Prognosis of Patients with Peripheral and Coronary Atherosclerotic Disease

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Prognosis of Patients with Peripheral and Coronary Atherosclerotic Disease

Prognose van perifeer en coronair vaatlijden

Thesis

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Chapter 1

Introduction and overview of the Thesis

Harm H.H. Feringa

Introduction and overview of the thesis

PERIPHERAL ARTERIAL DISEASE (PAD) affects more than 30 million people worldwide. In the United States, more than 8 million people suffer from this disease. The American College of Cardiology and the American Heart Association have recognized the importance of identifying and treating this disease and have initiated national campaigns to increase its awareness. Many patients, however, do not exhibit warning signs of the disease and remain undiagnosed. These missed diagnoses create a major health burden. When left untreated, PAD can lead to walking impairment and in more severe stages, to gangrene and leg amputation. Patients with PAD often have atherosclerotic disease in other parts of the body, which places the patient at risk for myocardial infarction, stroke and death. Especially coronary artery disease has been recognized as a complice of PAD. This thesis provides an insight in the prognosis of patients with peripheral and coronary artery disease and attempts to find solutions in improving the identification and management of this disease.

Peripheral arterial disease encompasses a range of disorders affecting the arterial beds exclusive of the coronary arteries. The most common disease process underlying PAD is atherosclerosis. Major risk factors of atherosclerosis are tobacco use, diabetes and hypertension. The ankle-brachial index is currently the standard diagnostic test for PAD in epidemiological surveys, vascular laboratories and in office practice. The ankle-brachial index can also be used as tool to monitor the efficacy of therapeutic interventions and for prognostic purposes. Prognostic information in patients with PAD may provide the basis for optimal management strategies. A risk index for long-term mortality, based on clinical risk factors, laboratory values, electrocardiography and ankle-brachial index values is presented in chapter 2. The prognostic value of postexercise ankle-brachial index values in addition to resting ankle-brachial index values is evaluated in chapter 3. Since coronary artery disease is highly prevalent among patients with PAD, refinement of risk stratification may be accomplished by routine cardiac testing. In chapter 4, the prognostic value of left ventricular ejection fraction and stress-induced ischemia is evaluated in addition to ankle-brachial index values and clinical risk factors. Chapter 5 presents a study in which serial ankle-brachial index measurements over time are correlated with mortality and cardiac outcome.

Although identification and risk stratification are important steps in the management of patients with PAD, it is treatment that will reduce the morbidity and mortality associated with PAD. Lifelong treatment should include modification and elimination of risk factors and promotion of daily exercise and use of a nonatherogenic diet. Underlying risk factors, such as dyslipidemia, diabetes and hypertension, should be optimally treated. Chapter 6 presents data from an observational study in which different cardiovascular medications are systematically evaluated for their cardioprotective and life-prolonging effect. Chapter 7 evaluates the effect of intensified lipid-lowering therapy on long-term prognosis and examines whether higher doses of statins and lower LDL-cholesterol levels are both independently associated with improved outcome. Renal dysfunction has been identified as a major risk factor in atherosclerotic disease. Chapter 8 evaluates whether statins and angiotensin-converting enzyme inhibitors are associated with a lower progression rate of end-stage renal disease in patients with PAD. Diabetes is another major risk factor, with dysglycemia contributing to atherosclerotic progression and development of micro- and macrovascular complications. Chapter 9 evaluates the potential of lipid lowering treatment in improving glycemic control and prognosis of diabetic patients with PAD.

Surgical interventions are indicated for individuals with claudication symptoms who have functional disability which is unresponsive to exercise or pharmacological therapy and have a reasonable likelihood to improve symptomatically. In patients with aortic aneurysms, reparative surgery may be indicated to eliminate the risk of rupture. Despite the various advantages of surgical intervention, mortality and cardiovascular morbidity are high in the perioperative period. Preoperative screening is essential in identifying patients at increased risk who benefit from perioperative protective medication. Chapter 10 reports the incidence of perioperative myocardial ischemia and relates the location of perioperative ischemia with the culprit coronary lesion as assessed with preoperative dobutamine stress echocardiography. Chapter 11 evaluates the prevalence of and prognosis of unrecognized myocardial infarction and silent myocardial ischemia in vascular surgery patients. The prognostic value of impaired fasting glucose and glycemic control for perioperative cardiac ischemic events is presented in chapter 12. N-terminal pro-B-type natriuretic peptide (NT-proBNP) has emerged as a

marker of left ventricular dysfunction and has prognostic value in patients with congestive heart failure and coronary artery disease. Chapters 13 and 14 evaluate the prognostic role of NT-proBNP in vascular surgery patients. The relation between NT-proBNP levels and the extent of myocardial ischemia, heart rate variability and changes in left ventricular function is evaluated in chapters 15, 16 and 17. Chapter 18 discusses preoperative risk stratification in patients with renal dysfunction and chapter 19 evaluates the impact of glomerular filtration rate on minor troponin T concentrations for cardiac risk stratification.

Beta-blockers have been demonstrated to protect vascular surgery patients from adverse perioperative cardiac events and mortality. However, optimal management strategies are essential in this setting, since inadequate management may compromise efficacy and safety. Chapter 20 provides a review of perioperative management to address current issues and controversies. Chapter 21 evaluates the effect of different cardiac medications that protects vascular surgery patients with left ventricular dysfunction. Chapter 22 evaluates the effect of high doses of beta-blockers and tight heart rate control on the incidence of perioperative myocardial ischemia, troponin T release and cardiovascular events. The effect of beta-blockers on in-hospital and long-term survival in patients with severe left ventricular dysfunction is examined in chapter 23. Selective or non-selective beta-blocker therapy may interfere with the interpretation of dobutamine stress echocardiography, which is recommended as screening tool for high-risk vascular surgery patients. The hemodynamic responses and long-term follow-up results of patients using selective or non-selective beta-blockers are presented in chapter 24. Recently, statins have emerged as medication with cardioprotective effects. Chapter 25 evaluates the intensity of statin therapy in relation to myocardial ischemia, troponin T release and clinical cardiac outcome in patients undergoing major vascular surgery.

With the safety of current surgical procedures, elderly patients are now commonly referred for surgical intervention. Perioperative management and risk factor control in elderly patients is discussed in chapter 26 and 27. Chapter 28 gives a comment on the use of preoperative revascularization before major vascular surgery. Finally, chapters 29 and 30 evaluate perioperative cardiac outcome between different surgical procedures for carotid artery stenosis and abdominal aortic aneurysm.

Atherosclerosis is a leading cause of death in industrialized countries. Hopefully, the results of these studies will contribute to our understanding of peripheral and coronary artery disease for the improvement in management and outcome of these patients

Chapter 2

A prognostic risk index for long-term mortality in patients with peripheral arterial disease

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A prognostic risk index for long-term mortality in patients with peripheral arterial disease

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Background: Prognostic information in patients with peripheral arterial disease (PAD) may provide the basis for optimal management strategies, including risk factor modification and pharmacologic treatment at an early stage. This study aimed to develop a prognostic risk index for long-term mortality in patients with PAD.
Methods: In a single-centre observational cohort study, 2,642 patients with ankle-brachial index ≤0.90 were randomly divided into derivation (n=1,332) and validation (n=1,310) cohorts. Cox hazards regression analysis with stepwise backward elimination identified predictors of 1-year, 5-year and 10-year mortality in the derivation cohort. Weighted points were assigned to each predictor. Discrimination of the index was determined in both the derivation and validation cohorts.
Results: During 10-year follow-up, 42.2% and 40.4 % of patients died in the derivation and validation cohort, respectively. The risk index for 10-year mortality (+points) included renal dysfunction (+12), heart failure (+7), ST-changes (+5), age>65 (+5), hypercholesterolemia (+5), ankle-brachial index <0.60 (+4), Q-waves (+4), diabetes (+3), cerebrovascular disease (+3) and pulmonary disease (+3). Statins (-6), aspirin (-4) and β-blockers (-4) were associated with reduced 10-year mortality. Patients were stratified into low (<0 points), low-intermediate (0-5 points), high-intermediate (6-9 points) and high (>9 points) risk categories, according to risk score. Ten-year mortality rates were 22.1%, 32.2%, 45.8% and 70.4%, respectively (p<0.001) and comparable to mortality rates in the validation cohort. C-statistics demonstrated good discrimination both in the derivation (0.72) and validation cohort (0.73).
Conclusion: A prognostic risk index for long-term mortality stratified patients with PAD into different risk categories. This may be useful for risk stratification, patient counseling and medical decision making.

LOWER EXTREMITY peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and is associated with increased cardiovascular morbidity and mortality [1-3]. Patients with PAD have a 3-fold increased risk to die from all causes and a 6-fold increased risk to die from cardiovascular disease within a period of 10 years, as compared to patients without PAD [1]. The prevalence of PAD has been reported to range from 4% in patients aged 40 years and older, to over 20% in patients aged 70 years and older [4-9]. It has been estimated that approximately 8 to 12 million people in the United States suffer from this disease [4]. However, prevalence values may even be higher since a substantial proportion of the population has undetected PAD [3,4,7].

An increased awareness of PAD may help to improve identification of patients with underlying PAD. Patients who present with PAD may benefit from antiplatelet therapy, walking exercise, risk factor reduction and life-style modifications [10,11]. Many clinical risk factors have been identified as predictors of adverse events, however, to our knowledge, a prognostic risk index including clinical risk factors, electrocardiographic data, ankle-brachial index values and chronic cardiovascular medication has not yet been developed in patients with PAD.

A comprehensive prognostic risk index may provide an overall framework for physicians to identify risk factors and to help making predictions based on these risk factors at an early stage of the disease. After risk factors in the individual patient have been identified, a risk score can be calculated and the patient can be classified into a particular risk category. Prognostic information may help the clinician in the decision for targeted treatment interventions. The objective of this study was to develop and provide an accurate and easy-to-use prognostic risk index for long-term mortality that could stratify patients with PAD into different risk groups. This risk index was validated in two independent patient samples.

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METHODS

The Erasmus Medical Center in Rotterdam, the Netherlands, serves a population of approximately 3 million people and acts as a tertiary referral center for approximately 30 affiliated hospitals. A total of 2,642 consecutive patients with PAD were referred to our department of Vascular Medicine between January 1983 and August 2005 for the evaluation and management of their disease.

Ankle-brachial index
The ankle-brachial index at rest was measured in each patient by trained technicians, using a Doppler ultrasonic instrument with an 8 MHz vascular probe (Imexdop CT+ Vascular Doppler, Miami Medical, USA). The ABI in the right and left leg was calculated by dividing the right and the left ankle pressure by the brachial pressure. The higher of the two brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Again, the higher of the dorsalis pedis and posterior tibial artery pressure was used if a discrepancy in systolic blood pressure between the two arteries was measured [11]. Of the ABI values obtained in each leg, the lower was used and PAD was defined as a resting ankle-brachial index of ≤0.90. An ankle-brachial index of <0.60 was considered as severe PAD.

Clinical variables
A detailed cardiovascular history was obtained, including a history of stable angina pectoris, myocardial infarction, coronary artery bypass grafting, congestive heart failure, and cerebrovascular event. Patients were also screened for the following clinical risk factors: diabetes mellitus, hypertension, hypercholesterolemia, renal dysfunction, current smoking and chronic obstructive pulmonary disease. Diabetes mellitus was recorded if patients presented with a fasting glucose level of ≥7.0 mmol/L, or in those who required medical treatment. Hypertension was recorded if patients presented with a blood pressure ≥140/90 mmHg or if patients received medical treatment. Hypercholesterolemia was recorded if patients presented with a plasma cholesterol level ≥5.5 mmol/L, or if the diagnosis was established by the referring physician. Renal dysfunction was recorded if patients presented with a serum creatinine level ≥ 2.0 mg/dL (177 μmol/L) or in those who required dialysis. The body mass index (Quetelet-index) was calculated as weight in kilograms divided by the square of height in meters. Patients with a body mass index >0.30 were considered obese. Baseline 12-lead electrocardiography was evaluated for Q-waves, ST-segment depression or elevation, left ventricular hypertrophy, right bundle branch block, left bundle branch block and atrial fibrillation. All patients were assessed for cardiac medication use, including aspirin, angiotensin converting enzyme inhibitors, β-blockers and statins. To ascertain the long-term use of cardiovascular medication, medication had to be documented at least at 2 months after the first visit.

Definition of outcome
The median follow-up period was 8 years (interquartile range: 4-11 years). End-point was all-cause mortality at 1-year, 5-year and 10-year. Mortality data was collected by reviewing the medical records, by approaching the Office of Civil Registry, and through follow-up interviews with patients, family-members and referring physicians.

Development of the prognostic risk index
A random sample of 1,332 patients (50%) of the total cohort was assigned to the derivation cohort, which was used for developing the prognostic index (Rotterdam derivation cohort) [12,13]. A total of 1,310 patients (50%) were assigned to the validation cohort (Rotterdam validation cohort). A descriptive comparison between the derivation and validation cohorts was performed using the chi-square test for categorical variables and the Student t test for continuous variables. Cox proportional hazards regression analysis was used to analyze the association between clinical variables and mortality. A prognostic risk index was developed for 1-year, 5-year and 10-year mortality. To select a final set of significant ($p<0.05$) risk factors in the derivation cohort, all baseline clinical variables were entered into a multivariate Cox proportional hazards regression model with stepwise backward elimination of the least significant variable. The non-modifiable variables age and gender were always entered into the multivariate regression model, despite the level of significance, and were eliminated at the final model if non-significant. Separate risk scoring systems for 1-year, 5-year and 10-year mortality were then constructed by assigning weighted points to each independent and significant predictor in the derivation cohort. Weighted points were calculated by multiplying the coefficient of the predictor by 10 and by rounding it off to the nearest integer. In each patient, a risk score for 1-year, 5-year and 10-year mortality was calculated by adding up the points for each risk factor present. Based on their risk score, patients were divided into four different risk groups (low, low-intermediate, high-intermediate, high), using the quartiles as cut-off values.

Validation of prognostic risk index
The 1-year, 5-year and 10-year prognostic risk index was applied to the Rotterdam validation cohort and predicted 1-year, 5-year and 10-year mortality rates

Table 1. Baseline characteristics of the derivation and validation cohorts

Characteristic	Rotterdam derivation cohort (n=1,332)	Rotterdam validation cohort (n=1,310)	p value
Age >65 years, No. (%)	686 (51.5)	636 (48.5%)	0.13
Male gender, No. (%)	964 (72.4)	934 (71.3)	0.56
Angina pectoris, No. (%)	317 (23.8)	316 (24.1)	0.85
Previous MI, No. (%)	506 (38.0)	481 (36.7)	0.50
Previous CABG, No. (%)	266 (20.0)	223 (17.0)	0.051
CAD (summary variable), No. (%)	601 (45.1)	584 (44.6)	0.78
History of CHF, No. (%)	105 (7.9)	119 (9.1)	0.27
History of CVA/TIA, No. (%)	101 (7.6)	99 (7.6)	0.98
Diabetes mellitus, No. (%)	229 (17.2)	234 (17.9)	0.65
Hypercholesterolemia, No. (%)	291 (21.8)	274 (20.9)	0.56
Hypertension, No. (%)	609 (45.7)	627 (47.9)	0.27
Current smoking, No. (%)	461 (34.6)	464 (35.4)	0.66
Renal dysfunction, No. (%)	67 (5.0)	66 (5.0)	0.99
COPD, No. (%)	149 (11.2)	171 (13.1)	0.14
Obesity, No. (%)	160 (12.0)	148 (11.3)	0.57
ABI <0.60, No. (%)	590 (44.3)	589 (45.0)	0.73
Electrocardiography, No. (%)			
Q waves	373 (28.0)	341 (26.0)	0.25
ST segment changes	204 (15.3)	195 (14.9)	0.76
Left ventricular hypertrophy	74 (5.6)	72 (5.5)	0.95
Right bundle branch block	20 (1.5)	27 (2.1)	0.28
Left bundle branch block	50 (3.8)	47 (3.6)	0.82
Atrial fibrillation	21 (1.6)	38 (2.9)	0.021
Medication			
Aspirin, No. (%)	291 (21.8)	284 (21.7)	0.92
ACE-inhibitors, No. (%)	340 (25.5)	347(26.5)	0.57
β-blocker, No. (%)	335 (25.2)	319 (24.4)	0.63
Statins, No. (%)	257 (19.3)	258 (19.7)	0.80
Enrollment after 1995, No. (%)	553 (41.5)	585 (44.7)	0.10

MI = myocardial infarction, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CHF = congestive heart failure, CVA/TIA = cerebrovascular accident/transient ischemic attack, COPD = chronic obstructive pulmonary disease, ABI = ankle-brachial index, ACE-inhibitors = angiotensin converting enzyme inhibitors.

were compared. The prognostic risk index was also validated in an independent cohort outside the Erasmus Medical Center (Netherlands Heart Survey cohort). This cohort constituted of 688 patients with PAD who came from 11 hospitals in the Netherlands. Five hospitals were located in the centre part of the country, three centers in the northern region and three in the southern region. The participating sites included 2 small centers (<400 beds), 5 of intermediate size (400 to 800 beds) and 4 large centers (>800 beds). Two centers were university hospitals. Data collection in this cohort was part of a survey of clinical practice supported by the Netherlands Heart Foundation in the context of the Euro Heart Survey Programme. Since follow-up in this cohort was 1 year, only the 1-year prognostic risk index was validated in this Netherlands Heart Survey cohort. To examine the discrimination of our prognostic risk indexes, we determined the area under the receiver operating characteristic (ROC) curve, which is comparable to the C-statistic [13]. C-statistics in the validation cohorts were calculated based on the mortality risk score system created from the derivation cohort. Hazard ratios are given with corresponding 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analysis was performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics are presented in Table 1.In the Rotterdam derivation cohort, median age was 65.2 years (interquartile range: 57.3 to 72.1 years), 72.4% were male and the median ankle-brachial index was 0.60 (interquartile range: 0.50 to 0.75). In the Rotterdam validation cohort, median age was 64.7 years (interquartile range: 56.5 to 72.1 years), 71.3% were male and the median ankle-brachial index was 0.60 (interquartile range: 0.45 to 0.75). No significant differences in baseline characteristics between the two cohorts were observed, except for atrial fibrillation which was less frequently determined in the derivation cohort compared to the validation cohort (1.6% vs. 2.9%, respectively, p=0.021). During 1-year, 5-year and 10-year of follow-up, 81 (6.1%), 298 (22.4%), and 562 (42.2%) patients, respectively, died in the derivation cohort and 88 (6.7%), 306 (23.4%), and 529 (40.4%) patients, respectively, died in the Rotterdam validation cohort. At 1-year follow-up, 74 (10.8%) patients died in the Netherlands Heart Survey validation cohort.

In univariate analysis, risk factors associated with increased 1-year, 5-year and 10-year mortality included age above 65 years, previous myocardial infarction, history of congestive heart failure, history of cerebrovascular events, renal dysfunction, ankle-brachial index less than 0.60 and electrocardiographic Q waves and ST segment deviations (Table 2). Angina pectoris and a history of coronary artery bypass grafting were associated with an increased risk of 1-year mortality. Diabetes mellitus and chronic pulmonary disease were associated with an increased risk of 5-year and 10-year mortality. Hypertension and right bundle branch block were associated with an increased risk of 10-year mortality. Univariate analysis also demonstrated that statin therapy was associated with a reduced risk of 1-year, 5-year and 10-year mortality, aspirin with a reduced risk of 5-year mortality and β-blocker therapy with a reduced risk of 1-year and 10-year mortality.

Multivariate proportional hazards regression analysis using stepwise backward deletion of the least significant variables identified 10, 12 and 13 clinical variables as independent and significant predictors of 1-year, 5-year and 10-year mortality, respectively (Table 3). A risk score for 1-year, 5-year and 10-year mortality from each

Table 2. Univariate analysis of clinical variables and mortality in the derivation cohort (n=1332).

Characteristic	Hazards ratio (95% CI) for 1-year mortality	p- value	Hazards ratio (95% CI) for 5-year mortality	p- value	Hazards ratio (95% CI) for 10-year mortality	p- value
Age >65 years	4.59 (2.63-8.02)	<0.001	2.10 (1.66-2.65)	<0.001	1.65 (1.39-1.95)	<0.001
Male gender	1.02 (0.63-1.66)	0.93	0.81 (0.64-1.03)	0.080	1.01 (0.83-1.22)	0.93
Angina pectoris	1.71 (1.09-2.68)	0.019	1.26 (0.99-1.60)	0.063	1.16 (0.96-1.41)	0.12
Previous MI	2.20 (1.43-3.38)	<0.001	1.61 (1.29-2.00)	<0.001	1.53 (1.30-1.81)	<0.001
Previous CABG	2.01 (1.28-3.16)	0.002	0.87 (0.66-1.15)	0.32	1.08 (0.88-1.32)	0.47
History of CHF	2.71 (1.55-4.74)	<0.001	3.07 (2.30-4.09)	<0.001	3.01 (2.35-3.85)	<0.001
History of CVA/TIA	2.41 (1.37-4.25)	0.002	2.34 (1.71-3.19)	<0.001	1.70 (1.28-2.25)	<0.001
Diabetes mellitus	1.41 (0.84-2.37)	0.20	1.61(1.23-2.10)	<0.001	1.45 (1.17-1.80)	0.001
Hypercholesterolemia	1.29 (0.76-2.19)	0.35	1.25 (0.93-1.66)	0.14	1.21 (0.97-1.51)	0.097
Hypertension	1.41 (0.92-2.15)	0.12	1.14 (0.91-1.42)	0.25	1.23 (1.04-1.46)	0.015
Current smoking	1.05 (0.68-1.63)	0.83	1.01 (0.81-1.27)	0.91	1.02 (0.86-1.22)	0.79
Renal dysfunction	5,49 (3.22-9.35)	<0.001	4.99 (3.60-6.93)	<0.001	4.11 (3.07-5.51)	<0.001
COPD	1.16 (0.62-2.15)	0.64	1.38 (1.01-1.88)	0.045	1.41 (1.11-1.79)	0.005
Obesity	1.38 (0.40-4.69)	0.61	0.80 (0.39-1.65)	0.55	0.72 (0.40-1.27)	0.26
ABI <0.60	3.02 (1.91-4.79)	<0.001	2.19 (1.75-2.73)	<0.001	1.62 (1.38-1.92)	<0.001
Electrocardiography						
Q waves	2.88 (1.88-4.41)	<0.001	1.75 (1.40-2.19)	<0.001	1.71 (1.44-2.04)	0.001
ST changes	2.18 (1.33-3.57)	0.002	1.73 (1.33-2.26)	<0.001	1.71 (1.36-2.13)	<0.001
LVH	0.62 (0.20-1.96)	0.41	1.12 (0.71-1.79)	0.62	1.38 (0.99-1.91)	0.059
RBBB	1.70 (0.42-6.91)	0.46	1.90 (0.90-4.02)	0.093	2.48 (1.43-4.31)	0.001
LBBB	0.62 (0.15-2.52)	0.50	1.19 (0.71-2.00)	0.51	1.20 (0.81-1.76)	0.37
Atrial fibrillation	2.48 (0.78-7.84)	0.12	1.21 (0.54-2.72)	0.64	1.39 (0.72-2.69)	0.33
Medication						
Aspirin	0.58 (0.32-1.07)	0.080	0.72 (0.54-0.95)	0.021	0.86 (0.70-1.06)	0.16
ACE-inhibitor	1.69 (1.09-2.61)	0.019	0.94 (0.73-1.20)	0.60	1.14 (0.94-1.37)	0.19
β-blocker	0.26 (0.12-0.57)	0.001	0.77 (0.58-1.01)	0.059	0.68 (0.54-0.84)	<0.001
Statins	0.43 (0.21-0.89)	0.023	0.65 (0.48-0.89)	0.008	0.63 (0.49-0.80)	<0.001
Enrollment after 1995	1.04 (0.68-1.60)	0.85	0.93 (0.74-1.17)	0.53	0.56 (0.46-0.69)	<0.001

MI = myocardial infarction, CABG = coronary artery bypass grafting, CHF = congestive heart failure, CVA/TIA = cerebrovascular accident/transient ischemic attack, COPD = chronic obstructive pulmonary disease, ABI = ankle-brachial index, LVH = left ventricular hypertrophy, RBBB = right bundle branch block, LBBB = left bundle branch block, ACE-inhibitors = angiotensin converting enzyme inhibitors.

multivariate model was calculated for each individual patient and scores ranged from -25 to 59 for 1-year mortality (median: 13, interquartile range: 0 to 22), from -11 to 32 for 5-year mortality (median: 7, interquartile range: 0-14) and from -13 to 38 for 10-year mortality (median: 5, interquartile range: -1 to 9). Figure 1 summarizes the proportion of patients who died within 1-year, 5-year and 10-year in the derivation cohort stratified according to the four different risk classification groups. One-year, 5-year and 10-year mortality rates increased significantly from the low risk group to the high risk group (all: $p<0.001$, Figure 1).

The mortality rate in each category in the derivation cohort was comparable to those in the Rotterdam validation cohort (Figure 1). Kaplan Meier curves stratified according to the four risk groups showed that Kaplan-Meier survival curves in the derivation cohort were comparable to survival curves in the Rotterdam validation cohort (Figure 2). The C-statistic discrimination of the final multivariate model for 1-year mortality was better in the derivation cohort (0.80), compared to the Rotterdam validation cohort (0.74) and the Netherlands Heart survey cohort (0.73). Also for 5-year mortality, a better discrimination of the final model was observed in the derivation cohort (area under the ROC curve: 0.74 and 0.73, respectively). Interestingly, the discrimination of the final model for 10-year mortality was less in the derivation cohort (0.72), compared to the Rotterdam validation cohort (0.73).

