoorbeeld vanwege progressie van al bekende coronaire hartziekte of de aanwezigheid van diabetes mellitus. Er is een zekere 'geldigheidsduur' van DSE en SPECT. In de eerste periode na DSE of SPECT is een goede inschatting van de prognose mogelijk, daarna kan het risico van de patiënt veranderen. De prognostische waarde van cardiaal stress onderzoek is onderzocht voor de korte – en middellange termijn. Lange-termijn follow-up data ontbreken echter in de literatuur.

In dit proefschrift wordt de lange-termijn prognostische waarde van cardiaal stress onderzoek beschreven in verschillende patiëntengroepen. De beschreven studies worden onderverdeeld in 3 hoofdonderwerpen:

A) De duur van een laag risico op overlijden of een hartinfarct na een normaal cardiaal stress onderzoek

B) Het voorspellen van de lange-termijn prognose bij patiënten met een verhoogd risico op overlijden of een hartinfarct.

C) De lange-termijn invloed van vroege coronaire revascularisatie op de prognose.

De duur van de laag risico periode na een normaal cardiaal stress onderzoek

Patiënten met een normaal cardiaal stress onderzoek hebben in de eerste jaren na het onderzoek een goede prognose. Na verloop van tijd stijgt de kans op een cardiaal event (zoals sterfte door een cardiovasculaire oorzaak of hartinfarct), ondanks de normale stress SPECT. De duur van een laag risico op cardiale events na een normale SPECT was vooralsnog onbekend. In **Hoofdstuk 2** worden de lange-termijn uitkomsten gepresenteerd van 233 patiënten die een inspannings SPECT ondergingen. Gedurende de lange follow-up periode van 15 jaar overleed 18% van de patiënten. Met name in de eerste 5 jaar van de follow-up periode hebben patiënten met een normale SPECT een gunstige prognose. Factoren zoals leeftijd, mannelijk geslacht en diabetes mellitus waren voorspellers voor een cardiaal event. Patiënten met deze eigenschappen moeten dan ook intensiever vervolgd worden. In **Hoofdstuk 3** werd onderzocht wat de waarde is van SPECT voor het voorspellen van lange-termijn uitkomsten bij patiënten met een normaal elektrocardiogram (ECG). In de onderzochte groep van 650 patiënten had 50% een afwijkende SPECT en 20% van de patiënten had een volledig of gedeeltelijk reversibel perfusie defect. SPECT heeft een toegevoegde prognostische waarde bij patiënten die een normaal ECG in rust hebben en bekend zijn met coronairziekte of een vermoeden daarop.

Het voorspellen van lange-termijn betekenis in patiënten met een verhoogd risico op cardiale events

Zowel SPECT als DSE worden gebruikt om patiënten te identificeren die een laag of hoog risico hebben op cardiale events. Dit is van belang om patiënten de juiste behandeling te kunnen bieden (medicatie en/of revascularisatie). Uit het onderzoek in **Hoofdstuk 4** blijkt dat SPECT toegevoegde prognostische waarde heeft gedurende een

vervolg periode van 11 jaar. Patiënten met een afwijkende SPECT hebben een slechtere prognose dan patiënten met een normale SPECT. Er zijn belangrijke risicofactoren voor coronaire hartziekten zoals, obesitas, diabetes mellitus, status na harttransplantatie en het hebben van een beperkte inspanningscapaciteit. De prognostische waarde van SPECT bij patiënten met deze risicofactoren kan beperkt zijn. In **Hoofdstuk 5** wordt de prognostische waarde van inspannings SPECT beschreven in 261 obesitas patiënten, die werden vervolgd gedurende 12 jaar. Obesitas patiënten met een normale SPECT hebben een gunstige overleving gedurende de eerste 6 jaar na de SPECT. Invasieve onderzoeken kunnen daarom worden vermeden bij deze patiënten. Inspannings SPECT levert waardevolle prognostische informatie bij obesitas patiënten tot 6 jaar na de SPECT scan. Coronaire hartziekten zijn een veelvoorkomende doodsoorzaak bij patiënten die een harttransplantatie hebben ondergaan. SPECT is een nuttige techniek om coronaire hartziekten te evalueren in deze patiëntengroep. **Hoofdstuk 6** beschrijft de rol van inspannings SPECT bij 166 patiënten met een harttransplantatie. Inspannings SPECT levert prognostische waarde tot 5 jaar na de SPECT scan.