DISCUSSION

In this study, we developed a prognostic risk index for 1-year, 5-year and 10-year mortality that can be used as a point scoring system to stratify patients with peripheral arterial disease into low, low-intermediate, high-intermediate, and high risk groups. The risk scoring system included non-modifiable variables, such as age and gender, and modifiable clinical variables obtained from medical history, physical examination, laboratory testing, electrocardiography and ankle-brachial index measurements. Chronic cardiac medication use was also included in the risk scoring system.

Table 3. The prognostic risk index for 1-year, 5-year and 10-year mortality.

One-year risk index	Hazards ratio (95% CI) for 1-year mortality*	p value	Coefficient	Points
Age >65 years	4.47 (2.54-7.88)	<0.001	1.50	+ 15
Renal dysfunction	4.37 (2.38-8.02)	<0.001	1.48	+ 15
Hypercholesterolemia	3.60 (1.91-6.78)	<0.001	1.28	+ 13
History of congestive heart failure	2.58 (1.42-4.69)	0.002	0.94	+ 9
Ankle-brachial index <0.60	2.26 (1.41-3.60)	0.001	0.81	+ 8
Q-waves	1.98 (1.24-3.15)	0.004	0.68	+ 7
Diabetes mellitus	1.77 (1.02-3.04)	0.041	0.57	+ 6
β-Blockers	0.53 (0.29-0.95)	0.034	-0.64	- 6
Aspirin	0.46 (0.24-0.87)	0.018	-0.77	- 8
Statins	0.17 (0.07-0.44)	<0.001	-1.78	- 18

Area under the Receiver Operating Characteristic Curve: 0.80 **Total points:_____+**
In multivariate regression analysis with stepwise deletion.

Five-year risk index	Hazards ratio (95% CI) for 5-year mortality*	p value	Coefficient	Points
Renal dysfunction	4.30 (3.05-6.08)	<0.001	1.46	+ 15
History of congestive heart failure	2.19 (1.58-3.02)	<0.001	0.78	+ 8
Ankle-brachial index <0.60	2.08 (1.64-2.62)	<0.001	0.73	+ 7
Age >65 years	1.93 (1.51-2.45)	<0.001	0.66	+ 7
History of cerebrovascular events	1.92 (1.37-2.69)	<0.001	0.65	+ 7
Hypercholesterolemia	1.67 (1.14-2.45)	0.008	0.51	+ 5
ST segment changes	1.62 (1.23-2.14)	0.001	0.48	+ 5
Diabetes mellitus	1.51 (1.14-1.99)	0.004	0.41	+ 4
Q-waves	1.34 (1.05-1.71)	0.020	0.29	+ 3
β-Blockers	0.70 (0.52-0.93)	0.013	-0.36	- 4
Statins	0.53 (0.35-0.80)	0.003	-0.64	- 6
Aspirin	0.49 (0.36-0.67)	<0.001	-0.71	- 7

Area under the Receiver Operating Characteristic Curve: 0.74 **Total points: _____+**
* In multivariate regression analysis with stepwise deletion.

Ten-year risk index	Hazards ratio (95% CI) for 10-year mortality*	p value	Coefficient	Points
Renal dysfunction	3.27 (2.40-4.46)	<0.001	1.19	+ 12
History of congestive heart failure	2.10 (1.60-2.75)	<0.001	0.74	+ 7
ST segment changes	1.60 (1.26-2.02)	<0.001	0.47	+ 5
Age >65 years	1.59 (1.33-1.89)	<0.001	0.46	+ 5
Hypercholesterolemia	1.56 (1.17-2.08)	0.002	0.45	+ 5
Ankle-brachial index <0.60	1.51 (1.28-1.80)	<0.001	0.41	+ 4
Q-waves	1.48 (1.23-1.78)	<0.001	0.39	+ 4
Diabetes mellitus	1.39 (1.11-1.74)	0.004	0.33	+ 3
History of cerebrovascular events	1.40 (1.04-1.88)	0.029	0.33	+ 3
Chronic obstructive pulmonary disease	1.34 (1.05-1.72)	0.019	0.29	+ 3
Aspirin	0.69 (0.55-0.87)	0.001	-0.37	- 4
β-Blockers	0.62 (0.50-0.78)	<0.001	-0.47	- 4
Statins	0.54 (0.39-0.75)	<0.001	-0.62	- 6

Area under the Receiver Operating Characteristic Curve: 0.72 **Total points: _____+**
* In multivariate regression analysis with stepwise deletion.

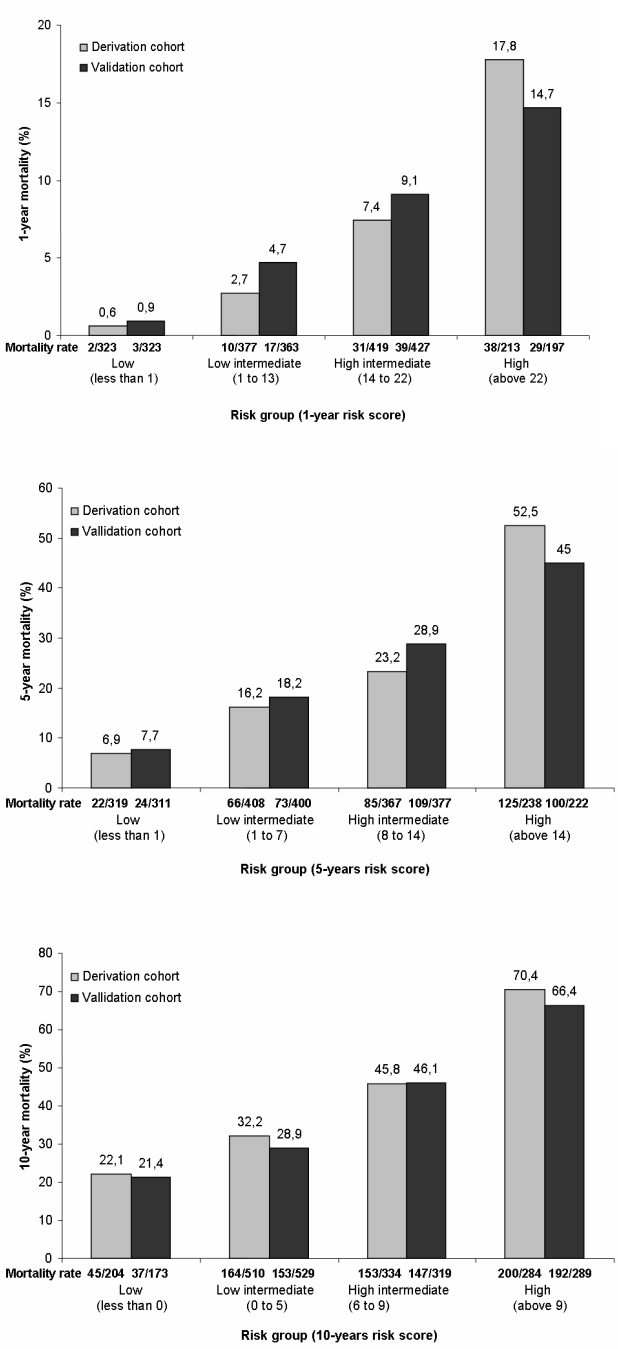


Figure 1. Mortality rates at 1-year, 5-year and 10-year follow-up in the derivation and validation cohort, stratified according to four different risk classification groups (low, low intermediate, high intermediate and high risk group).

Risk factors in PAD

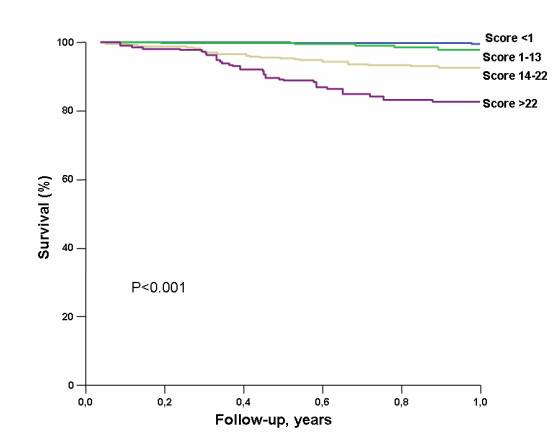
Results from the Framingham Heart Study identified age, male gender, serum cholesterol, hypertension, smoking, diabetes mellitus and coronary artery disease as risk factors for the occurrence of intermittent claudication [15]. The National Health and Nutrition Examination Survey revealed diabetes mellitus, hypercholesterolemia, low kidney function, coronary artery disease, smoking and black race/ethnicity as risk factors for prevalent PAD in adults aged 40 years and older [8]. The Rotterdam study showed that age over 75 years, smoking, diabetes mellitus, hypertension, low HDL cholesterol levels and increased fibrinogen levels were significant determinants for PAD [9]. Independent risk factors for PAD in the Cardiovascular Health Study included age, diabetes mellitus, smoking, hypertension, hypercholesterolemia, increased creatinine levels, low body mass index, and non-white ethnicity [16]. The above-mentioned risk factors are common to the development of atherosclerosis, and most were included in our risk index. In our study, coronary artery disease was present in almost half of the study population (49.2% in the derivation cohort and 48.0% in the validation cohort). ST-changes and Q-waves were strong predictors of long-term outcome. This finding supports the use of routine ECG screening for prognostic risk assessment in PAD patients.

Renal dysfunction

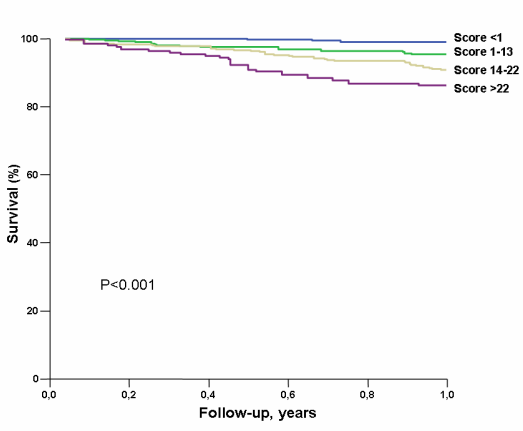
Incidental atherosclerotic renal artery stenosis is a frequent finding in patients with PAD, with prevalence values of 33% in patients with chronic ischemic PAD, as detected by angiography [17]. Atherosclerotic renal artery stenosis may lead to ischemic nephropathy and impaired renal function. Renal dysfunction is a strong predictor for cardiovascular disease and mortality. Moreover, it was one of the strongest predictors in our study cohort, associated with a 4.4-, 4.3- and 3.3-fold increased risk of 1-year, 5-year and 10-year mortality, respectively.

Ankle-brachial index and long-term mortality

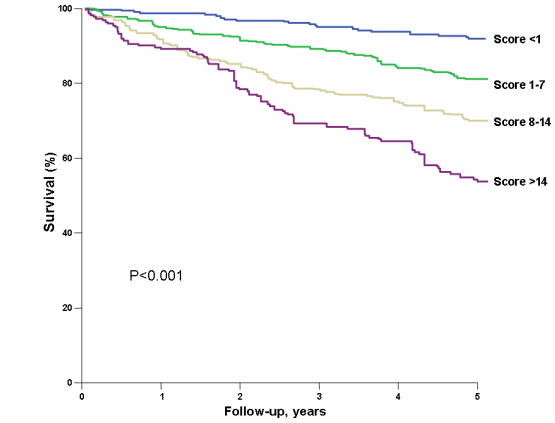
PAD is characterized by narrowing of the leg arteries. A decrease in the ankle-brachial index, a ratio of ankle systolic to brachial systolic blood pressure, is commonly used for the diagnosis of PAD [18]. An ankle-brachial index of ≤0.90 or ≤0.85 has been associated with an increased risk of overall and cardiovascular mortality, compared to ankle-brachial index values above 0.90 or 0.85 [1,16,19-23]. In our derivation cohort, we observed 1-year, 5-year and 10-year mortality rates of 6%, 22% and 42%, respectively. These values are in accordance with previously published studies reporting long-term mortality rates in patients with PAD. In a study by Newman et al, mortality during a mean follow-up of 16 months occurred in 27/392 (6.9%) patients with PAD [19]. McKenna et al showed estimated 5-year and 10-year mortality rates of 37% and 54%, respectively, in



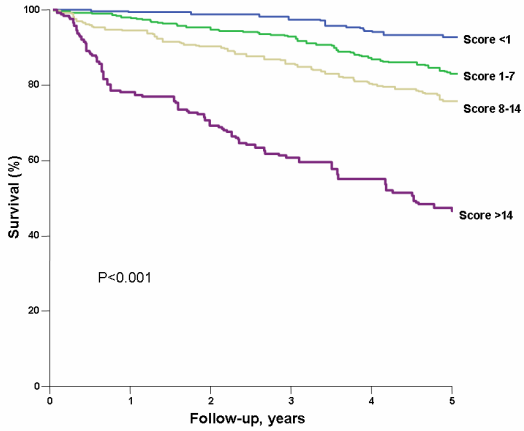
One-year risk index applied to the Rotterdam derivation cohort



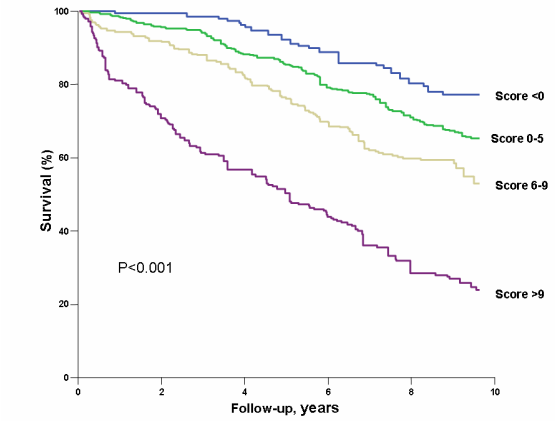
One-year risk index applied to the Rotterdam validation cohort



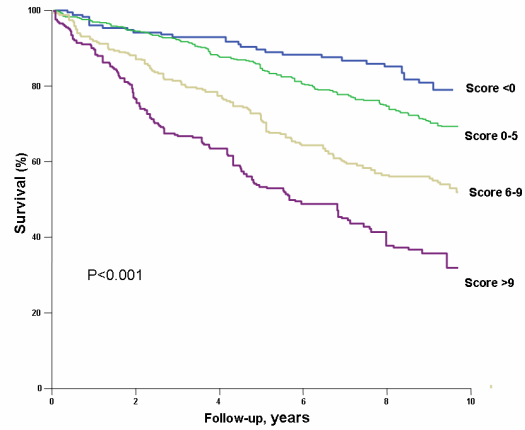
Five-year risk index applied to the Rotterdam derivation cohort



Five-year risk index applied to the Rotterdam derivation cohort



Ten-year risk index applied to the Rotterdam derivation cohort



Ten-year risk index applied to the Rotterdam validation cohort

Figure 2. Kaplan-Meier curves for 1-year (a), 5-year (b), and 10-year (c) survival in the derivation and validation cohort stratified according to four different risk classification groups (low, low intermediate, high intermediate and high risk group).

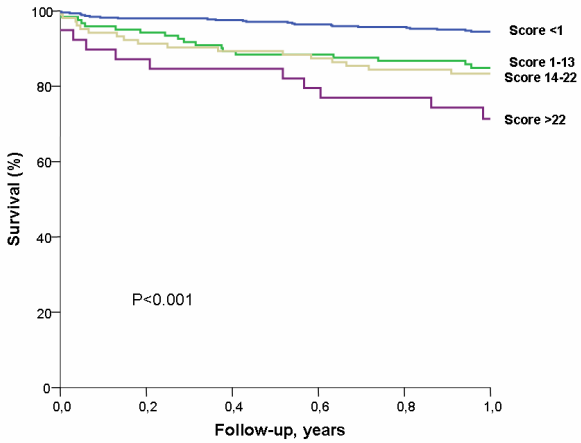


Figure 3. One-year survival in the Netherlands Heart survey cohort according to four different risk classification groups (low, low intermediate, high intermediate and high risk group).

patients with ABI values ≤0.85 [20]. Leng et al demonstrated an all-cause 5-year mortality rate of 63/288 (22%) in patients with ABI ≤0.90 [21]. Criqui et al found a 10-year mortality rate of 32/67 (48%) in patients with PAD [1]. The Edinburgh Artery Study found a 12-year mortality incidence of 119/245 (49%) in patients with ABI ≤0.90 [22]. In addition, significantly higher mortality rates have been reported in patients who had ankle-brachial index values less than 0.40 [20], and less than 0.70 [21], compared to patients within higher ankle-brachial index categories. This study demonstrated that measurement of ABI, even in patients who already present with ABI ≤0.90, was a consistent independent step-wise increased risk factor for mortality and therefore highly important in risk stratification.

Medication therapy

In our analysis, we included the use of cardiac drugs that have been demonstrated to improve prognosis in patients with peripheral arterial disease. Antiplatelet drugs are established agents for the prevention of cardiovascular and cerebrovascular events and form the cornerstone of pharmacologic intervention in PAD. The Anti-Thrombotic Trialists collaboration showed in a meta-analysis a proportional reduction of 23% in serious vascular events among 9214 patients with PAD using antiplatelet therapy (primary aspirin), compared to those using no antiplatelet therapy (5.8% vs. 7.1%, p<0.004) [24]. HMG-Co-A reductase inhibitor drugs (statins) have been demonstrated to improve leg functioning, walking performance, ABI values and symptoms of claudication [25-27]. The Heart Protection Study demonstrated that simvastatin significantly lowered the risk of vascular events in patients with PAD with or without clinically evident coronary heart disease [28]. Although β-blockers were relatively contraindicated in patients with PAD, Aronow et al showed that β-blocker therapy was associated with a 53% significant reduction in new coronary events, independent of other confounding variables [29]. This was confirmed in 78 post-infarction patients with intermittent claudication who demonstrated a 3-fold reduction in cumulative cardiac mortality when treated with β-blocker therapy [30]. As demonstrated in our prognostic risk index, patients with statin, aspirin and beta-blocker therapy were at significantly lower risk for 1-year, 5-year and 10-year mortality.

Risk classification model in PAD

A risk classification system in patients with PAD may help identify those at increased risk for long-term mortality and subsequently may improve management and treatment strategies [12]. A multivariate Cox hazard model showed in male patients with intermittent claudication that older age, history of stroke, lower ankle-brachial index values and diabetes mellitus were associated with long-term mortality [31]. To the best of our knowledge, no other risk indices have been developed in patients with PAD. We aimed to develop a simple risk scoring system in patients with PAD in which points are assigned to prognostic clinical variables obtained through medical history, laboratory testing, electrocardiography and ankle-brachial index measurement. The chance of 1-year, 5-year and 10-year mortality can then be estimated. Our risk index for 1-year, 5-year and 10-year mortality had good discrimination and was successfully validated in two independent patient samples, suggesting its generalizability to other PAD patient groups.

Limitations

Several limitations in our study should be addressed. Unfortunately, our study did not include recently emerging risk factors, such as fibrinogen, homocysteine, C-reactive protein and lipoprotein (a), which may have prognostic value in PAD patients [32]. Secondly, we used mortality from all causes as end-point. A better discriminatory capacity may have been achieved if mortality from cardiovascular causes was used as endpoint, especially because peripheral arterial disease is closely associated with the risk of myocardial infarction and death from vascular causes. Thirdly, interpretation of this index in non-caucasians should be done cautiously.

In conclusion, a prognostic risk index for long-term mortality based on cardiovascular risk factors, ankle-brachial index measurements, electrocardiographic

abnormalities and cardioprotective medication stratifies patients into different risk categories. This index may offer practical help to physicians in risk stratification, patient counseling and medical decision making at an early stage of the disease.

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Chapter 3

The long-term prognostic value of the resting and post-exercise ankle-brachial index

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The Long-term Prognostic Value of the Resting and Postexercise Ankle-Brachial Index

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Background: Peripheral arterial disease is associated with a high incidence of cardiovascular mortality. Peripheral arterial disease can be detected by using the ankle-brachial index (ABI). This study assessed the prognostic value of the postexercise ABI in addition to the resting ABI on long-term mortality in patients with suspected peripheral arterial disease.
Methods: In this prospective cohort study of 3209 patients (mean ± SD age, 63±12 years; 71.1% male), resting and postexercise ABI values were measured and a reduction of postexercise ABI over baseline resting readings was calculated. The mean follow-up was 8 years (interquartile range, 4-11 years).
Results: During follow-up, 1321 patients (41.2%) died. After adjusting for clinical risk factors, lower resting ABI values (hazard ratio per 0.10 lower ABI, 1.08; 95% confidence interval [CI], 1.06-1.10), lower postexercise ABI values (hazard ratio per 0.10 lower ABI, 1.09; 95% CI, 1.08-1.11), and higher reductions of ABI values over baseline readings (hazard ratio per 10% lower ABI, 1.12; 95% CI, 1.09-1.14) were significantly associated with a higher incidence of mortality. In patients with a normal resting ABI (n=789), a reduction of the postexercise ABI by 6% to 24%, 25% to 55%, and greater than 55% was associated with a 1.6-fold (95% CI, 1.2-2.2), 3.5-fold (95% CI, 2.4-5.0), and 4.8-fold (95% CI, 2.5-9.1) increased risk of mortality, respectively.
Conclusions: Resting and postexercise ABI values are strong and independent predictors of mortality. A reduction of postexercise ABI over baseline readings can identify additional patients (who have normal ABI values at rest) at increased risk of subsequent mortality.

PERIPHERAL ARTERIAL DISEASE (PAD) is a manifestation of systemic atherosclerosis and is associated with a significantly increased risk of cardiovascular morbidity and mortality [1-3]. In the Netherlands, the combined prevalence of symptomatic and asymptomatic PAD in the population of those 55 years and older is 19% [4]. In the United States, different prevalence values for PAD have been reported, ranging from 4% in patients 40 years and older to 29% in patients either older than 70 years or aged 50 to 59 years with a 10–pack year history of smoking or the presence of diabetes mellitus [1,5-8].

Management of PAD comprises walking exercise, modification of cardiovascular risk factors, and antiplatelet therapy [2,9]. Although the prevalence of PAD is high in industrialized countries, it is believed that PAD remains an underdiagnosed and undertreated disease in primary care [3,6,8]. Therefore, the identification of patients with suspected PAD who are at increased risk for cardiovascular events is necessary for disease control and appropriate application of treatment strategies.

The ankle-brachial index (ABI), a ratio of ankle systolic–brachial systolic blood pressure, is a simple, effective, and noninvasive test used for the assessment of lower extremity arterial obstruction and for the screening of patients with suspected PAD [8]. Several studies have demonstrated that low ABI values at rest predict cardiovascular and overall mortality [10-16]. Most studies have used a cutoff of 0.90 to define a low ABI value. However, knowledge about the association of long-term mortality across the whole range of ABI values at rest and after exercise is limited.

The ABI is commonly measured at rest, but ABI measurements coupled with exercise testing may enhance the sensitivity of the test and may identify additional patients with PAD who have normal resting ABI values [2,17]. In this study, we assessed the association of long-term mortality across the whole range of resting and postexercise ABI values, and hypothesized that a reduction in postexercise ABI over baseline resting readings may identify patients at increased risk of long-term mortality.

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Table 1. Baseline Characteristics of the 3209 Study Participants Divided According to the Period of Inclusion*

Characteristic	1983-1993 (n = 1375)	1994-2005 (n = 1834)	*P* Value
Demographics			
Age, mean ± SD, y	64 ± 11	63 ± 12	.06
Male sex	998 (72.6)	1283 (70.0)	.10
Cardiovascular history			
Angina pectoris	336 (24.4)	439 (23.9)	.70
Previous myocardial infarction	463 (33.7)	688 (37.5)	.03
History of congestive heart failure	104 (7.6)	163 (8.9)	.20
Previous coronary artery bypass surgery	232 (16.9)	340 (18.5)	.20
Previous PTCA	25 (1.8)	95 (5.2)	<.001
History of stroke or transient ischemic attack	95 (6.9)	140 (7.6)	.50
Clinical risk factors			
Diabetes mellitus	208 (15.1)	305 (16.6)	.30
Hypercholesterolemia	251 (18.3)	422 (23.0)	.001
Hypertension	470 (34.2)	645 (35.2)	.60
Cigarette smoking	491 (35.7)	588 (32.1)	.03
Renal failure	57 (4.1)	95 (5.2)	.20
Chronic obstructive pulmonary disease	159 (11.6)	221 (12.1)	.70
Electrocardiographic findings			
Q waves	361 (26.3)	444 (24.2)	.60
Left ventricular hypertrophy	21 (1.5)	33 (1.8)	.60
Bundle branch block			
Left	46 (3.3)	86 (4.7)	.07
Right	25 (1.8)	30 (1.6)	.80
Atrial fibrillation	21 (1.5)	45 (2.5)	.09
Medications			
Aspirin	191 (13.9)	463 (25.2)	<.001
Angiotensin-converting enzyme inhibitor	278 (20.2)	519 (28.3)	<.001
β-Blocker	231 (16.8)	589 (32.1)	<.001
Calcium channel blocker	354 (25.7)	507 (27.6)	.20
Coumarin	307 (22.3)	425 (23.2)	.60
Digoxin	58 (4.2)	139 (7.6)	<.001
Diuretic	163 (11.9)	278 (15.2)	.007
Nitrate	275 (20.0)	471 (25.7)	<.001
Statin	15 (1.1)	468 (25.5)	<.001

Abbreviation: PTCA, percutaneous transluminal coronary angioplasty.
*Data are given as number (percentage) of each group unless otherwise indicated.