Stress SPECT zal de hoeveelheid ischemie onderschatten als patiënten geen of een beperkte inspanningscapaciteit hebben. Daarom wordt in deze patiëntengroep inspanning nagebootst met medicijnen die de zuurstofvraag van het hart verhogen. In de studies beschreven in dit proefschrift is gebruik gemaakt van dobutamine. In **Hoofdstuk 7** is onderzocht wat de prognostische waarde is van dobutamine SPECT in een groep van 473 patiënten met een beperkte inspanningscapaciteit. Een afwijkende SPECT was een onafhankelijke lange-termijn voorspeller voor het gecombineerde eindpunt van cardiale dood, hartinfarct of coronaire revascularisatie. Een afwijkende SPECT bood een toegevoegde waarde voor het voorspellen van de lange termijn prognose, naast de klinische gegevens en de resultaten van de dobutamine inspanningstest. Vervolgens werd in **Hoofdstuk 8** de waarde van dobutamine SPECT onderzocht bij 247 patiënten van 65 jaar of ouder met een gemiddelde leeftijd van 71 jaar. Tijdens de lange-termijn follow-up van 14 jaar was zowel een afwijkende SPECT als de mate en ernst van de perfusiedefecten voorspellend voor cardiale events. Deze parameters kunnen gebruikt worden om patiënten ouder dan 65 jaar te stratificeren in een laag en hoog risico op cardiale events.

Het maken van een ECG is goedkoop, eenvoudig en waardevol in de diagnostiek van patiënten met coronaire hartziekten. Daarnaast maken deze eigenschappen het ECG tot een aantrekkelijk onderzoek voor risico stratificatie van patiënten. **Hoofdstuk 9** beschrijft de resultaten van het onderzoek naar de prognostische waarde van de QRS duur op het ECG bij 512 patiënten met bekende coronaire hartziekten of een vermoeden

daarop. Gedurende de lange-termijn follow-up van gemiddeld 9 jaar bleek dat een QRS duur van ≥120 ms een onafhankelijke voorspeller was van cardiale dood en hartinfarct. Deze studie toont aan dat zowel de QRS duur als de resultaten van de SPECT gebruikt kunnen worden voor optimale risicostratificatie van patiënten met coronaire hartziekten of een vermoeden daarop.

Naast de al genoemde risicofactoren is diabetes mellitus een belangrijke risicofactor voor coronaire hartziekten. **Hoofdstuk 10** beschrijft de lange-termijn (8 jaar) uitkomsten van dobutamine SPECT bij ruim 200 patiënten met diabetes mellitus en een verminderde inspanningscapaciteit. Patiënten met een normale dobutamine SPECT hadden een significant betere overleving dan patiënten met een afwijkende dobutamine SPECT tot 4 jaar na de scan. Na die periode had SPECT geen toegevoegde waarde meer. Een afwijkende SPECT en de aanwezigheid van reversibele perfusiedefecten waren belangrijke voorspellers voor cardiale dood. In **Hoofdstuk 11** worden de resultaten beschreven van het onderzoek naar de lange-termijn uitkomsten van DSE bij patiënten met diabetes mellitus. In totaal werden 396 patiënten met diabetes mellitus gevolgd gedurende 13 jaar. DSE had prognostische waarde tot circa 7 jaar. De sterkste voorspellers voor totale mortaliteit, cardiale dood en hartinfarct waren de wall motion score index tijdens maximale stress (pWMSI) en de linker ventrikel ejectie fractie (LVEF). Patiënten met een LVEF ≥50% en een peak WMSI=1 hadden een gunstige prognose gedurende follow-up, terwijl patiënten met een LVEF<50% en een pWMSI>1 een slechtere prognose hadden. Ook bleek uit dit onderzoek dat de prognose van patiënten met diabetes mellitus gerelateerd was aan zowel de hoeveelheid ischemie geïnduceerd tijdens inspanning als aan de functie van de linker ventrikel in rust. Patiënten met diabetes mellitus en een verminderde inspanningscapaciteit vormen een hoog-risico patiënten groep. Dit is de reden waarom de prognostische waarde van SPECT en DSE bij patiënten met diabetes mellitus beperkt is. Er is dus een beperkte geldigheidsduur voor beide technieken bij patiënten met diabetes mellitus.

Hoofdstuk 12 beschrijft de lange-termijn uitkomsten na DSE in een grote groep van 3381 patiënten, waarvan 45% van de patiënten bekend was met coronaire hartziekten. Patiënten met een normale DSE hadden een significant betere overleving dan patiënten met een afwijkende DSE (de overleving na 15 jaar was 44% versus 35%). De WMSI tijdens stress was voorspellend voor de totale mortaliteit en cardiale dood. Na een follow-up periode van 7 jaar bleek dat er geen verschil meer was tussen de overlevingscurves. Dit komt overeen met de resultaten van **Hoofdstuk 11**.

Vervolgens is in **Hoofdstuk 13** de lange-termijn prognostische waarde van dobutamine SPECT vergeleken met DSE. In totaal 301 patiënten ondergingen zowel

SPECT als DSE en werden vervolgd voor een periode van 14 jaar. Leeftijd, een hartinfarct in het verleden en de aanwezigheid van hartfalen waren voorspellers voor de lange-termijn prognose. Een multivariabele analyse toonde dat beide niet-invasieve technieken toegevoegde waarde hadden naast de klinische variabelen en de variabelen van de stress test. Beide technieken kunnen dan ook gebruikt worden om patiënten in te delen in een laag of hoog risico groep op het krijgen van cardiale events.

De lange-termijn invloed van vroege coronaire revascularisatie op de prognose

Coronaire revascularisatie bij patiënten met een acuut coronair syndroom leidt tot een reductie in mortaliteit. Patiënten met stabiele coronaire hartziekte kunnen zowel met medicatie als met coronaire revascularisatie (dotterbehandeling meestal met stent-implantatie of coronaire bypass operatie) behandeld worden. Het is nog niet geheel duidelijk wat de invloed van vroege coronaire revascularisatie is bij patiënten met stabiele coronaire hartziekte. In **Hoofdstuk 14** wordt beschreven wat de 10-jaars invloed is van vroege (≤90 dagen na de DSE) coronaire revascularisatie bij 905 patiënten met ischemie op DSE. De resultaten suggereren dat vroege revascularisatie een gunstig effect heeft op totale mortaliteit en cardiale dood in deze patiënten groep. Dit gold voor zowel patiënten met een matig afwijkende DSE (gedefinieerd als een pWMSI≤1.7) als voor patiënten met een ernstig afwijkende DSE (gedefinieerd als een pWMSI>1.7). Ten slotte beschrijft **Hoofdstuk 15** de invloed van vroege coronaire revascularisatie op totale mortaliteit en cardiale dood bij 538 patiënten met ischemie op SPECT. Matige ischemie was gedefinieerd als reversibele perfusiedefecten in minder dan 3 segmenten. Ernstige ischemie was gedefinieerd als reversibele perfusiedefecten in meer dan 3 segmenten. Tijdens de 12-jaar follow-up bleek dat patiënten die vroege revascularisatie ondergingen een betere overleving hadden en dat er minder cardiale dood optrad. Dit verschil werd met name veroorzaakt door het gunstige effect van vroege coronaire revascularisatie bij patiënten met een ernstig afwijkende DSE.