METHODS

Patients and assessment of baseline characteristics

The Erasmus Medical Centre serves a population of approximately 3 million people and acts as a tertiary referral center for approximately 30 affiliated hospitals. This cohort study prospectively included consecutive patients with suspected or known PAD referred to our university clinic of vascular surgery between January 14, 1983, and January 1, 2005, for the evaluation and management of their disease. Patients with suspected PAD had a typical history of intermittent claudication or other symptoms of chronic arterial insufficiency, including ulceration of the foot, hair loss, or reduced capillary refill. Patients with known PAD had a resting ABI of 0.90 or less. Excluded were patients who were unable to perform exercise and those who underwent previous vascular surgery. The hospital's Medical Ethical Committee approved the study protocol, and patients who fulfilled the inclusion criteria agreed to participate in the study. Based on hospital records and personal interviews at the visit, a medical history was recorded. Diabetes mellitus was recorded if patients presented with a fasting glucose level of 126 mg/dL or more (>7.0 mmol/L) or in those who required treatment. Hypertension was recorded if patients presented with a blood pressure of 140/90 mm Hg or higher or if patients were medically treated for hypertension. Hypercholesterolemia was recorded if patients presented with a plasma cholesterol level of 212 mg/dL or more (>5.5 mmol/L) or if patients were taking lipid-lowering agents. Renal dysfunction was recorded if patients presented with a serum creatinine level of 2.0 mg/dL or more (>177 μmol/L) or in those who required dialysis. Cigarette smoking included only current smoking. Patients were assessed for cardiac medication use. A baseline12-lead electrocardiogram was obtained, and the ABI at rest and after exercise was measured in each patient.

Measurement of the ABI

Trained technicians, using a Doppler ultrasonic instrument with an 8-MHz vascular probe (Imexdop CT Vascular Doppler; Miami Medical, Glen Allen, Va), measured systolic blood pressure readings in the right and left brachial arteries, right and left dorsalis pedis arteries, and right and left posterior tibial arteries. The ABI in the right and left legs was calculated by dividing the right and the left ankle pressure by the brachial pressure. The higher of the 2 brachial blood pressure readings was used if a discrepancy in systolic blood pressure was present. Again, the higher of the dorsalis pedis and posterior tibial artery pressures was used when a discrepancy in systolic blood pressure readings between the 2 arteries was measured. If no pressure in the dorsalis pedis artery was obtained because of an absent dorsalis pedis artery, the pressure in the posterior tibial artery was used. The ABI at rest was measured after the participants had been resting in the supine position for at least 10 minutes. Measurements were then repeated at both sides with the patient in the supine position, after 5 minutes of walking on a treadmill at 4.0 km/h. No inclining plane or graded inclines were used with treadmill testing, and the treadmill tests were performed without continuous electrocardiographic monitoring before, during, and after the testing. Of the ABI values obtained in each leg, the lower was used in all analyses. Interobserver and intraobserver agreement for resting ABI was 97%

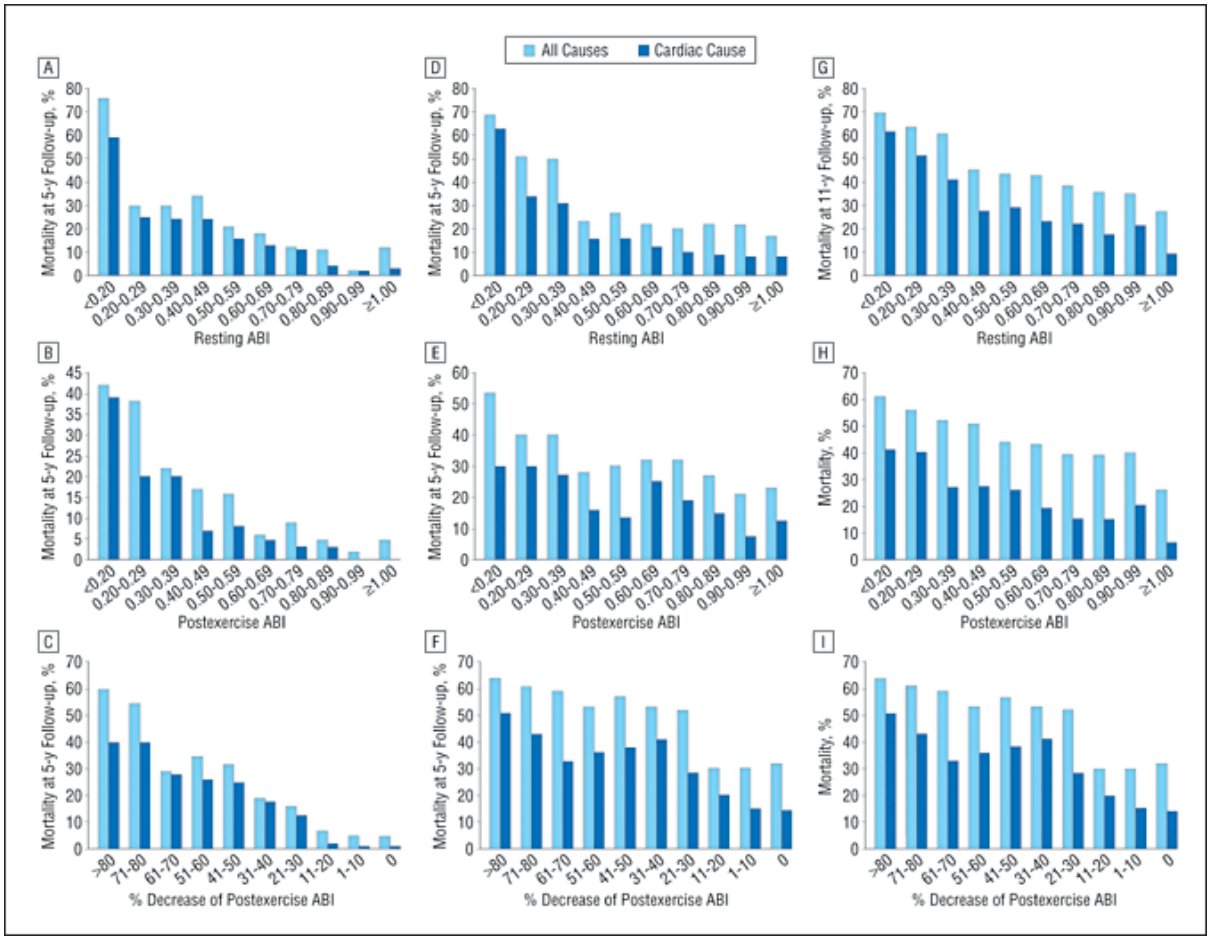

Figure 1. The estimated incidence of overall mortality and cardiac death in patients with varying resting ankle-brachial index (ABI) values, postexercise ABI values, and percentage decrease values of postexercise ABI according to different periods (January 14, 1983–December 31, 1993, January 1, 1994–January 1, 2005, and January 14, 1983–January 1, 2005). The mortality rate was calculated at the 75th percentile of follow-up. A, Data for resting ABI values from 1983 to 1993. B, Data for postexercise ABI values from 1983 to 1993. C, Data for percentage decrease values of postexercise ABI from 1983 to 1993. D, Data for resting ABI values from 1994 to 2005. E, Data for postexercise ABI values from 1994 to 2005. F, Data for percentage decrease values of postexercise ABI from 1994 to 2005. G, Data for resting ABI values from 1983 to 2005. H, Data for postexercise ABI values from 1983 to 2005. I, Data for percentage decrease values of postexercise ABI from 1983 to 2005.

and 98%, respectively; and for postexercise ABI, 96% and 97%, respectively. Although an ABI of greater than 1.30 has been used as a marker of calcified atherosclerosis, we considered patients with values greater than 1.50 to have calcified atherosclerosis, resulting in high ABI readings. These patients were excluded from the study.

Follow-up

We included 3209 patients who were examined during a median follow-up of 8 years (interquartile range, 4-11 years). No patients were lost to follow-up. Follow-up ended at the date of the last visit or the date of death. Information about the patient's vital status was obtained at the Office of Civil Registry. For patients who died at our hospital during follow-up, hospital records and autopsy results were reviewed. For patients who died elsewhere, general practitioners were approached to ascertain the cause of death. A cardiac cause of death was defined as death caused by acute myocardial infarction (postmortem evidence of acute myocardial infarction or definite criteria for myocardial infarction within the 4 weeks before death), cardiac arrhythmias, congestive heart failure, or sudden death.

Statistical analysis

Continuous data are expressed as mean and SD or median (interquartile range), and compared using the t test or Mann-Whitney test when appropriate. Categorical data are presented as percentage

frequencies, and differences between proportions were compared using the Chi-2 test with Yates correction. The primary end points were overall mortality and cardiac death. We used univariate and multivariate Cox proportional hazards models to analyze the effect of clinical characteristics and ABI values on survival. Hazard ratios are given with 95% confidence intervals (CIs). In multivariate analyses, all clinical variables, including medication, were entered, irrespective of the significance level in univariate analysis. The Kaplan-Meier method with the log-rank test was used for comparing survival curves in 2 or more groups. The reduction of the postexercise ABI compared with the resting ABI was calculated and expressed as a percentage. The prevalence of clinical risk factors, medication use, and mortality rate might have changed during the 22-year period in which the study was conducted. Therefore, we evaluated differences in baseline characteristics and mortality results between patients enrolled from January 14, 1983, to December 31, 1993, and those enrolled from January 1, 1994, to January 1, 2005. In multivariate analyses, the relation between ABI values (resting ABI, postexercise ABI, and reduction of postexercise ABI) and survival was evaluated separately for the periods from 1983 to 1993 and from 1994 to 2005, and an interaction term was evaluated to reveal possible heterogeneity between the different periods. In addition, tests for heterogeneity were used to evaluate the effect of a reduction of postexercise ABI in patients with different resting ABI values. For all tests, $P < .05$ (2-sided) was considered significant. All analyses were performed using a commercially available software program (SPSS-11.0 statistical software; SPSS Inc, Chicago, Ill).

RESULTS

The mean age of the patients was 63 ± 12 years, and 71.1% were male. The baseline characteristics of the 3209 patients are presented in Table 1. Patients included from 1994 to 2005 compared with those included from 1983 to 1993 more commonly presented with a history of myocardial infarction, percutaneous transluminal coronary angiography, and hypercholesterolemia, and less commonly smoked. Aspirin, angiotensin-converting enzyme inhibitors, -blockers, digoxin, diuretics, nitrates, and statins were more frequently prescribed in patients who were included from 1994 to 2005, compared with patients included from 1983 to 1993.

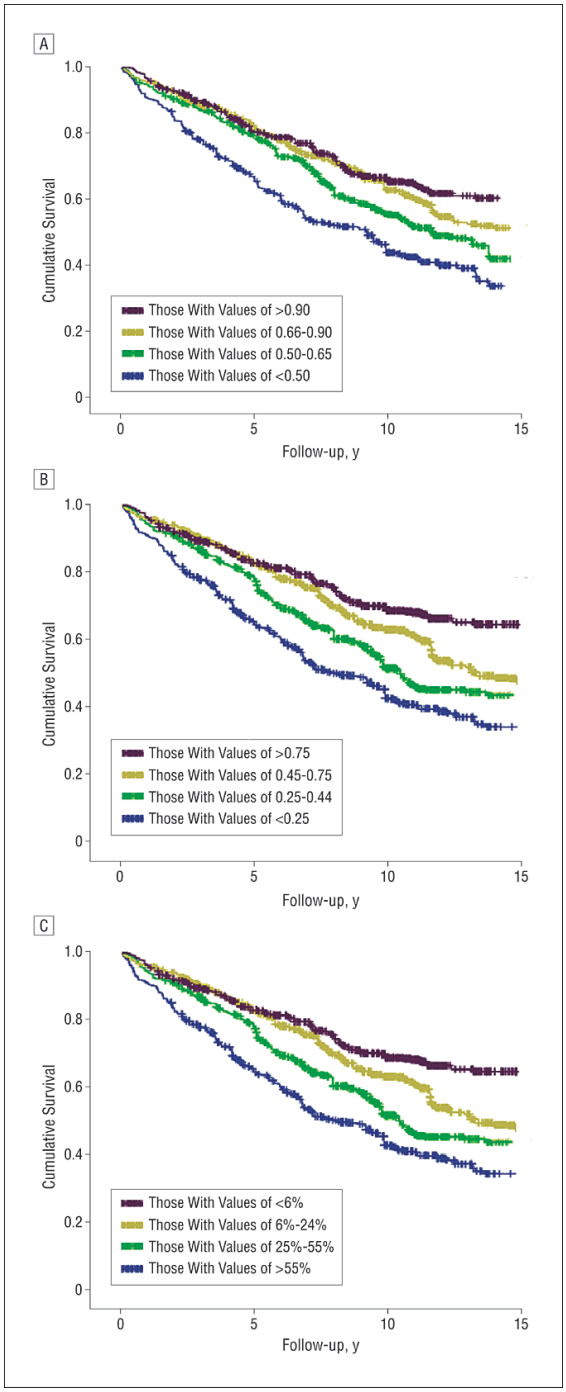

Figure 2. Kaplan-Meier survival curves in patients with varying resting ankle-brachial index (ABI) values (A), postexercise ABI values (B), and percentages of reduction of postexercise ABI compared with resting ABI (C). Subgroups were defined by using the quartiles as cutoffs.

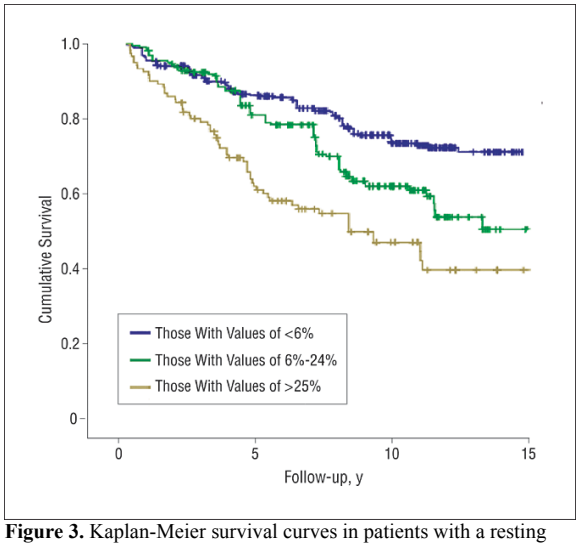

Figure 3. Kaplan-Meier survival curves in patients with a resting ankle-brachial index (ABI) of greater than 0.90, stratified according to varying percentages of reduction of postexercise ABI compared with resting ABI. The lower and middle quartiles were used as cutoffs.

The median ABI measured at rest was 0.65 (interquartile range, 0.50-0.90) (P = .80). A resting ABI of greater than 0.90 was measured in 789 patients (24.6%). The median ABI measured after exercise was 0.45 (interquartile range, 0.25-0.75) (P = .90). A postexercise ABI of greater than 0.90 was observed in 443 patients (13.8%). Baseline characteristics of the 443 patients with a postexercise ABI of greater than 0.90 were different compared with those of patients with a postexercise ABI of 0.90 or less. Patients with an ABI of greater than 0.90 were younger (mean age, 60 ± 13 vs. 64 ± 12 years; P<.001) and had a lower prevalence of coronary artery disease (35% vs. 43%; P<.001), hypertension (29% vs. 36%; P = .002), and smoking (27% vs. 35%; P<.001). A reduction of the postexercise ABI over baseline resting readings was observed in 2559 patients (79.7%), and was observed in 444 (56.3%) of 789 patients who had a normal resting ABI. The median reduction of ABI over baseline resting readings was 25% (interquartile range, 6%-55%). The postexercise ABI was similar to the resting ABI in 552 patients (17.2%), and was higher in only 98 patients (3.1%).

Follow-up data

During a median follow-up of 8 years (range, 0.1-22.2 years), death was recorded in 1321 patients (41.2%); 671 (50.8%) of these deaths were because of cardiac causes. Figure 1 shows the incidence of overall mortality and cardiac death in patients included from 1983 to 1993, from 1994 to 2005, and from 1983 to 2005, across the whole range of resting ABI values, postexercise ABI values, and reductions of ABI values over baseline resting readings. Tests for heterogeneity revealed no significant difference in unadjusted risk of resting ABI values, postexercise ABI values, and reductions of ABI over baseline readings for predicting overall (P = .60, .34, and .15, respectively) and cardiac mortality (P = .40, .15, and .09, respectively) between patients included from 1983 to 1993 and those included from 1994 to 2005. The unadjusted risk of overall mortality and cardiac death increased with decreasing resting ABI values (hazard ratio per 0.10 decrease, 1.11 [95% CI, 1.09-1.13] and 1.15 [95% CI, 1.13-1.18], respectively), with decreasing postexercise ABI values (hazard ratio per 0.10 decrease, 1.16 [95% CI, 1.13-1.18] and 1.10 [95% CI, 1.09-1.13], respectively), and with increasing reductions of ABI over baseline resting readings (hazard ratio per 10% decrease, 1.11 [95% CI, 1.09-1.14] and 1.17 [95% CI, 1.14-1.21], respectively) (P<.001 for all differences). In patients who died and who had normal resting ABI values and no reduction in the ABI after exercise, a cardiac cause of death was noted in 38.2%; in patients who died and who had normal resting ABI values and reductions in the ABI after exercise, a cardiac cause of death was noted in 55.1% (P<.001).

Kaplan-Meier survival curves for patients with varying resting ABI values, postexercise ABI values, and reductions of ABI are presented in Figure 2. Worse survival was observed in patients with lower resting ABI values, lower postexercise ABI values, and higher reductions of ABI values over baseline resting readings (P<.001 for all).

Multivariate analysis

We found that decreasing values of resting ABI, decreasing values of postexercise ABI, and higher reductions of ABI were significantly associated with an increased risk of overall mortality and cardiac death (Table 2). In a final multivariate model, we assessed the value of a reduction of the ABI with adjustment for clinical risk factors and resting ABI values, and observed that an increased reduction remained significantly associated with overall mortality and cardiac death (Table 2). Tests for heterogeneity revealed no significant difference in adjusted risk of resting ABI values, postexercise ABI values, and reductions of ABI over baseline readings for predicting overall and cardiac mortality between patients included from 1983 to 1993 and patients included from 1994 to 2005.

Table 2. Multivariate Cox Proportional Hazards Models That Predict Overall Mortality and Cardiac Death, Divided into Different Time Periods

Characteristic	1983-1993*	1994-2005*	*P* Value (Interaction)	1983-2005*	*P* Value
Data for Overall Death					
Model 1					
Resting ABI per 0.10 decrease	1.09 (1.05-1.12)	1.06 (1.04-1.09)	.72	1.08 (1.06-1.10)	<.001
Model 2					
Postexercise ABI per 0.10 decrease	1.10 (1.07-1.13)	1.07 (1.04-1.09)	.48	1.09 (1.08-1.11)	<.001
Model 3					
Reduction in ABI per 10%	1.13 (1.09-1.17)	1.09 (1.04-1.13)	.44	1.12 (1.09-1.14)	<.001
Model 4					
Resting ABI per 0.10 decrease	1.03 (0.99-1.04)	1.06 (1.02-1.09)	.53	1.04 (1.01-1.06)	.007
Reduction in ABI per 10%	1.12 (1.09-1.17)	1.07 (1.02-1.11)	.08	1.10 (1.08-1.13)	<.001
Data for Cardiac Death					
Model 1					
Resting ABI per 0.10 decrease	1.11 (1.06-1.17)	1.12 (1.08-1.16)	.80	1.12 (1.09-1.15)	<.001
Model 2					
Postexercise ABI per 0.10 decrease	1.16 (1.12-1.21)	1.10 (1.07-1.17)	.11	1.15 (1.12-1.17)	<.001
Model 3					
Reduction in ABI per 10%	1.22 (1.16-1.28)	1.15 (1.11-1.22)	.07	1.18 (1.14-1.21)	<.001
Model 4					
Resting ABI per 0.10 decrease	1.03 (0.97-1.10)	1.09 (1.07-1.13)	.10	1.06 (1.04-1.10)	.001
Reduction in ABI per 10%	1.17 (1.13-1.21)	1.11 (1.03-1.17)	.09	1.15 (1.11-1.19)	<.001

Abbreviation: ABI, ankle-brachial index.
*Data are given as hazard ratio (95% confidence interval) unless otherwise specified. Adjusted for the following risk factors: age, sex, coronary artery disease, history of congestive heart failure, previous stroke or transient ischemic attack, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, smoking, hypercholesterolemia, renal failure, and Q waves and ST-segment changes on an electrocardiogram.

Table 3 shows the relative risk ratios of a reduction of ABI in patients with resting ABI values of greater than 0.90 and those with resting ABI values of 0.90 or less, with adjustment for clinical risk factors and age. In both subgroups of patients, a 6% to 24%, a 25% to 55%, and a greater than 55% reduction of ABI over baseline resting readings was associated with an increased risk for late mortality, using a reduction of less than 6% as the comparator. More important, in patients with a resting ABI of greater than 0.90, the relative risk ratio for late mortality was 1.6 times greater for a reduction of 6% to 24%, 3.5 times greater for a reduction of 25% to 55%, and 4.8 times greater for a reduction of greater than 55% when a reduction of less than 6% was used as the comparator. Tests for heterogeneity revealed a significant interaction between resting ABI values and reductions of ABI over baseline readings (P = .03). Kaplan-Meier survival curves for patients with resting ABI values greater than 0.90 show a significantly worse outcome for those with a 6% to 24% and a greater than 25% reduction of the ABI (P<.001) (Figure 3).

COMMENTS

The present study shows that lower resting and postexercise ABI values and an increased reduction of ABI over baseline readings are significantly associated with an increased incidence of long-term overall mortality and cardiac death. In addition, in patients with resting ABI values of more than 0.90, a reduction of ABI over baseline readings identified those at increased risk for late mortality. These findings were independent of the presence of established clinical risk factors. The present study shows that lower resting and postexercise ABI values and an increased reduction of ABI over baseline readings are significantly associated with an increased incidence of long-term overall mortality and cardiac death. In addition, in patients with resting ABI values of more than 0.90, a reduction of ABI over baseline readings identified those at increased risk for late mortality. These findings were independent of the presence of established clinical risk factors.

Peripheral arterial disease

In the United States, different prevalence values for PAD have been reported, ranging from 4% in patients 40 years and older to more than 20% in patients 70 years and older [1, 5-8]. PAD is a manifestation of atherosclerosis, and its presence should be regarded as a marker for atherosclerosis in other vascular beds [17]. Important risk factors include cigarette smoking, hypercholesterolemia, and hypertension, and modification of these risk factors is a substantial part in managing PAD. In our study, patients included from

Table 3. Risk-Adjusted Relative Risk Ratios of Higher Percentage Decrease Values of Postexercise ABI in 4 Subgroups of Patients With Varying Resting ABI Values

ABI at Rest	Reduction of Postexercise ABI, %	HR (95% CI) for Overall Death*	*P* Value
≤0.90	<6†	1.0	
	6-24	1.3 (1.1-1.7)	.01
	25-55	2.0 (1.6-2.4)	<.001
	>55	2.1 (1.7-2.6)	<.001
>0.90	<6†	1.0	
	6-24	1.6 (1.2-2.2)	.005
	25-55	3.5 (2.4-5.0)	<.001
	>55	4.8 (2.5-9.1)	<.001

Abbreviations: ABI, ankle-brachial index; CI, confidence interval; HR, hazard ratio.
*Adjusted for the following risk factors: age, sex, coronary artery disease, history of congestive heart failure, previous stroke or transient ischemic attack, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, smoking, hypercholesterolemia, renal failure, and Q waves and ST-segment changes on an electrocardiogram.
†Relative risk ratio comparator.

1994 to 2005 compared with those included from 1983 to 1993 more commonly presented with a history of myocardial infarction and hypercholesterolemia, less commonly smoked, and more commonly received cardiovascular medication. This may reflect the trend in increasing awareness of detecting and treating clinical risk factors.

The ABI to predict mortality

The ABI is commonly used for the assessment of lower extremity arterial obstruction and for the screening of patients with suspected PAD [8]. The ABI correlates with the extent of angiographic coronary artery disease, reflecting the concept that PAD is a marker of generalized atherosclerosis [18]. It is well established that low ABI values at rest predict cardiac and overall mortality. A resting ABI of 0.90 or less has been associated with an increased risk of 2 to 7 for overall mortality and 2 to 4 for cardiovascular mortality, compared with a resting ABI of more than 0.90.10-16 Knowledge about the risk of mortality across the whole range of ABI values is limited. The Honolulu Heart Program study [19] compared the adjusted risk for the composite end point of cardiac death and nonfatal myocardial infarction in patients with an ABI of less than 0.80 and 0.80 to 1.00 vs. those with an ABI of 1.00 or more, and found a higher risk in patients with an ABI of less than 0.80 compared with patients with an ABI of 0.80 to 1.00. Another study [10] used resting ABI values of 0.40 and 0.85 as cutoffs to divide its population into subpopulations; the highest risk-adjusted relative risk for mortality was observed in patients with an ABI of less than 0.40. Leng et al [16] used resting ABI cutoff values of 1.10, 1.00, 0.90, and 0.70, and found a significant linear increase in mortality across decreasing ABI categories. In the present study, we found that the adjusted risk for overall mortality increased by 8% for every 0.10 decrease of the resting ABI, and by 9% for every 0.10 decrease of the postexercise ABI. The adjusted risk for cardiac death increased by 12% and 15% for every 0.10 decrease of the resting ABI and postexercise ABI, respectively.

The ABI after exercise

A healthy person can maintain ankle systolic pressures at normal levels during modest workloads. In patients with PAD, however, a decrease in systolic pressures is often measured during low levels of workload [20-21]. In a previously published study, Ouriel et al [22] investigated whether the diagnostic accuracy for PAD could be improved through the use of postexercise ABI measurements, and they suggested that postexercise ABI values may especially be useful in patients with normal ABI values at rest. To our knowledge, no studies have been published about the predictive value of postexercise testing on long-term mortality. Our results demonstrate that reductions of the postexercise ABI offered additional mortality information in patients with abnormal resting ABI values. More important, in symptomatic and asymptomatic patients with resting ABI values above 0.90, a reduction of ABI over baseline resting readings can also identify those at increased risk for mortality.