Conclusie – klinische toepassingen

De lange-termijn studies beschreven in dit proefschrift hebben verschillende toepassingen voor de dagelijkse klinische praktijk.

Patiënten met een normale inspannings SPECT hebben een gunstige prognose, ook op langere termijn. Een conservatieve behandeling is dan ook gerechtvaardigd. Zo kunnen invasieve onderzoeken worden vermeden.

Daarnaast kunnen verschillende klinische parameters, zoals leeftijd, mannelijk geslacht en diabetes mellitus, worden gebruikt om patiënten te identificeren die een verhoogd risico hebben op overlijden, een hartinfarct of het ondergaan van een coronaire revascularisatie. Patiënten met deze risicofactoren dienen intensiever vervolgd te worden.

Ten derde heeft ongeveer 20% van de patiënten met bekende coronaire hartziekten of een vermoeden daarop én een normaal inspannings ECG reversibele perfusiedefecten met SPECT. Een SPECT onderzoek kan bij bepaalde patiënten aanvullende informatie geven over de prognose, zelfs als het inspannings ECG normaal is.

Ten vierde, de lange-termijn resultaten van dit proefschrift bevestigen eerdere studies met betrekking tot de waarde van DSE en SPECT voor risico stratificatie van patiënten met een laag of hoog risico op cardiale events. Beide niet-invasieve testen kunnen artsen helpen bij het bepalen van een behandeling om het risico op overlijden of een hartinfarct te verminderen bij patiënten met obesitas, diabetes mellitus of met een harttransplantatie en oudere patiënten of patiënten met een verminderde inspanningscapaciteit.

Ten vijfde, de lange-termijn prognose van patiënten met diabetes mellitus is gerelateerd aan zowel de hoeveelheid ischemie geïnduceerd tijdens inspanning als aan de functie van de linker ventrikel in rust.

Ten zesde, DSE en SPECT hebben een vergelijkbare prognostische waarde voor de zeer lange-termijn. De prognostische waarde van beide afbeeldingstechnieken is nauwkeuriger dan klinische variabelen alleen (zoals leeftijd, geslacht, cardiale risicofactoren).

Ten slotte, zal de beslissing om patiënten wel of niet te revasculariseren afhangen van het risicoprofiel en de symptomatologie. De mate van ischemie, vastgesteld met DSE of SPECT, kan gebruikt worden bij de keuze van de juiste therapie.

Chapter 18

Additional information:

Dankwoord
List of publications
PhD portfolio
Curriculum Vitae

DANKWOORD

Promoveren, in welke fase van je carrière moet die research episode eigenlijk vallen? Sommigen promoveren al vóór hun co-schappen, anderen promoveren na hun specialistenopleiding. Kan het anders? Jazeker, maar promoveren tijdens je werk als arts is alleen mogelijk met veel hulp en steun. Aan het einde van mijn proefschrift wil ik daarom graag een aantal mensen in het bijzonder bedanken in de wetenschap dat God het was die mij de kracht en gezondheid gaf om dit werk te voltooien.

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LIST OF PUBLICATIONS

1. **Boiten HJ**, van Domburg RT, Valkema R, Zijlstra F, Schinkel AF. Ischemia burden on stress SPECT MPI predicts long-term outcomes after revascularization in stable coronary artery disease. Submitted.
2. **Boiten HJ**[a], Veenis J[a], Caliskan K, Maat APWM, Constantinescu A, Manintveld O, Van den Berge JC, Valkema R, Zijlstra F, van Domburg RT, Schinkel AF. Prediction of long-term (>10 year) cardiovascular outcomes in heart transplant recipients: value of stress technetium-99m tetrofosmin myocardial perfusion imaging. Submitted.
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[a]both authors contributed equally to this work.

PhD-PORTFOLIO: SUMMARY OF PhD TRAINING AND TEACHING ACTIVITIES

Erasmus MC
Universitair Medisch Centrum Rotterdam

Name PhD student: H.J. Boiten
Institution: Erasmus MC, Thoraxcenter
Research school: COEUR

Promotor: prof. dr. F. Zijlstra
Co-promotors: dr. A.F.L. Schinkel
dr. R.T. van Domburg

1. PhD TRAINING	**Workload (ECTS)**
General academic / research skills	
Basic academic skills	10
Bio-organic chemistry	10
Basic statistics	6
Training critical reading	1.2
Scientific English Writing	1.2
Team-Resource-Building	0.2
Conferences / seminars / symposia	
Cardiology & Vascular Medicine Update and Perspective 2010 - ESC	1
Cardiology & Vascular Medicine Update and Perspective 2011 - ESC	1
Cardiology & Vascular Medicine Update and Perspective 2012 - ESC	1
European Society of Cardiology – Congress, Rome, Italy	2
Presentation: Ten-year survival benefit of early coronary revascularization in patients with an ischemic dobutamine stress echocardiography. *Presentation: Long-term prognostic value of dobutamine stress SPECT in elderly patients unable to perform exercise testing.*	
Najaarscongres 2015 – NVVC - Arnhem	1
Voorjaarscongres 2016 – NVVC - Noordwijkerhout	1
Presentation: Long-term prognostic value of dobutamine stress SPECT in elderly patients	
Nederlandse Internisten Vereniging - Congres 2016 – NIV	1
Erasmus Winter Programme – NIHES – Erasmus MC	4
Junior Kamerdag – Cardiovascular Imaging – NVVC	0.5
Seminar: integrating hypertension and immunology: view from a cardiologist	0.1
Symposium: Quantitative Methods for Medical Research – Erasmus MC	0.2
Symposium: Translational Research – Erasmus MC	0.2
Symposium: Right Ventricular Failure – Erasmus MC	0.2
Klinische avonden Interne Geneeskunde – Erasmus MC	0.2
Presentation: Intravascular large B-cell lymphoma	

In-depth courses	
COEUR course: Arrhythmia Research Methodology	1.5
COEUR course: Heart Failure Research	1.5
COEUR course: Molecular Biology in Cardiovascular Research	1.5
Webinars EACVI: myocardial perfusion SPECT, nuclear cardiology, advanced nuclear cardiology, cardiac CT, strain imaging in clinical practice	0.5
2. TEACHING ACTIVITIES	
Course: didactic skills – Institute Desiderius School – Erasmus MC	1
Teaching assistant – department of Internal Medicine – Erasmus MC	1.5
Lecturer – department of Acute Medicine – Erasmus MC	4
Author – ABC van de Cardiologie; inleiding in de diagnostiek en behandeling van hartziekten. 2012. Rotterdam: 2010 Uitgevers.	2
Contributions: Chapter 11 'Heart failure' and Chapter 12 'Cardiomyopathy'	
Supervising (master) students – Erasmus MC	1

CURRICULUM VITAE

The author of this thesis, Hendrik Johannes Boiten (Henk-Jan), was born on October 4th 1988 in Schiedam, The Netherlands. Secondary school was the Guido de Brès in Rotterdam (part of the Wartburg College), where he graduated in 2007. For one year he studied 'Psychobiology' at the University of Amsterdam (UvA). He then went on to study 'Medicine' at the Erasmus University Rotterdam. After receiving his medical degree in the end of 2014 he started as an internal medicine resident (ANIOS) at the Albert Schweitzer Hospital in Dordrecht (supervisor: dr. E.F.H. van Bommel). In the middle of 2015 he started a PhD-project based on previous research and focused on the long-term outcome after cardiac stress imaging, both dobutamine stress echocardiography and stress single-photon emission computed tomography. The majority of that research is described in this thesis. He was supervised by prof. dr. F. Zijlstra (promotor), dr. R.T. van Domburg and dr. A.F.L. Schinkel (co-promotors). Besides all he is married to Daniëlle Huijzer. Together they have one daughter, Loïs.