Clinical implication

Although the prevalence of PAD is high in industrialized countries, PAD remains an underdiagnosed and undertreated disease in primary care [3, 6, 8]. Therefore, the identification of patients with suspected PAD who are at increased risk for late events is necessary for disease control and selection of appropriate treatment strategies [23]. During recent years, more attention has focused on the identification and treatment of underlying cardiovascular risk factors in patients with PAD, which may have resulted in an increased prescription of statins, angiotensin-converting enzyme inhibitors, aspirin, and -blockers. Measurements of resting and postexercise ABI values are simple, inexpensive, and noninvasive, and can be performed when patients are assessed for their risk factors. A recent study [13] showed that the measurement of resting ABI in addition to conventional risk factors significantly improved the prediction of fatal myocardial infarction. Results from this study suggest that measurement of ABI at rest may be incorporated among other tools for identifying patients at increased risk for cardiovascular events.

These patients may subsequently benefit from preventive pharmacologic and nonpharmacologic interventions, to reduce their risk of complications of systemic atherosclerosis.

In conclusion, this long-term prospective cohort study shows that resting and postexercise ABI values are independently associated with late overall mortality and cardiac death. In addition, in patients with normal resting ABI values, a reduction of the postexercise ABI over baseline readings can identify those at increased risk of long-term mortality.

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Chapter 4

Improving prognostic risk assessment with cardiac testing in patients with suspected and known peripheral arterial disease

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Improving Risk Assessment with Cardiac Testing in Peripheral Arterial Disease

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Purpose: The study's objective was to evaluate the prognostic value of left ventricular ejection fraction and stress-induced ischemia during dobutamine stress echocardiography in addition to ankle-brachial index measurements and clinical risk factors in patients with suspected or known peripheral arterial disease.
Methods: In 852 patients with suspected or known peripheral arterial disease (mean age 63 years, 70% male), the ankle-brachial index was measured, left ventricular ejection fraction was assessed and all patients underwent additional stress testing. Endpoints were all-cause mortality and hard cardiac events (cardiac death or non-fatal myocardial infarction).
Results: During a mean follow-up of 7.6 ± 4.4 years, death occurred in 288 patients (34%) and hard cardiac events occurred in 216 patients (25%). Mean left ventricular ejection fraction was 50 ± 17% and stress-induced ischemia was observed in 352 patients (41%). In multivariate analysis with adjustment for clinical risk factors and ankle-brachial index, each 5% decrease in left ventricular ejection fraction was associated with increased all-cause mortality (HR: 1.05, 95% CI: 1.02-1.09) and hard events (HR: 1.14, 95% CI: 1.08-1.21). Stress-induced ischemia also independently predicted all-cause mortality (HR: 2.01, 95% CI: 1.38-2.79) and hard events (HR: 2.06, 95% CI: 1.39-3.08). Left ventricular ejection fraction and stress-induced ischemia provided incremental prognostic information over clinical data and ankle-brachial index values ($p<0.001$).
Conclusions: Left ventricular ejection fraction and stress-induced ischemia independently predict long-term outcome and improve prognostic risk assessment in addition to ankle-brachial index and clinical risk factors in patients with suspected or known peripheral arterial disease.

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LOWER EXTREMITY peripheral arterial disease is a manifestation of systemic atherosclerosis and has been recognized as a growing health burden worldwide.[1] Prevalence rates up to 29% have been reported for peripheral arterial disease in the United States, depending on the age of the study cohort, the underlying atherosclerosis risk factor profile, and the presence of cardiovascular co-morbidities.[2-7] A high prevalence of left ventricular dysfunction among patients with symptomatic peripheral arterial disease has been observed.[8] Moreover, coronary artery disease frequently co-exists with peripheral arterial disease since both conditions share the same atherosclerotic risk factors. More than half of patients who present with peripheral arterial disease may have evidence of coronary artery disease based on electrocardiography or medical history.[1,9,10] The prognosis of patients with peripheral arterial disease is therefore characterized by a 2- to 6-fold increased risk of cardiovascular death.[11-17]

The American College of Cardiology/American Heart Association has emphasized in their guidelines for the management of patients with peripheral arterial disease the importance of identifying and treating underlying cardiovascular risk factors and obtaining ankle-brachial index data for prognostic risk stratification.[1] Although the detection of coronary artery disease and left ventricular dysfunction in this particular patient population may be important because of the benefit from subsequent medical therapy or coronary intervention, evidence-based recommendations for cardiac assessment in literature are limited.

Dobutamine stress echocardiography is an accurate, safe, and widely used non-invasive imaging technique for evaluation of coronary artery disease and for risk assessment.[18,19] However, because ankle-brachial index data can risk stratify this population, it is not known whether stress testing can further provide prognostic information in addition to ankle-brachial index values. The purpose of this study was to determine the prognostic value of dobutamine stress echocardiography in addition to ankle-brachial index measurements and

clinical risk factors in a large cohort of patients with suspected or known peripheral arterial disease.

METHODS

The study population consisted of consecutive patients referred for evaluation of peripheral arterial disease at the outpatient vascular clinic of the Erasmus MC, Rotterdam, the Netherlands between January 1990 and January 2005. The Erasmus MC is a metropolitan university hospital in the South-western area of the Netherlands, serving a population of approximately 3 million and acting as a tertiary referral center for approximately 30 affiliated hospitals. Patients with suspected peripheral arterial disease had a typical history of intermittent claudication or other symptoms of chronic arterial insufficiency, including ulceration of the foot, hair loss or reduced capillary refill. Patients with known peripheral arterial disease had a resting ankle-brachial index ≤0.90. Dobutamine stress echocardiography was performed to assess the presence and extent of concomitant coronary artery disease. Specific indications for stress echocardiography included typical or atypical chest pain, assessment for coronary artery revascularization and (pre-surgical) prognostic risk stratification. The hospital's Medical Ethical Committee approved the study protocol. Patients who fulfilled inclusion criteria agreed on participation in the study. Based on hospital records and personal interviews at the time of the visit, a medical history was recorded and data were prospectively entered into a computerized database. Diabetes mellitus was recorded if patients presented with a fasting glucose level of ≥7.0 mmol/L or in those who required insulin treatment. Hypertension was recorded if patients presented with a blood pressure ≥140/90 mmHg or if patients received anti-hypertensive drugs. Hypercholesterolemia was recorded if patients presented with a plasma cholesterol level ≥5.5 mmol/L or if patients were taking lipid-lowering agents. Patients were considered to have renal dysfunction if they presented with a serum creatinine level ≥2.0 mg/dL (177 μmol/L) or if they required dialysis. Cigarette smoking included only current smoking. Patients were assessed for cardiac medication use and a baseline 12-lead electrocardiography was obtained.

Ankle-Brachial Index Measurement

Systolic blood pressures in the right and left brachial artery, right and left dorsalis pedis artery and right and left posterior tibial artery were measured by trained technicians using a Doppler ultrasonic instrument with an 8 MHz vascular probe (Imexdop CT+ Vascular Doppler, Miami Medical, USA). The ankle-brachial index in the right and left leg was calculated by dividing the right and the left ankle pressure by the brachial pressure. The higher of the two brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Again, the higher of the dorsalis pedis and posterior tibial artery pressure was used when a discrepancy in systolic blood pressure between the two arteries was measured. The ankle-brachial index was measured after the participants had been resting in the supine position for at least 10 minutes. Of the ankle-brachial index values obtained in each leg, the lower was used in all analysis. Inter- and intraobserver agreement for the ankle-brachial index was 97% and 98%, respectively. We considered patients with values greater than 1.50 to have calcified atherosclerosis. These patients were excluded from the study.

Dobutamine Stress Echocardiography

The dobutamine stress echocardiography was performed as previously described.[20,21] Patients underwent a resting two-dimensional echocardiographic examination. Left ventricular end-diastolic and end-systolic volumes were obtained from the apical four- and two-chamber views by using the Simpson's rule formula, from which the ejection fraction was calculated. Dobutamine hydrochloride was then administered intravenously by infusion pump, starting at 10 μg/kg/min for 3 minutes, and increased by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. The dobutamine infusion was stopped if a target heart rate was achieved (85% of a theoretic maximal heart rate). If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulphate (starting with 0.25 mg, increased to a cumulative maximum of 2.0 mg) was given intravenously. Patients were excluded from the study if the test was prematurely terminated because of : (1) symptomatic decline in systolic blood pressure >40 mmHg from the resting value, or a systolic blood pressure <100 mmHg, (2) blood pressure >240/140 mmHg, (3) occurrence of cardiac arrhythmias, (4) intolerable adverse effects from dobutamine or atropine and (5) poor echocardiographic images. Off-line assessment of echocardiographic images was performed by two experienced investigators without knowledge of the patient's clinical data. From 1990 to 1993, a 14-segment 4-point ordinal scale was used . After 1993 a 16-segment 5-point score was used.[21-23] Stress-induced myocardial ischemia was considered if new wall motion abnormalities occurred (i.e., if wall motion in any segment worsened by ≥1 grade(s) during the test, with the exception of akinesis becoming dyskinesis). The extent and location of ischemia were evaluated and a wall-motion score index (total score divided by the number of segments scored) was calculated, both at rest and during peak stress. When there was disagreement

Table 1. Baseline Characteristics According to Groups Defined by Ankle-Brachial Index Values and Dobutamine Stress Echocardiography

Characteristic	DSE with no ischemia, Normal ABI (n=154)	DSE with no ischemia, Abnormal ABI (n=346)	DSE with ischemia, Normal ABI (n=77)	DSE with ischemia, Abnormal ABI (n=275)	P-value
Demographics					
Age (years) (+/-SD)	59 ± 12	63 ± 11	62 ± 12	65. ± 11	<0.001
Male gender	61.0	74.0	68.8	70.9	0.027
Angina	20.8	27.5	29.9	19.3	0.046
Previous myocardial infarction	23.4	41.6	31.2	34.5	0.001
Previous CABG	13.6	19.4	22.1	14.2	0.13
Previous PTCA	1.3	6.1	2.6	2.9	0.041
Known CAD (summary variable)	35.7	55.8	46.8	45.1	<0.001
History of congestive heart failure	8.4	8.1	3.9	6.5	0.53
History of stroke or TIA	3.2	9.0	7.8	5.8	0.11
Diabetes Mellitus	12.3	17.3	18.2	15.3	0.50
Hypercholesterolemia	22.7	20.5	27.3	16.0	0.11
Hypertension	27.9	41.3	20.8	37.5	<0.001
Cigarette smoking	28.6	37.9	29.9	26.2	0.013
Renal failure	3.9	4.0	1.3	6.2	0.26
Abnormal electrocardiography	31.8	47.7	45.5	45.1	0.01
Q waves	19.5	28.9	24.7	26.5	0.17
ST segment changes	1.9	2.3	6.5	5.8	0.042
Medications					
Aspirin	13.0	24.9	16.9	22.2	0.018
ACE-inhibitor	22.7	28.0	22.1	24.4	0.48
Beta-blocker	28.6	28.9	27.3	22.9	0.37
Calcium channel blocker	20.1	30.3	24.7	25.5	0.11
Digoxin	4.4	7.2	6.5	5.5	0.65
Diuretic	8.4	15.0	14.3	13.5	0.25
Nitrate	23.4	26.6	22.1	23.6	0.74
Statin	23.4	20.5	27.3	16.0	0.094
Ankle-brachial index	1.02 ± 0.07	0.62 ± 0.17	1.01 ± 0.06	0.60 ± 0.20	<0.001
Rest wall motion abnormalities	37.0	47.7	35.1	37.8	0.022
Left ventricular ejection fraction	53 ± 16	51 ± 17	49 ± 18	47 ± 17	0.12

DSE = dobutamine stress echocardiography; ABI = ankle-brachial index; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; CAD = coronary artery disease; TIA = transient ischemic attack; ACE = angiotensin converting enzyme. Values are expressed in percentages or mean ± SD. Abnormal ABI = ankle-brachial index ≤0.90. The p-values reflect overall differences in the four groups as compared by the Chi square test for categorical variables and analysis of variance techniques for continuous variables.

between the two assessors, a third investigator viewed the images and a majority decision was reached.

Follow-up

During follow-up, study endpoints were all-cause mortality and hard cardiac events (cardiac death or non-fatal myocardial infarction). Survival status was obtained by approaching the referring physician or the municipal civil registries. Clinical information was obtained by outpatients visits, mailed questionnaires, telephone interviews and reviewing hospital records. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: elevated cardiac enzyme levels (CK level > 190 U/L and CK-MB >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/mL), development of typical electrocardiographic changes (new Q waves >1 mm or > 30 ms), and typical symptoms of angina pectoris. Death certificates and autopsy reports were reviewed and general practitioners were approached to ascertain the cause of death. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, or congestive heart failure. Sudden unexpected death in a previously stable patients was considered as cardiac death.

Statistical Analysis

Continuous data were compared using the Student t test or ANOVA techniques when appropriate. Categorical data were compared using the Chi square test. A final set of independent predictors of left ventricular ejection fraction <35% and stress-induced myocardial ischemia was obtained by multivariate analysis with stepwise deletion of the least significant variable. The Kaplan-Meier method with the log-rank test was used to assess differences in survival between different groups of patients. Univariate and multivariate Cox hazard regression analysis was used to evaluate the prognostic value of dobutamine stress echocardiography, ankle-

brachial index and baseline clinical variables. The incremental value of dobutamine stress test results over clinical variables and ankle-brachial index values in the prediction of events was determined according to 3 models. In the first model, clinical variables, baseline electrocardiography and ankle-brachial index values were entered. In the second and third model, left ventricular ejection fraction and stress-induced ischemia, respectively, were added to the first model. Tests for heterogeneity were used to reveal a possible interaction between dobutamine stress echocardiography and ankle-brachial index values. For all tests, a p-value <0.05 (two-sided) was considered significant. Analysis was performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

A total of 944 patients were referred for ankle-brachial index measurement and dobutamine stress echocardiography. A total of 30 patients (3%) were excluded because of ankle-brachial index values >1.50 and 62 patients (7%) were excluded due to termination of the stress test prior to an ischemic endpoint (cardiac arrhythmia in 8 patients, hypotension in 14, chills and intolerable adverse effects in 11, and poor echocardiographic images in 29 patients). The remaining 852 patients were considered for follow-up and constituted our study population (Table 1). Follow-up was successful in all. Mean age was 63 years and 598 patients (70%) were male. Mean ankle-brachial index was 0.72 ±0.24, and 621 patients (73%) had an ankle-brachial index ≤0.90. During dobutamine stress echocardiography, no fatal complications occurred. Mean left ventricular ejection fraction was 50 ±17%, and 105 patients (12%) had an ejection fraction <35%. A total of 122 patients (14%) had an ejection fraction <40%. Rest wall motion abnormalities were observed in 469 patients (55%). Ischemia (new wall motion abnormalities) was detected in 352 patients (41%). In the patients who presented with left ventricular ejection fraction <35%, stress-induced ischemia occurred in 79 patients (75%, 9% of the total study population). In the current patient cohort, the prevalence rate of coronary artery disease by medical history alone (angina pectoris or history of myocardial infarction) was 47% and combined with dobutamine stress echocardiography 70%. Variables independently associated with left ventricular ejection fraction <0.35% included male gender, history coronary artery disease, history of heart failure, diabetes, renal failure and hypercholesterolemia. Variables independently associated with stress-induced myocardial ischemia included age, low ankle-brachial index values and ischemic baseline electrocardiogram (Table 2).

Prognostic Value of Dobutamine Stress Echocardiography

During a mean follow-up of 7.6 ± 4.4 years, death occurred in 288 patients (34%) and hard cardiac events in 216 patients (25%) (cardiac death in 145 patients and non-fatal myocardial infarction in 71). Kaplan Meier curves stratified according to ankle-brachial index and dobutamine stress echocardiography demonstrated that in patients with an ankle-brachial index ≤0.90, those with stress-induced ischemia had a decreased survival (annual mortality rate of 5.7%), compared to patients without ischemia (annual mortality rate of 3.2%, p<0.001), and compared to patients without ischemia and ankle-brachial index >0.90 (annual mortality rate of 2.5%, p<0.001) (Figure 1).

Table 2. Variables Independently Associated with Left Ventricular Ejection Fraction <0.35% and Stress-induced Myocardial Ischemia During Dobutamine Stress Echocardiography Identified By Stepwise Multivariate Analysis.

Characteristic	Odds ratio (95% CI) left ventricular ejection fraction <0.35% (n=105)
Male gender	2.08 (1.25-3.49)
Coronary artery disease	4.07 (2.60-6.36)
History of heart failure	3.48 (1.75-6.91)
Diabetes mellitus	2.48 (1.49-4.12)
Renal failure	3.54 (1.27-9.88)
Hypercholesterolemia	1.84 (1.14-2.97)
C-statistic: 0.76	

Characteristic	Odds ratio (95% CI) for stress- induced myocardial ischemia during DSE (n=352)
Ankle-brachial index (per 0.10 decrease)	1.06 (1.01-1.13)
Age (per year increase)	1.02 (1.00-1.03)
Ischemic baseline electrocardiogram	1.48 (1.10-2.01)
C-statistic: 0.60	

Table 3. Univariate and Multivariate Predictors of All-cause Mortality

Characteristic	Univariate	Multivariate		
	HR (95% CI)	Model 1 HR (95% CI)		Model 2 HR (95% CI)
Clinical Characteristics				
Age (per year increase)	1.06 (1.04-1.07)	1.05 (1.03-1.07)	1.04 (1.02-1.06)	1.04 (1.02-1.06)
Male gender	1.38 (1.05-1.80)	1.26 (0.95-1.66)	1.21 (0.84-1.73)	1.25 (0.60-2.57)
Previous myocardial infarction	1.53 (1.21-1.93)	1.32 (0.99-1.69)	1.15 (0.82-1.62)	1.08 (0.57-2.04)
Congestive heart failure	2.35 (1.64-3.37)	1.87 (1.22-2.88)	1.60 (0.99-2.41)	1.25 (0.48-3.24)
History of stroke or TIA	1.52 (1.01-2.29)	1.17 (0.77-1.78)	1.15 (0.72-1.84)	1.48 (0.49-4.52)
Diabetes mellitus	1.40 (1.03-1.90)	1.49 (1.09-2.05)	1.31 (0.87-1.95)	1.05 (0.50-2.05)
Hypercholesterolemia	0.76 (0.55-1.05)	0.94 (0.67-1.31)	0.90 (0.61-1.34)	0.96 (0.46-2.03)
Hypertension	1.09 (0.86-1.39)	1.01 (0.78-1.27)	0.98 (0.72-1.33)	1.04 (0.56-1.94)
Cigarette smoking	1.22 (0.96-1.55)	1.25 (0.98-1.60)	1.19 (0.88-1.61)	1.49 (0.81-2.75)
Renal failure	4.59 (3.12-6.76)	3.16 (1.80-5.55)	2.86 (1.63-5.01)	2.63 (1.50-4.62)
Ischemic baseline electrocardiogram	1.45 (1.13-1.85)	1.64 (1.21-2.22)	1.50 (1.10-2.04)	1.48 (1.08-2.01)
ABI (per 0.10 decrease)	1.14 (1.09-1.20)	1.06 (1.01-1.12)	1.05 (1.01-1.11)	1.05 (1.01-1.11)
Stress test results				
LVEF (per 5% decrease)	1.07 (1.03-1.11)		1.06 (1.02-1.11)	1.05 (1.02-1.09)
Angina pectoris during test	0.98 (0.65-1.48)			1.01 (0.47-1.89)
ST changes during test	1.26 (0.89-1.79)			1.05 (0.67-2.01)
New wall motion abnormalities	2.20 (1.57-3.08)			2.01 (1.38-2.79)
Global X^2		78	85	102
Incremental value			p=0.01	p<0.001

TIA = transient ischemic attack; ABI = ankle-brachial index; LVEF = left ventricular ejection fraction.

Table 4. Univariate and Multivariate Predictors of the Composite Endpoint of Cardiac Death or Non-fatal Myocardial Infarction

Characteristic	Univariate	Multivariate		
	HR (95% CI)	Model 1 HR (95% CI)		Model 2 HR (95% CI)
Clinical Characteristics				
Age (per year increase)	1.03 (1.02-1.04)	1.03 (1.01-1.05)	1.03 (1.00-1.05)	1.03 (1.00-1.05)
Male gender	1.46 (1.07-2.01)	1.24 (0.89-1.71)	1.09 (0.71-1.68)	0.67 (0.29-1.55)
Previous myocardial infarction	2.04 (1.56-2.67)	1.51 (0.97-2.37)	1.32 (0.79-2.23)	1.37 (0.60-3.10)
History of heart failure	2.41 (1.58-3.66)	1.99 (1.20-3.30)	1.70 (0.95-3.45)	1.31 (0.46-3.78)
History of stroke or TIA	1.17 (0.68-2.02)	1.05 (0.55-1.95)	1.00 (0.42-2.01)	1.03 (0.40-2.15)
Diabetes mellitus	2.02 (1.46-2.79)	1.63 (1.08-2.47)	1.52 (1.03-2.20)	1.73 (0.77-3.92)
Hypercholesterolemia	1.37 (1.01-1.88)	1.38 (0.99-1.94)	1.25 (0.84-1.88)	0.95 (0.43-2.11)
Hypertension	1.32 (1.00-1.71)	1.08 (0.81-1.44)	1.11 (0.77-1.59)	1.64 (0.81-3.32)
Cigarette smoking	0.97 (0.73-1.30)	1.02 (0.76-1.38)	1.06 (0.73-1.53)	1.03 (0.50-2.13)
Renal failure	5.40 (3.45-8.45)	3.21 (1.60-6.46)	2.87 (1.43-5.78)	2.92 (1.45-5.90)
Ischemic baseline electrocardiogram	1.71 (1.30-2.25)	1.65 (1.16-2.33)	1.45 (0.95-2.57)	1.40 (0.80-2.97)
ABI (per 0.10 decrease)	1.15 (1.08-1.21)	1.07 (1.00-1.13)	1.03 (0.98-1.10)	1.03 (0.97-1.11)
Stress test results				
LVEF (per 5% decrease)	1.17 (1.13-1.25)		1.15 (1.09-1.22)	1.14 (1.08-1.21)
Angina pectoris during test	0.87 (0.53-1.41)			1.13 (0.46-2.76)
ST changes during test	1.42 (0.96-2.11)			1.76 (0.74-4.19)
New wall motion abnormalities	2.34 (1.58-3.47)			2.06 (1.39-3.08)
Global X^2		53	80	93
Incremental value			p<0.001	p<0.001

TIA = transient ischemic attack; ABI = ankle-brachial index; LVEF = left ventricular ejection fraction

Comparable results were obtained for the endpoint of hard events (Figure 1). In univariate analysis, left ventricular ejection fraction and stress-induced ischemia were significantly associated with adverse outcome (Table 3 and 4). In multivariate analysis, left ventricular ejection fraction and stress-induced ischemia independently predicted all-cause mortality and hard cardiac events, and provided significant incremental prognostic information over clinical data and ankle-brachial index values (p<0.001) (Table 3 and 4). In a similar model including clinical baseline characteristics, electrocardiography, ankle-brachial index values, and left ventricular ejection fraction, a higher number of ischemic segments was also significantly associated with mortality (HR per ischemic segment: 1.06, 95% CI: 1.01-1.12, p=0.01) and hard cardiac events (HR per ischemic segment: 1.08, 95% CI: 1.02-1.14, p=0.006).Tests for heterogeneity revealed no evidence for a differential effect of dobutamine stress echocardiography results among patients with different

ankle-brachial index values (all interaction terms: p>0.05), indicating that decreased left ventricular ejection fraction and an ischemic stress test predicted the risk of death and hard cardiac events across the entire spectrum of ankle-brachial index values.

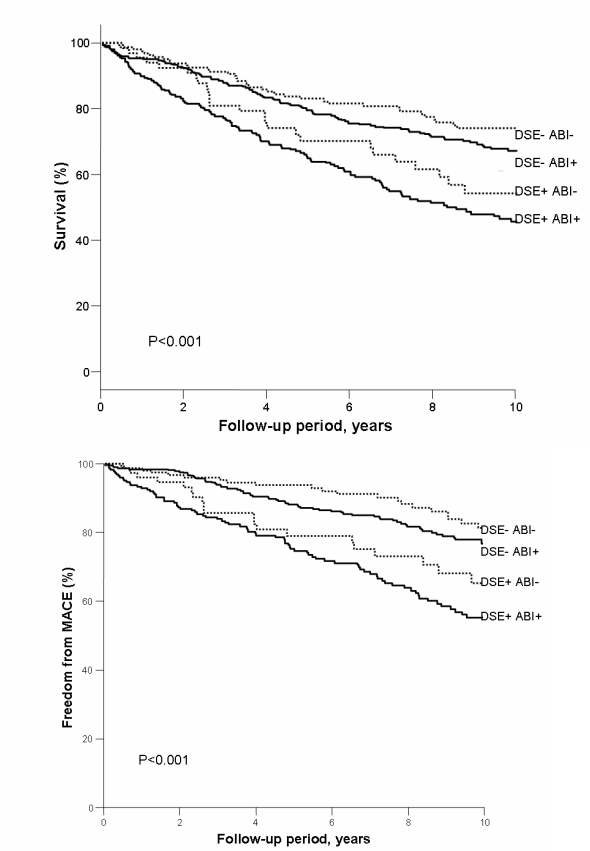

Figure 1. Kaplan Meier Curves in Patient with Suspected and Known Peripheral Arterial Disease Stratified According to Stress-induced Myocardial Ischemia (DSE+) and Ankle-Brachial Index Values ≤0.90 (ABI+).

DISCUSSION

Atherosclerosis has a common systemic pathogenesis and simultaneously affects multiple vascular beds.[24] Prevalence rates up to 75% of concomitant coronary artery disease in peripheral arterial disease have been published in literature, based on coronary angiography or clinical history.[9,10] The current results demonstrate that coronary artery disease, cerebrovascular disease and renal disease were remarkably high in our study population, with prevalence rates of 70%, 7% and 5%, respectively. In addition, 12% of the current study population presented with left ventricular ejection fraction <35%. The high risk of death and the impaired health-related quality of life in patients with peripheral arterial disease poses a significant health burden worldwide.[25] In the current study, death occurred in 34% and hard cardiac events occurred in 25% during a mean follow-up of 7.6 years, reflecting the significant adverse consequences of peripheral arterial disease. It is well established that low ankle-brachial index values predict overall and cardiovascular mortality and that ankle-brachial index measurements can be used for prognostic risk stratification.[26] The current study demonstrated supportive results and showed that each decrease in ankle-brachial index of 0.10 was associated with a 6% and 7% increased risk of all-cause mortality and hard cardiac events, respectively, independent of clinical risk factors and baseline electrocardiography.

Current Recommendations

The prognostic value of dobutamine stress echocardiography has previously been demonstrated in patients with suspected or known coronary artery disease.[27] A major finding in our study is that dobutamine stress echocardiography improves risk stratification in patients with suspected or known peripheral arterial disease in addition to ankle-brachial index values and clinical risk factors. Each 5% decrease in left ventricular ejection fraction was associated with a 5% and 14% increased risk of all-cause mortality and hard cardiac events, respectively. Stress-induced new wall motion abnormalities during dobutamine stress echocardiography were associated with a 2.0-fold and 2.1-fold increased risk, respectively. Furthermore, the extent of ischemia was also significantly associated with adverse outcome. The American College of Cardiology/American Heart Association has provided useful evidence-based guidelines regarding the management of patients with peripheral arterial disease and accentuate the frequent coexistence of coronary artery disease in these patients. Because of the paucity of published data, recommendations for cardiac risk assessment are limited. An improvement in the detection of (sub) clinical coronary artery disease and identification of those at increased risk for adverse events appears essential in order to obtain reductions in morbidity and mortality. The implication of dobutamine stress echocardiography in the work-up of patients with suspected or known peripheral arterial disease should therefore be considered.

When Should Dobutamine Stress Echocardiography Be Performed?

Although dobutamine stress echocardiography is a safe and accurate non-invasive procedure, the question remains whether all patients should undergo routine screening with this technique. This will probably depend on the availability of dobutamine stress echocardiography in the clinical practice, the presence

and local expertise of assessing and scoring echocardiographic images, and the consideration of costs versus benefit. The current results demonstrate that male patients with coronary artery disease, history of heart failure, diabetes, renal failure and hypercholesterolemia were more likely to present with left ventricular dysfunction. A subgroup of patients with advanced age, lower ankle-brachial index values and ischemic baseline electrocardiography were more likely to have stress-induced myocardial ischemia. Of note, lower ankle-brachial index values were directly associated with the severity of new wall motion abnormalities during dobutamine stress echocardiography. A limitation which should be addressed is that our study cohort consisted of patients referred to a tertiary referral centre with specific indications for stress echocardiography, and that it may not reflect "real-world" patients with peripheral arterial disease. Furthermore, it remains to be elucidated whether other non-invasive modalities such as exercise electrocardiographic testing and myocardial perfusion imaging are superior to dobutamine stress echocardiography for prognostic cardiac risk assessment in patients with suspected or known peripheral arterial disease. Exercise electrocardiography may not be suitable as test of screening for coronary artery disease, since patients with peripheral arterial disease often have limited exercise capacity and often present with baseline electrocardiographic abnormalities.

Conclusion

The current results reveal that decreased left ventricular ejection fraction and stress-induced myocardial ischemia during dobutamine stress echocardiography independently predict long-term outcome and improve prognostic risk assessment in addition to ankle-brachial index and clinical risk factors in patients with suspected or known peripheral arterial disease. The use of dobutamine stress echocardiography makes it possible to detect left ventricular dysfunction and coronary artery disease in an early stage, to identify patients at increased risk for future adverse events, and therefore to implement adequate preventive interventions.

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Chapter 5

Prognostic significance of declining ankle-brachial index values in patients with suspected or known peripheral arterial disease

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Prognostic significance of declining ankle-brachial index values in patients with suspected or known peripheral arterial disease

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Background: Peripheral arterial disease (PAD) is a risk factor for late cardiovascular events. This study assessed the prognostic significance of repeated ankle-brachial index (ABI) measurements at rest and during exercise in patients with PAD receiving conservative treatment.
Methods: In a cohort study of 606 patients (62 ±12 years, 68% male), ABI at rest and after exercise was measured at baseline and after 1 year. Patients with reductions in ABI were dived into three equally-sized groups (minor, intermediate and major reductions) and were compared to patients without reductions. During a mean follow-up of 5 ± 3 years, all-cause mortality, cardiac events, stroke and progression to kidney failure were noted.
Results: Death was recorded in 83 patients (14%) of which 49% was due to cardiac causes. Non-fatal myocardial infarction occurred in 38 patients (6%), stroke in 46 (8%) and progression to kidney failure in 35 (6%). In multivariate analysis, patients with major declines in resting (>20%) and post-exercise (>30%) ABI were at increased risk of all-cause mortality (HR: 3.3, 95% CI: 1.5-7.2, HR: 3.0, 95% CI: 1.4-6.4, respectively), cardiac events (HR: 3.1, 95% CI: 1.3-7.2, HR: 2.4, 95% CI: 1.1-5.6, respectively), stroke (HR: 4.2, 95% CI: 1.6-10.4, HR: 3.9, 95% CI: 1.4-10.2, respectively) and kidney failure (HR: 2.7, 95% CI: 1.1-7.5, HR: 6.9, 95% CI: 1.5-31.5, respectively), compared to patients with no declines in ABI.
Conclusions: This study shows that major declines in resting and post-exercise ABI are associated with all-cause mortality, cardiac events, stroke and kidney failure in patients with PAD.

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AS A MANIFESTION of systemic atherosclerosis, peripheral arterial disease (PAD) is significantly associated with an increased risk of vascular morbidity and mortality despite medical treatment [1-3]. In the Netherlands, the combined prevalence of symptomatic and asymptomatic peripheral arterial disease (PAD) in the population of 55 years and older is 19% [4]. In the United States, prevalence rates for PAD have been reported that range from 4% in patients aged 40 years and older to 29% in patients aged 70 years and older or aged 50 to 59 years with a history of smoking or diabetes mellitus [1,5-8]. Therefore, the identification of patients with PAD who are at increased risk of late events is necessary for disease control and selection of appropriate treatment strategies [3,9,10].

The ankle-brachial index (ABI) is a simple, inexpensive and non-invasive test used for the assessment of lower extremity arterial obstruction and for screening of patients with suspected PAD [8-10]. A resting ABI of less than 0.90 has been associated with a 2- to 7-fold increased risk of overall mortality and a 2- to 4-fold increased risk of cardiovascular mortality, compared to a resting ABI higher than 0.90 [11-17]. The prognostic value of declines in ABI over time is not well known. In this study, we assessed the association between changes in resting and post-exercise ABI over time and long-term outcome in patients with known or suspected PAD who are receiving conservative (non-surgical) treatment.

We hypothesized that a larger decline in both resting and post-exercise ABI can identify patients at increased risk of all-cause mortality, cardiac events, stroke and end-stage renal disease, irrespective of baseline ABI values and clinical risk factors.

METHODS

Study participants

We have prospectively included consecutive patients with suspected or known lower extremity PAD who were referred to our university clinic of vascular surgery for the evaluation and management of their disease between January 1996 and January 2005. Patients with known PAD had a resting or post-exercise ABI ≤0.90. In patients with suspected PAD, the diagnosis was based on a typical history of intermittent claudication or other symptoms of chronic arterial insufficiency, including ulceration of the foot, hair loss or reduced capillary refill. Patients unable to perform exercise, patients who underwent previous vascular surgery and patients who had foot or leg amputations were not included. We further considered patients with ABI values greater than 1.50 to have calcified atherosclerosis, resulting in high ABI readings. These patients were also not included in the study. The hospital's Medical Ethical Committee approved the study protocol and patients who fulfilled the inclusion criteria agreed on participation in the study.

Co-morbidities

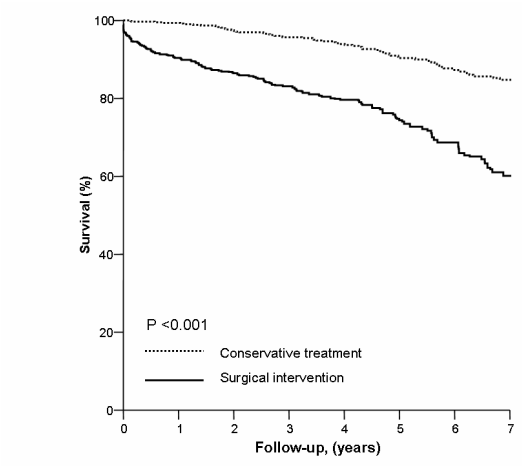
Based on hospital records and personal interviews at the time of the visit, a medical history was recorded including details of a previous myocardial infarction, angina pectoris, coronary artery revascularization, congestive heart failure, previous stroke or transient ischemic attack, diabetes mellitus, hypertension, smoking, hypercholesterolemia and renal dysfunction. Diabetes mellitus was recorded if patients presented with a fasting glucose level of ≥7.0 mmol/L, or in those who required medical treatment. Hypertension was recorded if patients presented with a blood pressure ≥140/90 mmHg or if patients received antihypertensive treatment. Hypercholesterolemia was recorded if patients presented with a plasma cholesterol level ≥5.5 mmol/L, or if patients were taking lipid-lowering agents. Renal dysfunction was recorded if patients presented with a serum creatinine level ≥2.0 mg/dL (177 μmol/L) or in those who required dialysis. Patients were assessed for chronic cardiac medication use. A baseline 12-lead electrocardiography was obtained and the ABI at rest and after exercise was measured in each patient.

Table 1. Baseline characteristics of patients with peripheral arterial disease receiving conservative management (n=606) and patients receiving lower extremity revascularization surgery (n=974).

Characteristic	Conservative management (n=606)	Surgical treatment (n=974)	P value
Age (years), mean +/- SD	62 ± 12	63 ± 12	0.2
Male gender, No. (%)	414 (68)	709 (73)	0.06
Angina pectoris, No. (%)	112 (18)	250 (26)	0.001
Previous myocardial infarction, No. (%)	200 (33)	351 (36)	0.2
History of heart failure, No. (%)	40 (7)	64 (7)	0.9
History of stroke, No. (%)	51 (8)	101 (10)	0.2
Diabetes mellitus, No. (%)	112 (19)	155 (16)	0.054
Hypercholesterolemia, No. (%)	147 (24)	292 (30)	0.02
Hypertension, No. (%)	222 (37)	470 (48)	<0.001
Current smoking, No. (%)	169 (28)	289 (30)	0.5
Renal dysfunction, No. (%)	31 (5)	59 (6)	0.5
Chronic pulmonary disease, No. (%)	57 (9)	145 (15)	0.002
Rest ankle-brachial index, mean +/- SD	0.69 ± 0.23	0.65 ± 0.24	0.03
Post-exercise ankle-brachial index, mean +/- SD	0.48 ± 0.29	0.46 ± 0.29	0.3
Aspirin, No. (%)	179 (30)	297 (30)	0.7
Angiotensin-converting enzyme inhibitors, No. (%)	174 (29)	290 (30)	0.7
β-blockers, No. (%)	193 (32)	355 (36)	0.07
Statins, No. (%)	218 (36)	329 (34)	0.4

Measurement of the ankle-brachial index
Trained technicians, using a Doppler ultrasonic instrument with an 8 MHz vascular probe (Imexdop CT+ Vascular Doppler, Miami Medical, USA), measured systolic blood pressures in the right and left brachial artery, right and left dorsalis pedis artery and right and left posterior tibial artery. The ABI in the right and left leg was calculated by dividing the right and the left ankle pressure by the brachial pressure. The higher of the two brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Again, the higher of the dorsalis pedis and posterior tibial artery pressure was used when a discrepancy in systolic blood pressure between the two arteries was measured. If no pressure in the dorsalis pedis artery was obtained due to an absent dorsalis pedis artery, the pressure in the posterior tibial artery was used. The ABI at rest was measured after the participants had been resting in the supine position for at least 10 minutes. Measurements were then repeated at both sides with the patient in the supine position, after 5 minutes of walking on a treadmill with a speed of 2.5 miles/hour. No inclining plane or graded inclines were used with treadmill testing, and the treadmill tests were performed without continuous electrocardiographic monitoring before, during and after the testing. Inter- and intraobserver agreement for rest ABI was 97% and 98%, respectively and for post-exercise ABI 96% and 97%, respectively.

Figure 1. Kaplan-Meier survival curves in 1580 patients with peripheral arterial disease according to conservative treatment or surgical intervention.



Conservative versus surgical management
The decision for conservative management or surgical intervention was at the discretion of the treating physician. In general, surgical treatment was indicated when a significant improvement of symptoms could be expected and when the expected benefits would outweigh the risk of surgery. In patients who received conservative treatment, i.e. walking exercise and/or pharmacotherapy, ABI measurements were repeated at least every year after enrollment. Patients who died before the second ABI measurement and in whom an ABI change over time could not be determined were excluded from the study (n=13).

Follow-up
Follow-up ended at the date of the last visit or the date of death. Information about the patient's vital status was obtained at the Office of Civil Registry. For patients who died at our hospital during follow-up, hospital records and autopsy results were reviewed. For patients who died outside our hospital, general practitioners were approached to ascertain the cause of death. A cardiac cause of death was defined as death caused by acute myocardial infarction (postmortem evidence of acute myocardial infarction or definite criteria for myocardial infarction within the four weeks before death), cardiac arrhythmias, congestive heart failure, or sudden death. Details on non-fatal myocardial infarction, stroke and end-stage renal disease were obtained by regularly scheduled follow-up visits. Additional information was obtained by approaching the general practitioners or referring clinicians. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: elevated cardiac enzyme levels (CK level >190 U/L and CK-MB >14 U/L, or CK-MB fraction >6% of total CK, or cardiac troponin T >0.1 ng/mL), development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms), and typical symptoms of angina pectoris. Stroke was diagnosed when patients presented with typical neurological symptoms lasting for more than 24 hours. In all cases of stroke, the diagnosis was established by a neurologist. End-stage renal disease was defined as an estimated glomerular filtration rate less than 15 ml/min per 1.73 m^2 or a need to start kidney replacement therapy, which included dialysis or renal transplantation. The estimated glomerular filtration rate was calculated using the following equation: glomerular filtration rate (ml/min/1.73 m^2) = 186 x (serum creatinine level)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.210 if of African descent) [18].

Statistical analysis
Continuous data are expressed as mean (+/- SD) or median (+/- interquartile range) and compared using the Student t test or Mann-Whitney U test as appropriate. Categorical data are presented as percent frequencies and differences between proportions were compared using the chi-square test with Yates' correction. Comparisons of categorical variables with continuous

measures were calculated with analysis-of-variance techniques. Initially, we compared patients receiving conservative treatment (n=606) to patients receiving lower extremity surgical revascularization (n=974). We then focused our analysis on the 606 patients receiving conservative treatment to assess the prognostic value of declines in ABI. The change of the serial ABI measurements was calculated in each leg and expressed as a percentage value. Of the changes in ABI obtained in each leg, the lower was used in all analyses. Although repeat ABI measurements were obtained annually, the change in ABI was calculated over the first year and expressed as both percentage and absolute change. Only 1-year changes were used in our analysis. Patients with declining ABI were compared to patients with no declines in ABI. Patients with declining ABI were further divided into minor, intermediate and major decline according to the tertiles as cut-off value (5% and 20% for the decline in resting ABI and 6% and 30% for the decline in post-exercise ABI). For the prediction of a major decline in ABI, a final set of baseline variables was identified by multivariate analysis with stepwise deletion of the least significant variable. Only variables with a $p \leq 0.20$ were retained in the final model. The primary endpoints were overall mortality and cardiac events (cardiac death or non-fatal myocardial infarction). Secondary endpoints were stroke and progression to end-stage renal disease. For the outcome analysis, we used univariate and multivariate Cox proportional hazard regression models to analyze the association between ABI decline and outcome. In multivariate analyses, all clinical variables were entered, irrespective of the significance level in univariate analysis. Hazard ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Conservative treatment versus surgical treatment
Baseline characteristics of patients receiving either conservative or surgical treatment are presented in Table 1. Patients receiving surgical treatment were more likely to present with hypercholesterolemia, hypertension, angina pectoris, chronic pulmonary disease and lower resting ABI values. Mean follow-up was 5.3 ± 3.3 years. In patients receiving surgical and conservative treatment, death was recorded in 293 patients (30%) and 83 patients (14%), respectively. As shown in Figure 1, survival was significantly lower in patients receiving surgical treatment.

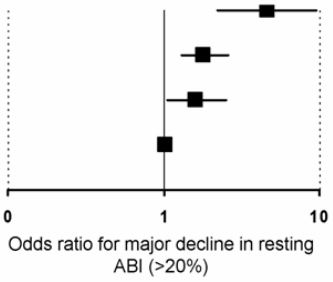
Declines in ABI
In the 606 patients receiving conservative treatment, the mean baseline ABI at rest (the lower of the right and left ABI) was 0.69 ± 0.23. A resting ABI >0.90 in both legs was measured in 99 patients (16%). The mean ABI measured after exercise (the lower of the right and left ABI) was 0.48 ± 0.29. A post-exercise ABI >0.90 in both legs was observed in 59 patients (10%). A total of 29 patients (5%) had both a resting and post-exercise ABI of more than 0.90. These 29 patients all had a typical history of claudication and all had signs of arterial insufficiency, including weak peripheral pulses and reduced capillary refill. A total of 459 patients (76%) had declining ABI values at rest and 456 patients (75%) had declining ABI values after exercise. Declining ABI values at rest were observed in 67 (68%) out of 99 patients with a normal resting ABI (ABI >0.90). Declining ABI values after exercise were observed in 40 (68%) out of 59 patients with normal post-exercise ABI (ABI >0.90). The median change in resting ABI in patients with no declining ABI was +13% and in patients with declining ABI -12%. The median change in post-exercise ABI in patients with no declining ABI was +21% and in patients with declining ABI -17%.

Predictors of declines in ABI values
Significant predictors of major declines in resting ABI values (>20%) were age ($p=0.003$), cigarette smoking ($p<0.001$), history of stroke ($p<0.001$) and a previous myocardial infarction ($p=0.042$) (Figure 2). Significant predictors of major declines in post-exercise ABI values (>30%) were age ($p<0.001$), diabetes mellitus ($p<0.001$), cigarette smoking ($p<0.001$) and a history of stroke ($p=0.031$) (Figure 2).

Figure 2. Baseline clinical variables associated with a major 1-year decline in resting ankle-brachial index (ABI) (decline of more than 20%) and post-exercise ankle-brachial index (decline of more than 30%) in patients with peripheral arterial disease receiving conservative management.

Predictors of a major decline in resting ABI (>20%)	Hazard ratio (95% CI)	p value	β-coefficient
History of stroke	4.6 (2.2-9.6)	<0.001	1.53
Current cigarette smoking	1.8 (1.3-2.6)	<0.001	0.59
Previous myocardial infarction	1.6 (1.02-2.5)	0.042	0.46
Age (per year increase)	1.03 (1.01-1.05)	0.003	0.03

Chi-square: 32.9, p<0.0001



Predictors of a major decline in postexercise ABI (>20%)	Hazard ratio (95% CI)	p value	β-coefficient
Diabetes mellitus	3.0 (1.9-4.9)	<0.001	1.11
History of stroke	2.3 (1.1-4.7)	0.031	0.81
Current cigarette smoking	1.9 (1.3-2.8)	<0.001	0.68
Age (per year increase)	1.05 (1.03-1.07)	<0.001	0.05

Chi-square: 38.7, p<0.0001

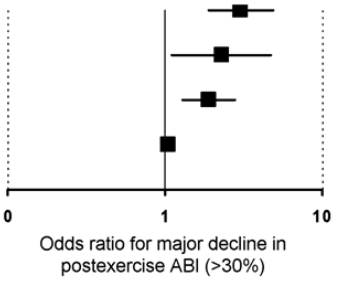
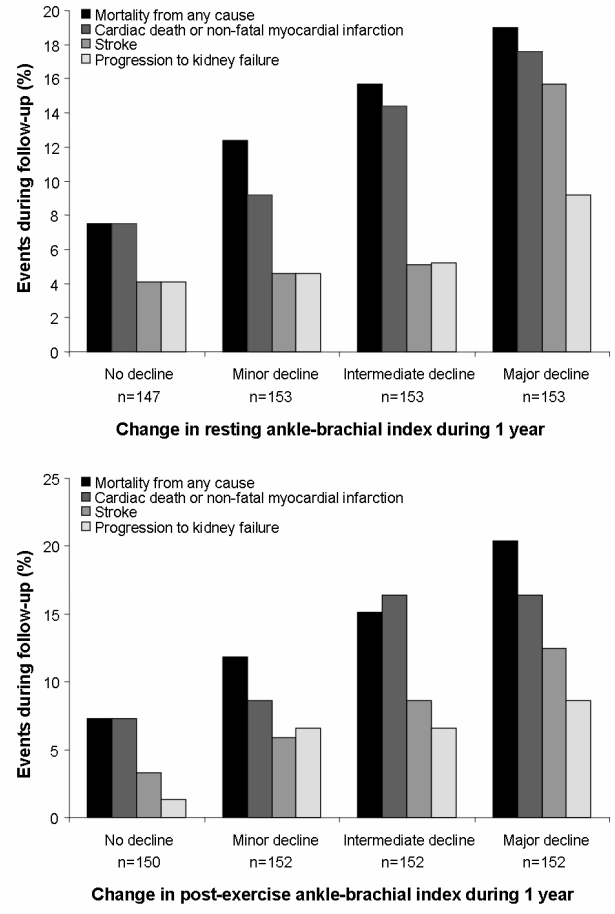


Figure 3. Absolute event rate during follow-up according to the 1-year decline in resting (minor decline: 1-5%, intermediate decline: 6-20%, major decline: >20%) and post-exercise ankle-brachial index (minor decline: 1-6%, intermediate decline: 7-30%, major decline: >30%) in patients with peripheral arterial disease receiving conservative medical management.



Predictive value of declines in ABI

Of the 83 patients receiving conservative treatment who died during follow-up, 49% was due to cardiac causes (41 patients). Non-fatal myocardial infarction occurred in 38 patients (6%), stroke in 46 patients (8%) and progression to end-stage renal disease in 35 patients (6%). Figure 3 shows the incidence of overall mortality, cardiac events, stroke and progression to end-stage renal disease in patients with no, minor, intermediate and major declines in resting and post-exercise ABI. In univariate analysis, patients with major declines in resting and post-exercise ABI had the highest hazard of all-cause mortality, cardiac events, stroke and end-stage renal disease (Table 2). Patients with intermediate declines in resting and post-exercise ABI were also at significantly increased risk of death and hard cardiac events (Table 2). After adjustment for baseline clinical variables, baseline ankle-brachial index values, β-blockers statins, aspirin and angiotensin-converting enzyme inhibitors, major declines in resting and post-exercise ABI remained significantly associated with all-cause mortality, cardiac events, stroke and kidney (Table 2). Intermediate declines remained significantly associated with death and hard cardiac events (Table 2). As demonstrated in Table 3, absolute declines in ABI (per 0.10 decline) were significantly associated with all-cause mortality, cardiac events, stroke and end-stage renal disease.

DISCUSSION

The current study found that major declines in resting and post-exercise ABI values are significantly associated with increased long-term mortality, cardiac events, stroke and progression to end-stage renal disease. These findings were independent of baseline ABI values, established clinical risk factors and cardiovascular therapy.

Given the fact that the presence of PAD should be regarded as a marker of atherosclerosis in other vascular beds, it is not surprising that many of these patients die due to cardiovascular disease, stroke or renal dysfunction [10]. The management of PAD comprises of walking exercise, aggressive management of risk factors, life-style modifications, antiplatelet therapy and statins [19]. Patients who have extensive functional disability, who are unresponsive to exercise or pharmacotherapy, and who have a reasonable likelihood of symptomatic improvement may benefit from surgical intervention [19]. The higher mortality rate in patients undergoing surgery in relation to conservative management may be explained by the presence of more co-morbidities. The high prevalence and associated morbidity and mortality of PAD in the general population warrants the identification of patients at increased risk so that preventive measures can be applied to reduce the incidence of atherosclerosis related complication.

Large cohort studies have consistently demonstrated that lower ABI values are associated with increased mortality and cardiovascular events. In a study of Leng and colleagues, a significant linear increase in mortality across decreasing ABI categories was observed using resting ABI cut-off values of 1.10, 1.00, 0.90 and 0.70 [17]. We have previously demonstrated that the adjusted risk for overall mortality increased with 8% for every 0.10 decrease of the resting ABI, and with 9% for every

Table 2. The long-term prognostic value of percentage declines in ankle-brachial index values in multivariate analysis in patients with peripheral arterial disease receiving conservative management.

		HR (95% CI) for all-cause mortality		HR (95% CI) for cardiac events		HR (95% CI) for stroke		HR (95% CI) for end-stage renal disease	
	N	Unadjusted	Adjusted *	Unadjusted	Adjusted *	Unadjusted	Adjusted *	Unadjusted	Adjusted*
TOTAL POPULATION									
ABI at rest									
No decline**	147	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Minor (1-5%)	153	1.8 (0.9-3.7)	2.0 (0.9-4.6)	1.4 (0.6-3.0)	1.5 (0.6-3.8)	1.1 (0.4-3.4)	1.2 (0.4-3.5)	1.1 (0.4-3.4)	1.2 (0.4-3.7)
Intermediate (6-20%)	153	2.4 (1.2-4.8)	3.0 (1.3-6.7)	2.3 (1.1-4.8)	2.5 (1.03-5.8)	1.5 (0.5-4.2)	1.5 (0.5-4.2)	1.3 (0.4-3.8)	1.4 (0.5-4.1)
Major (>20%)	153	2.5 (1.2-4.9)	3.3 (1.5-7.2)	2.4 (1.2-4.7)	3.1 (1.3-7.2)	4.3 (1.7-11.0)	4.2 (1.6-10.4)	2.4 (1.1-3.4)	2.7 (1.1-7.5)
Post-exercise ABI									
No decline**	150	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Minor (1-6%)	152	1.2 (0.5-2.7)	1.4 (0.6-3.2)	1.7 (0.8-3.7)	1.0 (0.4-2.6)	1.8 (0.6-5.5)	1.7 (0.6-5.4)	5.2 (1.2-24.2)	4.8 (1.01-22.8)
Intermediate (6-30%)	152	2.4 (1.2-5.2)	2.1 (1.03-4.8)	2.3 (1.1-4.8)	2.2 (1.05-5.2)	2.7 (0.9-7.8)	2.7 (0.9-7.9)	5.1 (1.1-22.9)	4.7 (1.01-22.6)
Major decline (>30%)	152	2.6 (1.3-5.8)	3.0 (1.4-6.4)	3.2 (1.6-6.7)	2.4 (1.1-5.6)	4.2 (1.5-11.4)	3.9 (1.4-10.2)	6.9 (1.5-31.2)	6.9 (1.5-31.5)

ABI = ankle-brachial index. *Adjusted for age, gender, coronary artery disease, history of heart failure, history of stroke, diabetes, hypercholesterolemia, hypertension, smoking, renal dysfunction, baseline ankle-brachial index values and cardioprotective medication.
** Reference category

0.10 decrease of the post-exercise ABI. The adjusted risk for cardiac death increased with 12% and 15% for every 0.10 decrease of the resting ABI and post-exercise ABI, respectively [20]. The concept that PAD is a marker of generalized atherosclerosis has been reflected by the fact that ABI values correlate with the extent of angiographic coronary artery disease [21]. The prognostic value of post-exercise ABI has been supported by the view that a healthy person can maintain ankle systolic pressures at normal levels during modest workloads, but that larger falls in systolic pressure in the legs are measured during low levels of workload in patients with more extensive PAD [22-24]. Based on the greater accuracy of the postexercise ABI to detect PAD, the American College of Cardiology/American Heart Association has recommended its use, especially in patients with suspected PAD who have normal resting ABI values [19].

Important predictors of declining ABI values in our study included advanced age and smoking. The association between a history of myocardial infarction or stroke and declining ABI may signify the systemic nature of atherosclerosis. Our results are supported by the Cardiovascular Health study, which found that advanced age, smoking, male gender, hypertension and higher LDL-cholesterol concentrations were risk factors for declines in ABI [25]. Smoking was also identified as a strong predictor of large vessel peripheral arterial disease in a study by Aboyans and colleagues [26]. We found that diabetes only predicted major declines in post-exercise ABI in contrast to resting ABI. Similarly, diabetes was not a significant predictor of ABI decline [25], of large vessel PAD progression [26] and of declines in post-exercise ABI [27]. In the current study, however, a significant correlation between diabetes and major declines in post-exercise ABI was found. Concomitant arterial wall stiffening, medial calcinosis and higher ankle systolic pressures in diabetic patients may mask arterial occlusive disease, leading to pseudo-normal resting ABI values. We speculate that the value of postexercise ABI lies in its ability to measure larger decreases in ankle systolic pressures in the presence of atherosclerotic obstructive lesions, and that obstructive arterial disease can become more evident after exercise in diabetic patients.

To our knowledge, the current study is the first to describe the association between declines in ABI and prognosis in patients with PAD receiving conservative treatment. Declines in ABI may reflect active and progressive atherosclerosis, precipitating acute coronary and cerebrovascular events. The association between progression in atherosclerosis and progression to kidney failure is less well-defined. The Atherosclerosis Risk in Communities Study showed that patients with an ABI of 0.90-0.99 and <0.90 were at increased risk of serum creatinine increases over a 3-year time period, compared to patients with ABI values above 1.00 [28]. It has been proposed that atherosclerosis has indirect effects on the kidney because of atherosclerotic lesions in the renal artery and that atherosclerosis or atherogenic factors may induce directly intrarenal microvascular disease and renal injury [29].

Repeated measurements of resting and post-exercise ABI values are simple, inexpensive and non-invasive. Results from this study suggest that repeated ABI measurements at rest and after exercise may be incorporated among other tools for identifying patients at increased risk of late events. Either resting and post-

Table 3. The long-term prognostic value of absolute declines in ankle-brachial index values in multivariate analysis in patients with peripheral arterial disease receiving conservative management.

	Resting ABI per 0.10 decline	Postexercise ABI per 0.10 decline
All-cause mortality		
• Unadjusted Hazard Ratio (95% CI)	1.12 (1.01-1.26)	1.12 (1.02-1.25)
• Adjusted Hazard Ratio (95% CI)*	1.13 (1.01-1.26)	1.11 (1.01-1.23)
Cardiac events		
• Unadjusted Hazard Ratio (95% CI)	1.17 (1.05-1.31)	1.15 (1.03-1.30)
• Adjusted Hazard Ratio (95% CI)*	1.18 (1.05-1.33)	1.17 (1.04-1.33)
Stroke		
• Unadjusted Hazard Ratio (95% CI)	1.30 (1.14-1.48)	1.24 (1.09-1.40)
• Adjusted Hazard Ratio (95% CI)*	1.35 (1.18-1.55)	1.22 (1.06-1.38)
End-stage renal disease		
• Unadjusted Hazard Ratio (95% CI)	1.20 (1.02-1.41)	1.19 (1.03-1.38)
• Adjusted Hazard Ratio (95% CI)*	1.20 (1.03-1.41)	1.18 (1.02-1.36)

*Adjusted for age, gender, coronary artery disease, history of heart failure, history of stroke, diabetes, hypercholesterolemia, hypertension, smoking, renal dysfunction, baseline ankle-brachial index values and cardioprotective medication.

exercise ABI declines after 1 year can already identify a subgroup of patients at increased risk. Post-exercise ABI testing may be useful in patients with no declines in serial resting ABI. Therefore, both methods may be recommended.
Especially patients with major declines in ABI values may be referred for further cardiovascular, cerebrovascular or renal evaluation and may subsequently benefit from preventive pharmacologic and non-pharmacologic interventions.

Several limitations should be addressed. It should be emphasized that the event rate in the groups of patients with different declines in ABI was relatively small which may have affected the statistical power of the study. However, the hazard of adverse events was consistently increased in those with major declines in resting and post-exercise ABI. Secondly, the results apply to patients referred to a university hospital. These patients may have a higher risk profile compared to patients with suspected or known PAD in the general population.

In conclusion, this observational cohort study of patients with PAD receiving conservative treatment shows that major declines in resting and post-exercise ABI are associated with late overall mortality, hard cardiac events, stroke and end-stage renal disease. The results support the view that progression of atherosclerosis in the lower extremities is associated with morbidity in the coronary, cerebrovascular and renal circulation. Repeated measurements of resting and post-exercise ABI are simple and non-invasive and should be considered in the follow-up of patients with PAD receiving conservative treatment for identifying those at increased risk of adverse events and for enabling optimal prevention of complications.

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Chapter 6

Cardioprotective medication is associated with improved survival in patients with peripheral arterial disease

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Cardioprotective medication is associated with improved survival in patients with peripheral arterial disease

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Objectives: To investigate the effect of cardiac medication on long-term mortality in patients with peripheral arterial disease (PAD).
Background: PAD is associated with increased cardiovascular morbidity and mortality. Treatment guidelines recommend aggressive management of risk factors and life-style modifications. However, the potential benefit of cardiac medication in patients with PAD remains ill defined.
Methods: In this prospective observational cohort study, 2420 consecutive patients (age: 64 ±11 years, 72% male) with PAD (ankle brachial index ≤0.90) were screened for clinical risk factors and cardiac medication. Follow-up endpoint was death from any cause. Propensity scores for statins, β-blockers, aspirin, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, diuretics, nitrates, coumarins and digoxin were calculated. Cox regression models were used to analyze the relation between cardiac medication and long-term mortality.
Results: Medical history included diabetes mellitus in 436 patients (18%), hypercholesterolemia in 581 (24%), smoking in 837 (35%), hypertension in 1162 (48%), coronary artery disease in 1065 (44%), and a history of heart failure in 214 (9%). Mean ankle brachial index was 0.58 (± 0.18). During a median follow-up of 8 years, 1067 patients (44%) died. After adjustment for risk factors and propensity scores, statins (HR 0.46, 95% CI 0.36-0.58), β-blockers (HR 0.68, 95% CI 0.58-0.80), aspirins (HR 0.72, 95% CI 0.61-0.84) and ACE-inhibitors (HR 0.80, 95% CI 0.69-0.94) were significantly associated with a reduced risk of long-term mortality.
Conclusion: Based on this observational longitudinal study, statins, β-blockers, aspirins and ACE-inhibitors are associated with a reduction in long-term mortality in patients with PAD.

PERIPHERAL ARTERIAL DISEASE (PAD) is a common manifestation of systemic atherosclerosis and carries a poor prognosis due to the frequent association with cerebral, renal and coronary artery disease [1-4]. Although patients with PAD may present with symptoms ranging from pain on exertion that is relieved by rest (intermittent claudication), to pain at rest, ulceration, or gangrene (critical limb ischemia), the majority of patients with PAD are asymptomatic [1]. The prevalence of PAD ranges from 4% in patients aged 40 years and older to over 20% in patients aged 70 years and older [5-10].

PAD remains an underdiagnosed disease in the primary care and patients with PAD are not treated as aggressively as are patients with other manifestations of atherosclerotic disease [7,11]. The management of PAD comprises of walking exercise, aggressive management of risk factors, life-style modifications, and antiplatelet therapy [12,13]. Cardiovascular events are a major cause of morbidity and mortality in patients with PAD. However, the potential benefit of cardiac medication therapy remains ill defined. β-Adrenergic receptor blockers were considered relatively contraindicated in PAD, however, several studies revealed that β-blockers do not adversely affect walking capacity, symptoms of intermittent claudication and peripheral skin microcirculation [14-16].

We sought to determine the effect of chronic treatment with cardiac medication, including statins, β-blockers, aspirins, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, diuretics, nitrates, coumarins and digoxin on long-term mortality among patients with PAD. In this observational cohort study, we used propensity analyses to adjust for selection bias in the comparison of treatments.

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METHODS

Assessment of baseline characteristics

The Erasmus Medical Centre is serving a population of approximately 3 million people and acts as a tertiary referral centre for approximately 30 affiliated hospitals. Patients with suspected or known PAD, who were referred to the Erasmus Medical Centre, Rotterdam, the Netherlands, between January 1983 and January 2005 for the diagnosis and management of PAD, were evaluated. The ABI at rest was measured in each patient and patients with PAD (an ankle brachial index (ABI) ≤0.90) were included in the study.

Based on hospital records and personal interviews at the time of the visit, a medical history was recorded. Information on the presence of previous myocardial infarction, angina pectoris, previous coronary artery revascularization, congestive heart failure, previous stroke or transient ischemic attack, diabetes mellitus, hypertension, current smoking, hypercholesterolemia and renal dysfunction were obtained. Diabetes mellitus was recorded if patients presented with a fasting glucose level of ≥7.0 mmol/L, or in those who required treatment. Hypertension was recorded if patients presented with a blood pressure ≥140/90 mmHg or if patients were medically treated for hypertension. Hypercholesterolemia was recorded when patients presented with the diagnosis, made by the referring physician, or if patients were taking lipid-lowering agents. Renal dysfunction was recorded if patients presented with a serum creatinine level ≥ 2.0 mg/dL (177 μmol/L) or in those who required dialysis. A baseline 12-lead electrocardiography was obtained and was considered abnormal in the presence of one or more of the following; Q-waves, ST-segment depression or elevation, left ventricular hypertrophy, right or left bundle branch block and atrial fibrillation.

Medication use

All prescription and over-the-counter medications were noted at the time of the visit and were classified as follows: statins, β-blockers, aspirins, ACE-inhibitors, calcium channel blockers (dihydropyridines or non-dihydropyridines), diuretics, nitrates, coumarins and digoxin. To ascertain the long-term use of cardiovascular medication, medication had to be documented at least at 2 months after the visit.

Follow-up

Patients were followed-up during a median time of 8 years (interquartile range: 4-11 years) for the occurrence of all-cause death. Endpoint was mortality. Information about the patient's vital status was obtained by approaching the Office of Civil Registry. For patients who died at our hospital during follow-up, hospital records and autopsy results were retrieved and reviewed. For patients who died outside our hospital, general practitioners were approached to ascertain the cause of death.

Table 1. Baseline characteristics of the 2420 study participants.

Characteristic	Total population (n=2420)
Demographics	
Age (years)	64 +/-11
Male gender	1748 (72%)
Cardiovascular history	
Angina pectoris	567 (23%)
Previous myocardial infarction	923 (38%)
History of congestive heart failure	214 (9%)
History of cerebrovascular disease	195 (8%)
Previous coronary revascularization	464 (19%)
Clinical risk factors	
Diabetes Mellitus	436 (18%)
Hypercholesterolemia	581 (24%)
Hypertension	1162 (48%)
Current smoking	837 (35%)
Renal failure	127 (5%)
Chronic pulmonary disease	288 (12%)
Ankle brachial index >0.70 and ≤0.90	557 (23%)
Ankle brachial index ≤0.70	1863 (77%)
Electrocardiography	
Q waves	630 (26%)
ST segment changes	382 (16%)
Left ventricular hypertrophy	113 (5%)
Left bundle branch block	98 (4%)
Right bundle branch block	56 (2%)
Atrial fibrillation	54 (2%)

Values are expressed as number (%) or mean +/- SD.

Statistical analysis

Continuous data are expressed as mean (+/- SD) or median (+/- interquartile range) and compared using the Student t test or Mann-Whitney U test when appropriate. Categorical data are presented as percent frequencies and differences between proportions were compared using the chi-square test with Yates' correction. The Kaplan-Meier method with log-rank test was used to compare survival curves in two or more groups. We applied univariate and multivariate Cox hazards regression analyses to study the relation between cardiac medication therapy and long-term survival. Cardiac medication use was not randomly assigned in these patients, and the impact of selection bias may profoundly distort the results of our study.

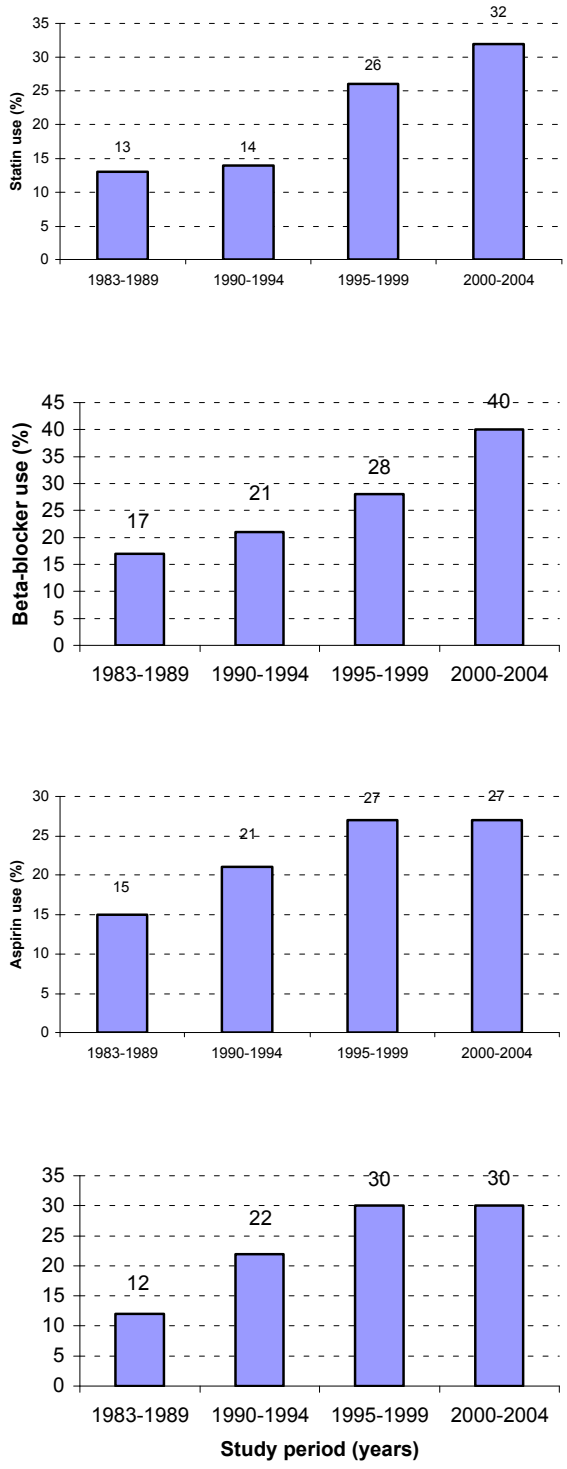

Figure 1. The prescription of statins, β-blockers, aspirins and angiotensin-converting enzyme (ACE) inhibitors in patients who were included in different periods of time.

Propensity analyses are reliable tools to correct for selection bias and the rationale for using propensity scores has been described previously [17]. Therefore, we calculated separate propensity scores for statins, β-blockers, aspirin, ACE-inhibitors, calcium channel blockers, diuretics, nitrates, coumarins and digoxin, which were constructed using multiple logistic regression analyses. Variables (including baseline characteristics as listed in Table 1 and medication use as listed in Table 2) that were independently associated with the decision to prescribe statins, β-blockers, aspirin, ACE-inhibitors, calcium channel blockers, diuretics, nitrates, coumarins and digoxin ($p<0.25$) were included in the multivariate propensity score. In multivariate analyses we adjusted for baseline clinical variables, irrespective of the significance level in univariate analysis. Propensity scores were added in separate multivariate models. Hazard ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics of the 2420 study participants are presented in Table 1. The mean age was 64 +/-11 years and 1748 patients (72%) were male. Severe PAD (ABI was ≤0.70) was identified in 1863 patients (77%). The mean ABI was 0.58 +/-18. An abnormal electrocardiogram was observed in 1127 patients (47%). Table 2 shows cardiac medication in the study population. As demonstrated in Figure 1, the prescription of statins, β-blockers, aspirin and ACE-inhibitors has increased from 12%, 13%, 15% and 17%, respectively, in the period 1983-1989, to 30%, 32%, 27% and 40%, respectively, in the period 2000-2004 (all p-values <0.001).

During follow-up, death occurred in 1067 patients (44%). The unadjusted and adjusted associations between clinical variables and long-term mortality are presented in Table 3. In a multivariate model that mutually adjusted for clinical risk factors and propensity scores, statins, β-blockers, aspirin and ACE-inhibitors were independently associated with a reduced incidence of long-term mortality (HR: 0.46 (95% CI: 0.36-0.58), HR: 0.68, (95% CI: 0.58-0.80), HR: 0.72 (95% CI: 0.61-0.84), HR: 0.80 (95% CI: 0.69-0.94)) (Table 4). Calcium channel blockers, diuretics, nitrates, coumarins and digoxin, however, were not significantly and independently associated with long-term mortality. In patients using β-blockers, no difference was observed between selective and non-selective β-blockers on the long-term outcome (selective β-blockers: HR of 1.31 (95% CI: 0.87-1.72)).

Table 2. The number of patients (%) receiving cardiac medication.

Medications	Total population (n=2420)
Statin	457 (19%)
β -Blocker	602 (25%)
Selective β-blockers	468 (19%)
Non-selective β-blockers	134 (6%)
Aspirin	542 (22%)
ACE-inhibitors	626 (26%)
Calcium channel blockers	677 (28%)
Dihydropyridines	460 (19%)
Non-dihydropyridines	217 (9%)
Coumarin	597 (25%)
Nitrates	568 (23%)
Diuretics	365 (15%)
Digoxin	159 (7%)

ACE-inhibitor = angiotensin-converting enzyme inhibitor**;**
Values are expressed as number (%) or mean +/-SD.

DISCUSSION

In this cohort study of consecutive patients referred to our center for the evaluation of PAD, we found that statins, β-blockers, aspirins and ACE-inhibitors were significantly associated with a reduction of all-cause mortality, independent of baseline clinical variables and independent of PAD severity.

HMC-Co-A reductase inhibitor drugs (statins) have been shown to reduce cardiovascular morbidity and mortality in high-risk patients [18-22]. The beneficial effect of statins may not only be due to its lipid-lowering effect, but also to the inhibition of the inflammatory processes of atherosclerosis [23]. It has been shown that a reduction in the inflammatory component through the use of statins improved the clinical outcome in patients with coronary artery disease, regardless of the reduction in cholesterol levels [24,25]. In patients with PAD, statin use has been demonstrated to favorably influence leg functioning, walking performance, ABI values and symptoms of claudication [26-28]. The association of statin use and superior leg functioning was also demonstrated in patients with an ABI of 0.90 to 1.49, which may reflect the favorable influence of statins on subclinical PAD [26]. A recent study by Schillinger et al showed that statin therapy was associated with an improved survival of patients with severe PAD with elevated high-sensitivity C-reactive protein levels (>0.42 mg/dL) [29]. The observation that patients with low inflammatory activity had no survival benefit supports the view that statins may exert beneficial effect though anti-inflammatory properties.

Table 3. Univariate and multivariate associations of clinical variables and overall mortality.

Characteristic	Univariate analysis	P-value	Multivariate analysis	P-value
	HR and 95% CI		HR and 95% CI	
Age >70 years	1.75 (1.55-1.97)	<0.001	1.68 (1.48-1.91)	<0.001
Male gender	1.08 (0.94-1.24)	0.3	1.05 (0.91-1.22)	0.5
Coronary artery disease	1.59 (1.41-1.80)	<0.001	1.39 (1.19-1.62)	<0.001
History of heart failure	2.69 (2.26-3.19)	<0.001	1.73 (1.42-2.11)	<0.001
History of cerebrovascular accident	1.55 (1.26-1.90)	<0.001	1.28 (1.04-1.57)	0.02
Diabetes Mellitus	1.42 (1.22-1.66)	<0.001	1.35 (1.15-1.60)	<0.001
Hypercholesterolemia	1.54 (1.29-1.84)	<0.001	1.77 (1.44-2.18)	<0.001
Hypertension	1.22 (1.08-1.38)	0.002	1.26 (1.10-1.45)	<0.001
Current smoking	1.25 (1.11-1.42)	<0.001	1.27 (1.12-1.44)	<0.001
Renal failure	3.81 (3.09-4.69)	<0.001	3.34 (2.68-4.16)	<0.001
Chronic pulmonary disease	1.52 (1.29-1.80)	<0.001	1.37 (1.15-1.65)	<0.001
Severe PAD (ABI ≤0.70)	1.40 (1.20-1.62)	<0.001	1.21 (1.05-1.41)	0.01
Abnormal electrocardiogram	1.71 (1.52-1.93)	<0.001	1.36 (1.17-1.59)	<0.001
Statin	0.65 (0.54-0.78)	<0.001	0.42 (0.34-0.53)	<0.001
Beta-blocker	0.76 (0.65-0.88)	<0.001	0.64 (0.55-0.75)	<0.001
Aspirin	0.87 (0.77-1.01)	0.08	0.78 (0.67-0.91)	0.002
ACE-inhibitors	1.13 (0.98-1.30)	0.08	0.80 (0.69-0.93)	0.004
Calcium channel blockers	1.14 (1.01-1.30)	0.04	1.04 (0.91-1.19)	0.6
Coumarins	1.15 (1.01-1.32)	0.03	1.13 (0.98-1.29)	0.08
Diuretics	1.22 (1.03-1.43)	0.02	0.82 (0.68-0.98)	0.03
Nitrates	1.36 (1.19-1.56)	<0.001	1.00 (0.86-1.16)	1.0
Digoxin.	1.91 (1.57-2.33)	<0.001	1.2 (1.01-1.57)	0.04

ABI = ankle brachial index;
ACE-inhibitor = angiotensin-converting enzyme inhibitor
PAD = peripheral arterial disease;

Table 4. Cox regression models, adjusted for baseline variables and propensity scores.

Medication	HR and 95% CI for overall death	P-value
	Adjusted for baseline variables and propensity scores	
Statin	0.46 (0.36-0.58)	<0.001
β-Blocker	0.68 (0.58-0.80)	<0.001
Aspirin	0.72 (0.61-0.84)	<0.001
ACE-inhibitors	0.80 (0.69-0.94)	0.005
Diuretics	0.85 (0.71-1.02)	0.09
Calcium-blockers	1.03 (0.90-1.18)	0.7
Nitrates	1.00 (1.86-1.16)	1.0
Coumarins	1.13 (0.98-1.29)	0.08
Digoxin.	1.21 (1.95-1.53)	0.1

ACE-inhibitor = angiotensin-converting enzyme inhibitor

Although β-blockers were considered relatively contraindicated in patients with PAD, several studies showed that β-blockers do not adversely affect walking capacity, symptoms of intermittent claudication and peripheral skin microcirculation [14-16]. β-Blockers are effective anti-hypertensive agents and improve prognosis in patients with ischemic heart disease and congestive heart failure and are thus indicated in a majority of patients with PAD. However, it seems that β-blockers have been underused by vascular surgeons and primary care providers, perhaps because of concerns that β-blockers will aggravate symptoms of intermittent claudication [30,31]. Patients with PAD are at increased risk for cardiovascular morbidity and mortality, and recent studies have demonstrated the beneficial effect of β -blockers in these patients. In a study cohort of 575 patients with symptomatic PAD and with a previous myocardial infarction, Aronow et al demonstrated that β-blocker therapy was associated with a 53% significant reduction in new coronary events, independent of other confounding variables [32]. This was confirmed in a more recently published study, which demonstrated a 3-fold reduction in cumulative cardiac mortality in 78 post-infarction patients with intermittent claudication who were treated with β-blocker therapy, compared to patients not treated with β-blocker therapy [33]. It has been shown that hemodynamic forces (blood pressure and heart rate) are associated with the development of disruption of the vulnerable plaque, which consists of an atheromatous plaque core covered by a thin fibrous cap with ongoing inflammation [34]. B-blockers may prevent plaque disruption by reducing heart rate and blood pressure. In addition, it can be hypothesized that anti-inflammatory properties of β-blockers may limit the phased progression of cardiovascular disease [35].
Antiplatelet drugs are now established agents for preventing cardiovascular and cerebrovascular ischemic events. However, a randomized controlled trial in patients with PAD demonstrating the effect of aspirin in reducing cardiovascular events still has to be awaited. The meta-analysis of the anti-thrombotic trialists collaboration showed a proportional reduction of 23% in serious vascular events among 9214 patients with PAD using antiplatelet therapy (primarily aspirin), compared to those using no antiplatelet therapy (5.8 vs. 7.1%, $p<0.004$) [36]. Limited information is available regarding the optimal antiplatelet treatment choice in patients with PAD. Potential adverse effects, including diarrhea, neutropenia and thrombotic thrombocytopenic purpura, may limit the use of ticlopidine. Based on current evidence, aspirin or clopidogrel seem to be the first-line oral antiplatelet drugs of choice.
ACE-inhibitors have been shown to inhibit the atherosclerotic process and to improve peripheral blood pressure and blood flow in patients with PAD [37]. The HOPE study investigators showed that ramipril significantly reduced the rate of mortality, myocardial infarction and stroke in 9297 high-risk patients without a low ejection fraction or heart failure [38]. A recent randomized placebo-controlled study demonstrated the effect of ramipril in patients with clinical or subclinical PAD for preventing major cardiovascular events [39]. Activation of the renin-angiotensin system seems to be associated with an increased risk of cardiovascular events. Growing evidence suggest that ACE-inhibitors directly inhibit the atherosclerotic process and improve vascular endothelial function [40, 41]. In addition, the benefit of ACE-inhibitors seems to be independent of the antihypertensive properties of these agents [42].
The results of our study are in accordance with previously published studies demonstrating the effect of statins, β-blockers, aspirin and ACE-inhibitors for reducing complications in patients with PAD. Several limitations of our study should be addressed. The major limitation of this study is that the use of cardiac medication was not randomly assigned to patients with PAD. However, properly conducted observational studies might not produce misleading or biased results [43]. Moreover, we used propensity analysis to adjust for selection bias and in multivariate analysis we adjusted for known possible confounding factors.
PAD is a highly prevalent disease and its presence should be a marker for atherosclerosis in other vascular beds. Although patients are at increased risk for cardiovascular morbidity and mortality, PAD seems to be undertreated and underdiagnosed. Therefore, the identification of patients with clinical or subclinical PAD is important for disease control and selection of appropriate treatment strategies. Conventional treatment strategies have focused on risk factor modification and antiplatelet therapy. Our study, as well as several other previously published studies, has proven the beneficial

effect of statins, β-blockers, aspirin and ACE-inhibitors. It might be hypothesized that its beneficial effects are exerted not only through their conventional therapeutic effects, but also through their plaque-stabilizing and anti-inflammatory properties. Based on current evidence, we suggest aggressive risk factor modification and pharmacological treatment in patients with PAD who are at increased risk of future cardiovascular events.

Conclusion

Based on this observational longitudinal study, statin, β-blocker, aspirin and ACE-inhibitor therapy are associated with a reduction in long-term mortality risk in patients with PAD, independent of clinical risk factors and adjusted for propensity scores. The use of cardiac medications as therapeutic and preventive agents in patients with PAD seems to be promising in reducing long-term mortality and could be incorporated among other management strategies, including walking exercise and risk factor modification. Future studies should be conducted to determine which patients with PAD would mostly benefit from statins, β-blockers, aspirin and ACE-inhibitor therapy.

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Chapter 7

The effect of intensified lipid-lowering therapy on long-term prognosis in patients with peripheral arterial disease

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The effect of intensified lipid lowering therapy on long-term prognosis in patients with peripheral arterial disease

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Context: HMG-CoA reductase inhibitors (statins) are associated with improved outcome in patients with peripheral arterial disease. Statins may also have beneficial properties beyond its lipid lowering effect.
Objective: To examine whether higher doses of statins and lower LDL-cholesterol levels are both independently associated with improved outcome in peripheral arterial disease.
Design, setting, participants: A prospective observational cohort study, conducted at a university hospital from 1990 to 2005. A total of 1374 consecutive patients (age: 61 ± 10 years, 73% male) with peripheral arterial disease (ankle-brachial index ≤0.90) were enrolled and screened for clinical risk factors, statin therapy and LDL-cholesterol levels. Serial LDL-cholesterol levels were measured at 6 months and every 1 year after enrollment. The mean follow-up time was 6.4 ± 3.6 years and no patients were lost to follow-up.
Main Outcome Measure(s): The primary endpoints of the study were all-cause and cardiac mortality. Secondary endpoint was the progression to kidney failure.
Results: Overall mortality, cardiac death and progression to kidney failure occurred in 29%, 20% and 5% of patients, respectively. Multivariate analysis revealed that higher doses of statins (per 10% increase) and lower 6-month LDL-cholesterol levels (per 10 mg/dL decrease) were both independently associated with lower all-cause mortality (HR: 0.71, 95% CI: 0.62-0.80 and HR: 0.96, 95% CI: 0.93-0.98, respectively) and cardiac death (HR: 0.76, 95% CI: 0.67-0.86 and HR 0.95, 95% CI: 0.92-0.98, respectively). Higher HDL-cholesterol levels also correlated significantly with lower all-cause and cardiac mortality. Higher doses of statins (per 10% increase) were associated with less progression to kidney failure (HR: 0.69, 95% CI: 0.54-0.89).
Conclusions: This study showed that higher doses of statins and lower LDL-cholesterol levels are both independently associated with improved outcome in patients with peripheral arterial disease. These results support the view that statins have beneficial effects beyond its lipid lowering properties and should be considered in all patients with PAD, irrespective of LDL-cholesterol levels.

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THE BENEFICIAL PROPERTIES of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) beyond the lipid-lowering effect include atherosclerotic plaque stabilization, oxidative stress reduction and decrease in vascular inflammation [1]. It has been shown that a reduction in the inflammatory component through the use of statins improved the clinical outcome in patients with coronary artery disease [2,3].

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and has been recognized as a growing health burden worldwide [4]. Prevalence rates up to 29% have been reported for PAD in the United States, depending on the age of the study cohort, the underlying atherosclerosis risk factor profile, and the presence of cardiovascular co-morbidities [5]. In patients with PAD, statin use has been demonstrated to favorably influence leg functioning, walking performance, ABI values, symptoms of claudication, and mortality [6-8]. The guidelines of the American College of Cardiology/American Heart Association on the management of patients with PAD recommend statin treatment in all patients with PAD to achieve a target low-density lipoprotein cholesterol level less than 100 mg per dL [4]. Despite the use of statin therapy, mortality and morbidity among patients with PAD remain high [5]. In addition, patients with low ankle-brachial index values are at risk of progressive renal dysfunction which may be due to the underlying atherosclerotic risk profile [9]. In these patients, statins may also exert a renoprotective effect.

We hypothesized that intensive statin treatment improves outcome in patients with PAD and may have a beneficial effect on long-term outcome due to properties other than reducing cholesterol levels. In a large observational cohort study, we therefore sought to determine the independent effect of high-dose statin therapy and low target LDL-cholesterol levels on all-cause mortality, cardiac death and progression to kidney dysfunction during a long-term follow-up period in patients with PAD. In this observational study, we used propensity analysis to adjust for selection bias in the comparison of treatments.

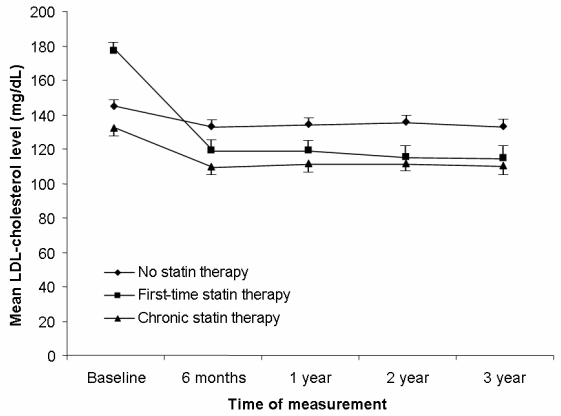

Figure 1. Mean LDL-cholesterol level (standard error of the mean) at different times of measurement.

METHODS

Study design and participants

This was a single-center observational cohort study of 1374 consecutive patients with PAD who were referred to our university clinic for ankle-brachial index measurement, clinical evaluation and therapeutic management between January 1990 and January 2005. Patients presented with typical symptoms of PAD including typical intermittent claudication or other symptoms of chronic arterial insufficiency, such as ulceration of the foot, hair loss, or reduced capillary refill. Patients eligible for the study had to be older than 18 years of age and only patients with an ankle-brachial index (ABI) of 0.90 or less were included. Patients were excluded from the study if they had a myocardial infarction or coronary revascularization procedure within the previous 6 months, or if they presented with chronic liver disease (cirrhosis or hepatitis). All patients agreed on participation in the study after given informed consent and the study was conducted according to the declaration of Helsinki. The Institutional Review Board approved the protocol. During the first visit, patients were screened for clinical risk factors, ankle-brachial index values, 12-lead electrocardiographic abnormalities, serum cholesterol levels and medication use. Diabetes mellitus was recorded if patients presented with a fasting glucose level of ≥7.0 mmol/L, or in those who required treatment. Hypertension was recorded if patients presented with a blood pressure ≥140/90 mmHg or if patients were medically treated for hypertension. Renal dysfunction was recorded if patients presented with a serum creatinine level ≥ 2.0 mg/dL (177 μmol/L) or in those who required dialysis. Smoking included only current smoking. Clinical data were prospectively collected and stored into a computerized registry. Risk factor reduction, life style modification and a lipid-lowering diet were encouraged in all patients presenting with clinical risk factors.

Ankle-brachial index measurement

Systolic blood pressures in the right and left brachial artery, right and left dorsalis pedis artery and right and left posterior tibial artery were measured by trained technicians, using a Doppler ultrasonic instrument with an 8 MHz vascular probe (Imexdop CT+ Vascular Doppler, Miami Medical, USA). The ankle-brachial index in the right and left leg was calculated by dividing the right and the left ankle pressure by the brachial pressure. The higher of the two brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Again, the higher of the dorsalis pedis and posterior tibial artery pressure was used when a discrepancy in systolic blood pressure between the two arteries was measured. If no pressure in the dorsalis pedis artery was obtained due to a congenitally absent or occluded dorsalis pedis artery, the pressure in the posterior tibial artery was used. The ankle-brachial index was measured after the participants had been resting in the supine position for at least 10 minutes. Of the ankle-brachial index values obtained in each leg, the lower was used in all analyses. Inter- and intra-observer agreement for the ankle-brachial index was 97% and 98%, respectively.

Statin therapy and cholesterol measurements

During the initial visit, patients were screened for statin use. The duration of statin treatment prior to enrollment was recorded in patients who were already being treated with statins (chronic statin users). In non-statin users presenting with indications for cholesterol reduction, statins were prescribed according to standard guidelines of the Erasmus Medical Center (first-time statin users). According to these guidelines, statin treatment was indicated in patients with hypercholesterolemia (LDL-cholesterol >200 mg/dL). After 2003, LDL-cholesterol level was targeted to levels less than 100 mg/dL. During the initial visit, the daily dosage of statin therapy was recorded and converted to a percentage value of the

maximum recommended therapeutic dose (MRTD) according to the FDA's Center for Drug Evaluation and Research database [10]. During follow-up, patients were monitored for medication adherence and for the occurrence of side effects, which included myopathy, elevated serum transaminases, rhabdomyolysis, proteinuria and diarrhea or nausea. Serial cholesterol levels were measured at 6 months and every year after the initial visit. Measurements were obtained with an automated enzymatic method and included low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides and total cholesterol. Cholesterol measurements at 6-months were obtained in all patients and these values were used for survival analysis. Cholesterol measurements at 1 year , 2 year and 3 year were obtained in 1281 patients (93%), 1219 patients (89%), and 1110 patients (81%), respectively.

Definition of study endpoints

Primary endpoints of the study were all-cause mortality and cardiac death. Information about the patient's vital status was obtained at the Office of Civil Registry. For patients who died at our hospital during follow-up, hospital records and autopsy results were reviewed. For patients who died outside our hospital, death certificates were reviewed and general practitioners were approached to ascertain the cause of death. A cardiac cause of death was defined as death caused by cardiac arrhythmias, congestive heart failure or acute myocardial infarction (post-mortem evidence of acute myocardial infarction or the presence of at least two of the following within the 4 weeks prior to death: elevated cardiac enzyme levels (CK level > 190 U/L and CK-MB >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/mL), development of typical electrocardiographic changes (new Q waves >1 mm or > 30 ms), and typical symptoms of angina pectoris). Sudden unexpected death in a previously stable patient was also considered cardiac death if pathology did not reveal a conclusive cause of death.

Secondary endpoint was progression to kidney failure. Serum creatinine measurements were regularly obtained during follow-up visits and the estimated glomerular filtration rate (eGFR) was calculated using the following equation: glomerular filtration rate (ml/min/1.73 m^2) = 186 x (serum creatinine level)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.210 if of African descent) [11]. Kidney failure was defined as eGFR less than 15 ml/min per 1.73 m^2 or a need to start kidney replacement therapy, which included dialysis or renal transplantation.

Data analysis

Continuous data were compared using the Student t test or the Mann-Whitney U test, when appropriate.

Categorical data were compared using the Chi square test. Group comparisons were performed with analysis of variance (ANOVA) techniques. Univariate and multivariate Cox proportional hazard regression analysis was used to evaluate the effect of statin therapy and cholesterol levels on the study endpoints. All clinical risk factors were entered in multivariate analysis, irrespective of the significance level in univariate analysis. Statin therapy was not randomly assigned in these patients and the impact of selection bias may distort the results of our study. Propensity analyses are reliable tools to correct for selection bias and the rationale for using propensity scores has been described previously [12]. Therefore, propensity scores for statin therapy were calculated, which were constructed by using multiple logistic regression analysis. Variables as listed in Table I that were independently associated with the decision to prescribe statins ($p<0.25$) were included in the multivariate propensity score. In propensity analysis, important

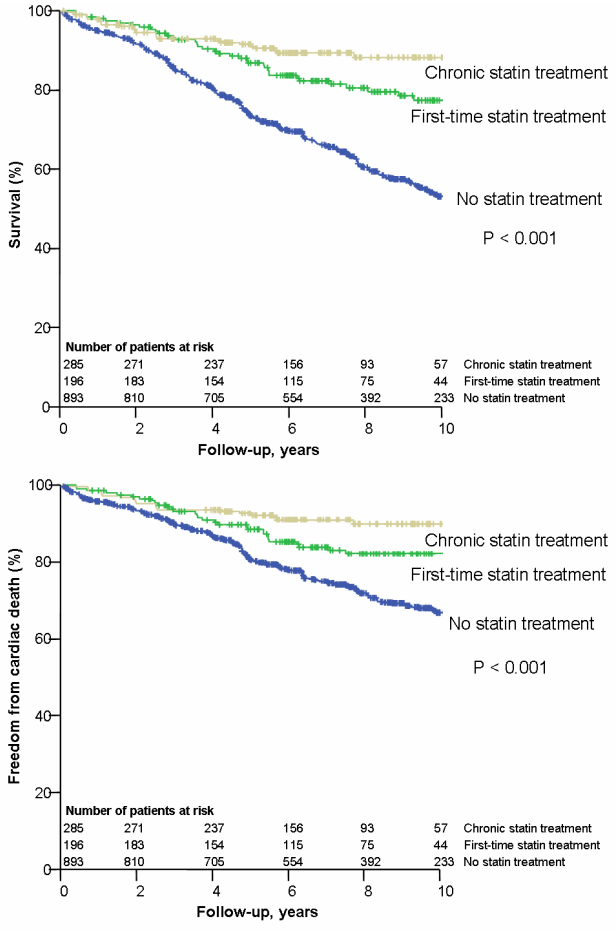

Figure 2. Kaplan-Meier curves for all-cause mortality (a) and cardiac death (b) stratified according to the duration of statin therapy.

Table I. Baseline characteristics of the patients.

Characteristic	Total population (n=1374)
Age (years), mean ± SD	61 ± 10
Male gender, no (%)	1001 (72.9)
Angina pectoris, no (%)	345 (25.1)
Previous myocardial infarction, no (%)	484 (35.2)
History of congestive heart failure, no (%)	102 (7.4)
Previous coronary artery bypass grafting, no (%)	264 (19.2)
Previous percutaneous coronary intervention, no (%)	84 (6.1)
History of stroke or transient ischemic attack, no (%)	105 (7.6)
Diabetes mellitus, no (%)	232 (16.9)
Hypertension, no (%)	602 (43.8)
Current smoking, no (%)	385 (28.0)
Renal failure, no (%)	83 (6.0)
Chronic obstructive pulmonary disease, no (%)	139 (10.1)
Q waves, no (%)	348 (25.3)
ST segment changes	250 (18.2)
Left bundle branch block, no (%)	62 (4.5)
Right bundle branch block, no (%)	30 (2.2)
Ankle-brachial index at rest, mean ± SD	0.60 ± 18
Aspirin, no (%)	353 (25.7)
Angiotensin-converting enzyme inhibitor, no (%)	397 (28.9)
Beta-blocker, no (%)	443 (32.2)
Calcium channel blocker, no (%)	453 (32.9)
Statins, no (%)	481 (35.0)
LDL-cholesterol level (mg/dL), mean ± SD	144 ± 51
HDL-cholesterol level (mg/dL), mean ± SD	44 ± 19
Triglyceride level (mg/dL), mean ± SD	194 ± 158
Total cholesterol level (mg/dL), mean ± SD	215 ± 55
Ratio of LDL-cholesterol to HDL-cholesterol	3.2 ± 1.5
Ratio of total cholesterol to HDL-cholesterol	5.3 ± 2.6

variables (p<0.001) associated with the prescription of statin therapy were high baseline LDL-cholesterol levels, coronary artery disease, smoking, male gender, diabetes mellitus and previous coronary intervention. The propensity score ranged from 0.03 to 0.93. The Kaplan-Meier method with the log-rank test was used to assess differences in survival between different groups of patients. For all tests, a P value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics

Baseline characteristics of the 1374 study participants are presented in Table I. The mean age was 61 ± 10 years and 1001 patients (73%) were male. The mean ABI was 0.60 ± 0.18 and ranged from 0.05 to 0.90. ABI of 0.70 or less was identified in 1070 patients (78%). During the initial visit, 285 patients (21%) presented with chronic statin therapy and statin therapy was started in 196 patients (14%). The following statins were used in our study cohort: simvastatin in 293 patients, pravastatin in 55, fluvastatin in 15 patients, atorvastatin in 88 patients, and rosuvastatin in 30 patients. In patients with chronic statin therapy, median duration of statin therapy prior to enrollment was 3.1 years (interquartile range: 1.3-5.0 years). The mean percentage (±SD) of maximum recommended dose was 37 ± 27% in first-time statin users and 34 ± 27% in chronic statin users (p=0.30).

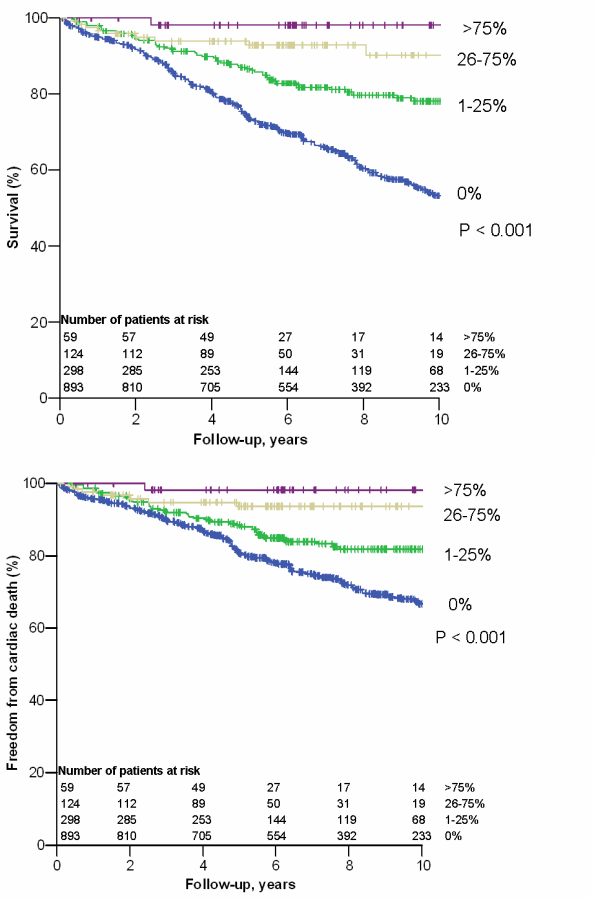

Figure 3. Kaplan-Meier curves for all-cause mortality (a) and cardiac death (b) stratified according to the dose of statin therapy, expressed as percentage of maximum recommended therapeutic dose (MRTD).

Figure 1 demonstrates mean LDL-cholesterol levels at baseline and during follow-up stratified according to no, chronic or first-time statin use. A reduction of LDL-cholesterol at 6 months from baseline values was observed in 900 patients (66%). A total of 257 patients (19%) had a LDL-cholesterol reduction of more than 35%. Higher statin doses were significantly associated with larger reductions in LDL-cholesterol (β-coefficient: -0.24, p<0.0001). Six months after enrollment, 423 patients (30.8%) had a LDL-cholesterol level less than 100 mg/dL and 133 patients (9.7%) had a LDL-cholesterol less than 70 mg/dL.

Follow-up

During a mean follow-up time of 6.4 ± 3.6 years, death was recorded in 404 patients (29%) and cardiac death in 278 patients (20%). Non-cardiac causes of death were renal disease in 23 patients (2%), respiratory failure in 32 patients (2%), cancer in 23 patients (2%), stroke in 21 patients (2%), sepsis in 12 patients (1%) and other or unknown causes in 15 patients (1%). During follow-up, 68 patients (5%) progressed to kidney failure. Statin therapy during follow-up was discontinued in 6 patients (1%) due to myopathy and in 3 patients (1%) due to nausea and/or diarrhea. Kaplan-Meier survival curves demonstrate that first-time and chronic statin users were at significantly lower risk for all-cause mortality (p<0.001) and cardiac death (p<0.001), compared to patients who were not using statins (Figure 2). An improved survival (p<0.001) and freedom from cardiac death (p<0.001) was also observed in patients who were using higher doses of statin therapy (Figure 3). Figure 4 demonstrates that all-cause mortality (15%) and cardiac death (10%) were lowest in patients with the largest percentage LDL-cholesterol reduction (reduction >35%) (p<0.001 and p<0.001, respectively). Figure 5 demonstrates the incidence of overall and cardiac mortality stratified according to different LDL-cholesterol levels at 6 months. The lowest all-cause mortality rate (18%) and cardiac death rate (13%) was observed in the group of patients with LDL-cholesterol levels less than 70 mg/dL (p<0.001 and p<0.001, respectively). Overall and cardiac mortality rates were gradually increasing in patients with higher 6-month LDL-cholesterol levels (p<0.001 and p<0.001, respectively).

Multivariate analysis

Cox hazard regression analysis with adjustment for clinical variables, ABI values, electrocardiography and propensity scores demonstrated that chronic statin therapy, higher doses of statin therapy, larger reductions in LDL-cholesterol during the first 6 months and lower LDL-cholesterol levels at 6-month were significantly

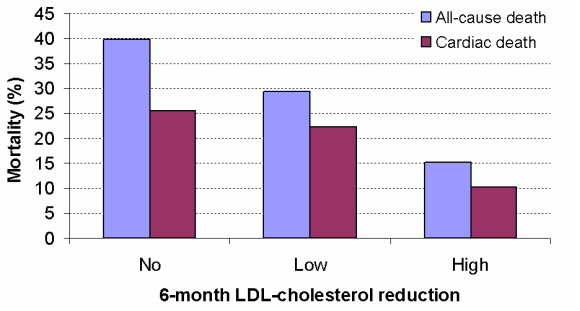

Figure 4. The estimated incidence of overall mortality and cardiac death at 10 years of follow-up in patients with no, low (1-35%) and high (>35%) 6-months LDL-cholesterol reduction from baseline values.

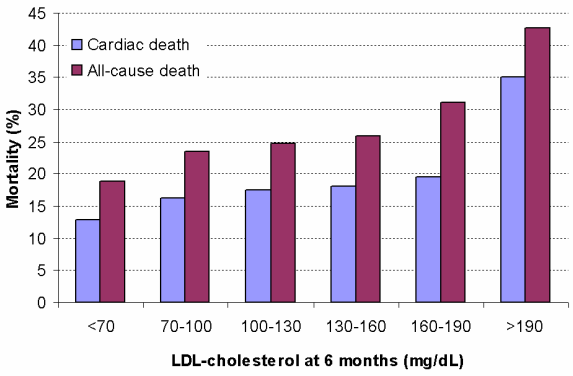

Figure 5. The estimated incidence of overall mortality and cardiac death at 10 years of follow-up in patients with varying LDL-cholesterol levels after 6 months of study enrollment.

associated with a lower risk of overall and cardiac mortality (Table II and III). Higher triglyceride concentrations, higher total cholesterol levels, a higher LDL/HDL-cholesterol ratio and a higher total/HDL-cholesterol ratio at 6 months also proved to be significantly correlated with higher all-cause and cardiac mortality rate (Table II and III). Higher mean cholesterol levels during follow-up were also significantly associated with adverse outcome (Table II and III). A final multivariate model including statin dose, baseline and 6-month cholesterol levels supported our hypothesis that higher statin doses (per 10% increase) and lower 6-month LDL-cholesterol levels (per 10 mg/dL decrease) were both independently associated with lower all-cause mortality (HR: 0.71, 95% CI: 0.62-0.80 and HR: 0.96, 95% CI: 0.93-0.98, respectively) and cardiac death (HR: 0.76, 95% CI:0.67-0.86 and HR 0.95, 95% CI: 0.92-0.98, respectively).

Table II. Univariate and multivariate Cox proportional hazards models to predict overall mortality.

	Univariate HR (95% CI)	P value	Multivariate* HR (95% CI)	P value
Statin therapy at enrollment				
No statins (reference group)	1.0		1.0	
First-time statin therapy	0.42 (0.30-0.59)	<.001	0.37 (0.25-0.54)	<.001
Chronic statin therapy	0.27 (0.18-0.39)	<.001	0.24 (0.16-0.37)	<.001
Statin dose (per 10% increase)**	0.70 (0.63-0.77)	<.001	0.69 (0.61-0.77)	<.001
LDL-cholesterol reduction (per 10%)***	0.94 (0.91-0.97)	<.001	0.93 (0.90-0.96)	<.001
Cholesterol levels at 6 months				
LDL-cholesterol (per 10 mg/dL decrease)	0.96 (0.93-0.98)	<.001	0.97 (0.94-0.99)	.009
HDL-cholesterol (per 10 mg/dL increase)	0.94 (0.87-1.01)	.09	0.94 (0.86-1.03)	.17
Triglycerides (per 10 mg/dL decrease)	0.99 (0.98-1.00)	.02	0.99 (0.98-1.00)	.01
Total cholesterol (per 10 mg/dL decrease)	0.94 (0.92-0.97)	<.001	0.94 (0.90-0.97)	<.001
LDL/HDL-cholesterol	1.16 (1.08-1.24)	<.001	1.13 (1.05-1.22)	<.001
Total/HDL-cholesterol	1.12 (1.06-1.17)	<.001	1.13 (1.07-1.19)	<.001
Mean cholesterol levels during follow-up				
LDL-cholesterol (per 10 mg/dL decrease)	0.94 (0.92-0.96)	<.001	0.95 (0.92-0.97)	<.001
HDL-cholesterol (per 10 mg/dL increase)	0.89 (0.82-0.97)	.004	0.90 (0.82-0.98)	.02
Triglycerides (per 10 mg/dL decrease)	0.99 (0.98-1.00)	.1	0.99 (0.98-1.00)	.04
Total cholesterol (per 10 mg/dL decrease)	0.94 (0.91-0.97)	<.001	0.95 (0.91-0.98)	<.001
LDL/HDL-cholesterol	1.26 (1.17-1.35)	<.001	1.24 (1.15-1.34)	<.001
Total/HDL-cholesterol	1.16 (1.08-1.25)	<.001	1.17 (1.07-1.27)	<.001

*Adjusted for clinical risk factors, ankle-brachial index values, electrocardiography and propensity scores. **Expressed as percentage of maximum recommended therapeutic dose. ***The relative reduction (%) in LDL-cholesterol at 6-months from baseline measurements.

Table III. Univariate and multivariate Cox proportional hazards models to predict cardiac mortality.

	Univariate HR (95% CI)	P value	Multivariate* HR (95% CI)	P value
Statin therapy at enrollment				
No statins (reference group)	1.0		1.0	
First-time statin therapy	0.53 (0.36-0.78)	.001	0.44 (0.29-0.68)	<.001
Chronic statin therapy	0.34 (0.22-0.52)	<.001	0.28 (0.17-0.46)	<.001
Statin dose (per 10% increase)**	0.74 (0.67-0.82)	<.001	0.71 (0.63-0.80)	<.001
LDL-cholesterol reduction (per 10%)***	0.95 (0.91-0.99)	.01	0.94 (0.90-0.98)	.004
Cholesterol levels at 6 months				
LDL-cholesterol (per 10 mg/dL decrease)	0.95 (0.92-0.98)	<.001	0.95 (0.93-0.98)	<.001
HDL-cholesterol (per 10 mg/dL increase)	0.91 (0.88-0.99)	.04	0.90 (0.82-0.98)	.01
Triglycerides (per 10 mg/dL decrease)	0.98 (0.98-0.99)	<.001	0.99 (0.98-0.99)	<.001
Total cholesterol (per 10 mg/dL decrease)	0.93 (0.90-0.96)	<.001	0.92 (0.89-0.96)	<.001
LDL/HDL-cholesterol	1.16 (1.07-1.26)	<.001	1.15 (1.06-1.25)	<.001
Total/HDL-cholesterol	1.15 (1.09-1.20)	<.001	1.16 (1.10-1.23)	<.001
Mean cholesterol levels during follow-up				
LDL-cholesterol (per 10 mg/dL decrease)	0.93 (0.90-0.96)	<.001	0.94 (0.91-0.96)	<.001
HDL-cholesterol (per 10 mg/dL increase)	0.88 (0.80-0.97)	.008	0.87 (0.78-0.96)	.008
Triglycerides (per 10 mg/dL decrease)	0.99 (0.98-1.00)	.01	0.98 (0.97-0.99)	.004
Total cholesterol (per 10 mg/dL decrease)	0.92 (0.89-0.96)	<.001	0.93 (0.89-0.97)	<.001
LDL/HDL-cholesterol	1.23 (1.13-1.35)	<.001	1.22 (1.12-1.34)	<.001
Total/HDL-cholesterol	1.19 (1.10-1.29)	<.001	1.21 (1.10-1.33)	<.001

*Adjusted for clinical risk factors, ankle-brachial index values, electrocardiography and propensity scores. **Expressed as percentage of maximum recommended therapeutic dose. ***The relative reduction (%) in LDL-cholesterol at 6-months from baseline measurements.

Secondary endpoint outcome

Multivariate analysis demonstrated that first time statin users and chronic statin users were at lower risk of progression to kidney failure, compared to patients not using statins (HR: 0.16, 95% CI: 0.04-0.65 and HR: 0.29, 95% CI: 0.12-0.71, respectively). In addition, higher doses of statin therapy were associated with a lower occurrence of the secondary endpoint of kidney failure (HR per 10% increase: 0.69, 95% CI: 0.54-0.89), independent of baseline characteristics and cholesterol levels. In the same model, a non-significant association was observed between lower 6-month LDL-cholesterol levels (per 10 mg/dL decrease) and a lower rate of kidney failure (HR: 0.97, 95% CI: 0.91-1.03).

DISCUSSION

The present study shows that intensified statin therapy and lower target LDL-cholesterol levels are significantly associated with improved survival in patients with PAD. The beneficial effects of higher statin doses and lower target LDL-cholesterol levels were independent of each other and independent of the presence of clinical risk factors, ABI values, electrocardiography and propensity scores for statin therapy. These findings suggest the importance of achieving low target LDL-cholesterol levels in patients with PAD. Secondly, they suggest that statins have beneficial long-term effects, due to properties other than reducing cholesterol levels.

Statins in peripheral arterial disease

The Heart Protection Study provided convincing evidence that 40 mg of daily simvastatin significantly lowered the risk of vascular events in 6748 patients with PAD, when compared to placebo [13]. During 5 years of follow-up, first major vascular events were observed in 26% of statin users versus 33% in placebo-allocated patients [13]. Schillinger and colleagues also demonstrated that statin therapy was associated with improved survival in patients with severe PAD with elevated high-sensitivity C-reactive protein levels [14]. Several earlier studies have confirmed the beneficial effects of statins on symptoms of claudication, walking performance, ABI values and leg functioning [6-8].

LDL-cholesterol threshold in coronary artery disease

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines and the European guidelines on cardiovascular disease prevention in clinical practice recommend a target LDL-cholesterol level less than 100 mg/dL in persons with (risk equivalents of) coronary artery disease [15,16]. Recent clinical trials have shown the beneficial effect of LDL-cholesterol levels below 100 mg/dL on cardiovascular outcome. The Treating to New Targets trial showed that intensive lipid-lowering therapy with 80 mg of daily atorvastatin significantly reduced first major cardiovascular event rate during a median follow-up of 5 years, compared to 10 mg of daily atorvastatin (8.7% vs. 10.9%, respectively) [17]. Mean LDL cholesterol levels were 77 mg/dL during 80 mg atorvastatin treatment and 101 mg/dL during 10 mg atorvastatin treatment [17]. Cannon and colleagues enrolled patients after acute coronary syndromes and compared 40 mg of pravastatin to 80 mg of atorvastatin [18]. Median LDL-cholesterol levels during treatment were 95 mg/dL and 62 mg/dL, respectively. After 2 years of follow-up, a 16% reduction in the hazard ratio was found in favor of atorvastatin. Nissen and colleagues demonstrated that intensive treatment with 80 mg of atorvastatin (mean LDL-cholesterol level: 79 mg/dL) reduced the percentage change in atheroma volume, compared to 40 mg of pravastatin (mean LDL-cholesterol level: 110 mg/dL) [19]. Moreover, it has been demonstrated that intensive 40 mg rosuvastatin therapy with mean LDL-cholesterol reduction of 53.2% to a mean LDL-cholesterol of 61 mg/dL resulted in significant regression of atherosclerosis during serial intravascular ultrasound examinations [20].

Recommendations in PAD

After the revision of the NCEP Adult Treatment Panel III guidelines in July 2004 [21], the American College of Cardiology/American Heart Association has recommended in “very high” risk patients with PAD a LDL-cholesterol level <70 mg/dL [4]. Very high risk patients included those with established PAD plus multiple major risk factors, severe and poorly controlled risk factors or multiple risk factors of the metabolic syndrome. These recommendations have mainly been extrapolated from studies including patients with coronary artery disease or from post hoc analysis of patients with PAD [13]. The current study suggests that all patients with ankle-brachial index values less than 0.90 may benefit from LDL-cholesterol levels less than 70 mg/dL. Although much attention has given to LDL-cholesterol as measure of risk, our study demonstrated that higher HDL-cholesterol, lower triglyceride, lower total cholesterol, lower LDL/HDL-cholesterol and total/HDL-cholesterol ratio were also significant correlates of improved survival.

Pleiotropic effects of statins

In the current study, higher statin doses were associated with improved outcome independent of LDL-cholesterol levels, suggesting that other than lipid-lowering properties of statins are beneficial in PAD patients. The cholesterol-independent effects of statins have been suggested in previous studies. In human carotid plaques, statins decrease lipids, lipid oxidation, inflammation, matrix metalloproteinase 2 and cell death and increase tissue inhibitor of metalloproteinase 1 and collagen, suggesting a plaque-stabilizing effect [22]. Studies also demonstrated that statins lower the concentration of C-reactive protein and improve the outcome in patients with coronary artery disease, independent of the effect on LDL-cholesterol levels [2,3,23]. Therefore, long-term intensive statin therapy should be considered in all patients with PAD.

Statins and renal outcome

Atherosclerosis is now becoming a recognized cause of renal deterioration. Experimental studies have suggested

a preventive effect of statins on nephropathy by halting extracellular matrix accumulation, overexpression of connective growth factors [24], and tubular-interstitial fibrosis [25]. A meta-analysis showed that statins can reduce proteinuria or albuminuria, especially in patients with cardiovascular disease [26]. Finally, a recent study demonstrated in 103 consecutive patients with hyperlipidemia and PAD that creatinine levels decreased after 3-4 months of treatment with simvastatin, independent of the degree of low-density lipoprotein cholesterol reduction [27]. In the current study, every 10% increase in statin dose was associated with a 31% lower risk of progression to kidney failure, irrespective of cholesterol levels. However, these results should be interpreted in the context of the study design in which the occurrence of kidney failure was relatively low (5%).

Study limitations

The findings apply to patients with PAD referred to a university hospital. Adverse outcome rates may therefore be higher than in the general population. The study population consisted mostly of Caucasian men with a high prevalence of cardiovascular risk factors. The study was observational in nature and the major limitation which should be addressed is that statins were not assigned in a random fashion. However, in multivariate analysis we have adjusted for known possible confounding factors and for the propensity to prescribe statin therapy to reduce a possible selection bias [28]. This study did not systematically recorded the number of patients who became eligible for statin therapy during follow-up. Since analysis was based on treatment at enrolment, the results for statin therapy may have been underestimated, assuming that all patients with statin treatment continued their medication. Before recommending low LDL-cholesterol levels and high statin doses in all patients with PAD, it should be noted that concerns about the safety of very low cholesterol levels have been raised, as cholesterol plays an important role in cell membrane composition and in neuronal and optic development. In addition, higher statin doses may result in higher rates of side effects, such as treatment-related myalgia and liver toxicity [29]. Future studies should further evaluate the safety of high-dose statin therapy and very-low LDL-cholesterol concentrations in patients with PAD.

Conclusion

In conclusion, the current prospective observational cohort study of 1374 patients with peripheral arterial disease demonstrated that intensified statin therapy and lower target LDL cholesterol levels are independently associated with improved outcome. Target LDL-cholesterol levels below 70 mg/dL were associated with the lowest overall and cardiac mortality rate during a mean follow-up of 6 years. Higher statin doses were also associated with a lower occurrence of progression to kidney failure. The current results support the view that statins have beneficial effects beyond its lipid lowering properties and should be considered in all patients with PAD, irrespective of LDL-cholesterol levels.

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Chapter 8

Lower progression rate of end-stage renal disease in patients with peripheral arterial disease using statins or angiotensin-converting enzyme inhibitors

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Lower progression rate of end-stage renal disease in patients with peripheral arterial disease using statins or angiotensin-converting enzyme inhibitors

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Background. Patients with peripheral atherosclerotic disease (PAD) are at increased risk of end-stage renal disease and cardiovascular events.
Aim. Primary objective was to assess the association between ankle-brachial index values and renal outcome. Secondary objective was to evaluate whether statins and angiotensin-converting enzyme (ACE-)inhibitors are associated with improved renal and cardiovascular outcome in patients with PAD
Methods. In a prospective observational cohort study of 1,940 consecutive patients with PAD, ankle-brachial index was measured and chronic statin and ACE-inhibitor therapy was noted at baseline. Serial creatinine concentrations were obtained at baseline, 6 months and every year after enrolment. Endpoints were end-stage renal disease, all-cause mortality and cardiac events during a median follow-up period of 8 years.
Results: Baseline eGFR <60 ml/min/1.73 m^2 was assessed in 27% of patients. End-stage renal disease, all-cause mortality and cardiac events occurred in 10%, 46% and 31% of patients, respectively. In multivariate analysis, a lower baseline ankle-brachial index was significantly associated with a higher progression rate of end-stage renal disease (HR per 0.10 decrease: 1.34, 95% CI: 1.21-1.49). Chronic use of statins and ACE-inhibitors were significantly associated with lower end-stage renal disease (HR [95% CI]: 0.41 [0,28-0.63] and 0.74 [0.54-0.98], respectively), mortality (HR [95% CI]: 0.66 [0.55-0.82] and 0.84 [78-0.95], respectively) and cardiac events (HR [95% CI]: 0.71 [0.56-0.91] and 0.81 [0.68-0.96], respectively).
Conclusion. In patients with PAD, low ankle-brachial index values independently predict the onset of end-stage renal disease. Less progression towards end-stage renal disease and improved cardiovascular outcome was observed among patients with chronic statins and ACE-inhibitors.

LOWER EXTREMITY peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and has been recognized as a growing health burden worldwide [1]. In the United states, prevalence rates for PAD have been reported ranging from 4% in patients 40 years and older to 29% in patients older than 70 years or aged 50 to 59 years with a history of smoking or diabetes mellitus [2-6].

The prevalence and incidence of PAD is high among patients with renal insufficiency [7-9]. Little information is available about the prognostic value of renal insufficiency in patients with peripheral arterial disease, although this may be useful to identify high risk patients who may benefit from subsequent medical therapy. [10]. Due to atherosclerotic lesions in the renal artery or renal microvascular system, patients with PAD may be at increased risk of developing end-stage renal disease. The association between the extent of atherosclerosis, as defined by ankle-brachial index (ABI) values, and the onset of end-stage renal disease remains ill-defined.

Several studies have suggested that statins and angiotensin-converting enzyme (ACE) inhibitors can slow or halt the progression of chronic kidney disease [11]. Given the fact that statins and ACE-inhibitors can inhibit the atherosclerotic process and reduce cardiovascular events [12-15], a beneficial effect of statins and ACE-inhibitors on renal outcome may be anticipated in patients who present with lower extremity PAD

In this observational cohort study, our primary aim was to determine the association between baseline ABI values and renal outcome in patients with PAD. Our secondary objective was to evaluate whether chronic use of statins and ACE-inhibitors was associated with a lower progression rate of end-stage renal disease, mortality and cardiovascular events during long-term follow-up.

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METHODS

Study participants

This was a single-center observational cohort study of consecutive patients with PAD who were referred to the Erasmus Medical Center between January 1988 and January 2006. The Erasmus MC serves a population of approximately 3 million people and acts as a tertiary referral enter for approximately 30 affiliated hospitals. Patients were referred for ABI measurement, clinical evaluation and therapeutic management. These patients presented with symptoms of PAD, which included typical intermittent claudication or other symptoms of chronic arterial insufficiency, such as ulceration of the foot, hair loss, or reduced capillary refill. Patients eligible for the study had to be older than 18 years of age and only patients with an ABI of 0.90 or less were included. Patients with one or more episodes of dialysis during the 6 months prior to enrolment were excluded. All patients agreed on participation in the study and the study was conducted according to the declaration of Helsinki. During the first visit, patients were screened for clinical risk factors, ABI values and 12-lead electrocardiographic abnormalities. The chronic use of statins and ACE-inhibitors was ascertained if patients were taking these medications for at least 1 year after the first visit. According to the hospital's protocol, ACE-inhibitors were not prescribed in patients presenting with significant bilateral renal artery stenosis (>70% or >50% with post-stenotic dilatation), stenosis to a solitary kidney or to patients with decompensated congestive heart failure in a sodium-depleted state. Diabetes mellitus was recorded if patients presented with a fasting glucose level of ≥126 mg/dL (7.0 mmol/L), or in those who required treatment. Hypertension was recorded if patients presented with a blood pressure ≥140/90 mmHg or if patients were medically treated for hypertension. Smoking included only current smoking. A baseline electrocardiogram was obtained in all patients and was considered abnormal in the presence of one or more of the following: Q waves, left ventricular hypertrophy, left bundle branch block, right bundle branch block or atrial fibrillation. Clinical data were prospectively collected and stored into a computerized database. Risk factor reduction and life style modifications were encouraged in all patients presenting with clinical risk factors. During follow-up visits, blood pressure was monitored to achieve levels less than 140/90 mmHg or less than 130/80 mmHg for those with diabetes or kidney disease.

Ankle-brachial index measurement

Systolic blood pressures in the right and left brachial artery, right and left dorsalis pedis artery and right and left posterior tibial artery were measured by trained technicians, using a Doppler ultrasonic instrument with an 8 MHz vascular probe (Imexdop CT+ Vascular Doppler, Miami Medical, USA). The ABI in the right and left leg was calculated by dividing the right and the left ankle pressure by the brachial pressure. The higher of the two brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Again, the higher of the dorsalis pedis and posterior tibial artery pressure was used when a discrepancy in systolic blood pressure between the two arteries was measured. If no pressure in the dorsalis pedis artery was obtained due to an absent dorsalis pedis artery, the pressure in the posterior tibial artery was used. The ABI was measured after the participants had been resting in the supine position for at least 10 minutes. Of the ABI values obtained in each leg, the lower was used in all analyses. Inter- and intra-observer agreement for the ABI was 97% and 98%, respectively.

Renal function

In all patients, a baseline serum creatinine level was obtained during the first visit from a central laboratory. Using serum creatinine, age, gender and race, the eGFR was calculated by the following equation: glomerular filtration rate (ml/min/1.73 m^2) = 186 x (serum creatinine level)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.210 if of African descent) [16,17]. Patients were classified according to the level of renal function as recommended by the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation: normal renal function (eGFR ≥90 ml/min per 1.73 m^2), mildly reduced renal function (eGFR 60-89 ml/min per 1.73 m^2), moderately reduced renal function (eGFR 30-59 ml/min per 1.73 m^2), severely reduced renal function (eGFR 15-29 ml/min per 1.73 m^2) and kidney failure (eGFR <15 ml/min per 1.73 m^2). During regularly scheduled follow-up visits, serial creatinine levels were measured at 6 months, 1 year and every year after the initial visit to determine deterioration in renal function, compared to baseline renal function. Baseline serum creatinine measurements were obtained in all patients and creatinine measurements at 1-year were obtained in 99% of the patients. Progression to end-stage renal disease was defined as the need for kidney replacement therapy (treatment with dialysis or kidney transplantation).

All-cause mortality and cardiac events

During follow-up, primary study endpoints were all-cause mortality and cardiac events, which included cardiac death or non-fatal myocardial infarction.

Table 1. Baseline characteristics of the study population, divided by level of renal function.

Characteristic	Normal renal function (n=603)	Mildly reduced renal function (n=812)	Moderately reduced renal function (n=423)	Severely reduced renal function (n=56)	Kidney failure (n=46)	P-value
Age (years) (± SD)	60 ± 12	65 ± 10	68 ± 9	66 ± 10	58 ± 13	<0.001
Male gender	77.1%	70.2%	68.1%	62.5%	58.7%	0.001
Current stable or unstable AP	19.4%	17. 2%	19.4%	30.4%	23.9%	0.13
Previous myocardial infarction	21.7%	27.7%	33.1%	46.4%	39.1%	<0.001
Previous CABG	9.5%	15.0%	12.8%	16.1%	4.3%	0.01
CAD (summary variable)	33.3%	38.4%	44.7%	60.7%	45.7%	<0.001
History of heart failure	3.5%	5.9%	9.7%	25.0%	10.9%	<0.001
Diabetes mellitus	11.9%	11.5%	13.5%	19.6%	28.3%	0.007
Hypertension	23.2%	34.1%	40.7%	46.4%	45.7%	<0.001
Cigarette smoking	24.9%	25.5%	23.2%	19.6%	21.7%	0.78
COPD	15.1%	14.0%	11.3%	3.6%	6.5%	0.042
Electrocardiography						
Q waves	22.6%	26.8%	24.1%	35.7%	37.0%	0.051
Left ventricular hypertrophy	5.6%	4.8%	10.5%	6.7%	6.7%	0.077
Left bundle branch block	2.5%	2.7%	4.3%	7.1%	2.2%	0.18
Right bundle branch block	0.5%	1.2%	2.1%	1.8%	0%	0.17
Medication						
Aspirin	23.7%	21.8%	22.5%	16.1%	6.5%	0.07
ACE-inhibitors	17.9%	26.0%	37.4%	41.1%	32.6%	<0.001
Beta-blocker	21.6%	26.2%	22.9%	23.2%	43.5%	0.008
Calcium channel blocker	19.4%	22.5%	29.6%	28.6%	41.3%	<0.001
Digoxin	4.1%	3.7%	5.7%	10.7%	4.3%	0.10
Diuretic	6.8%	12.4%	22.2%	41.1%	4.3%	<0.001
Nitrate	14.3%	16.1%	21.5%	42.9%	32.6%	<0.001
Statin	27.5%	29.6%	27.4%	30.4%	26.1%	0.88
Ankle-brachial index	61 ± 17	59 ± 17	58 ± 19	54 ± 13	47 ± 22	<0.001
Estimated Glomerular Filtration Rate (mL/min/1.73 m^2)	112 ± 20	76 ± 8	48 ± 8	23 ± 4	7 ± 3	<0.001

AP = angina pectoris; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; CAD = coronary artery disease; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; ACE-= angiotensin converting enzyme. Values are expressed in number (%) or mean (± SD).

Information on all-cause mortality and cardiac events was obtained during out-patient follow-up visits, by mailed questionnaires, by telephone interviews, by reviewing hospital records, by contacting the referring physician or by approaching the municipal civil registry to determine survival status. In patients who died during follow-up, death certificates and autopsy reports were reviewed and general practitioners were approached to ascertain the cause of death. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, or congestive heart failure. Sudden unexpected death in a previously stable patients was considered as cardiac death. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: elevated cardiac enzyme levels (CK level > 190 U/L and CK-MB >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/mL), development of typical electrocardiographic changes (new Q waves >1 mm or > 30 ms), and typical symptoms of angina pectoris.

Statistical analysis

Continuous data were compared using the Student t test or ANOVA techniques when appropriate. Categorical data were compared using the Chi square test. The Kaplan-Meier method with the log-rank test was used to assess differences in survival between patients with different levels of renal function. Statins and ACE-inhibitors were not randomly assigned in these patients, and the impact of selection bias may profoundly distort the results of our study. Propensity analyses are reliable tools to correct for selection bias and the rationale for using propensity scores has been described previously [18]. Therefore, we calculated separate propensity scores for statins and ACE-inhibitors. Variables that were independently associated with the decision to prescribe statins and ACE-inhibitors ($p<0.25$) were included in the multivariate propensity score, which was constructed using multiple logistic regression analysis. Multivariate Cox proportional hazard regression analysis was used to evaluate whether statins and ACE-inhibitors were associated with lower progression towards end-stage renal disease, all-cause mortality and cardiac events during long-term follow-up. Multivariate

Cox proportional hazard regression analysis with stepwise backward deletion of the least significant variable was used to determine independent predictors of all-cause mortality and cardiac events. Propensity scores were added to all multivariate regression models. However, results were comparable in multivariate analysis with or without adjusting for weighted propensity scores. Tests for heterogeneity were used to evaluate the effect of statins and ACE-inhibitors on outcome between patients with different levels of baseline renal function and between patients with or without diabetes mellitus. For all tests, a p value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

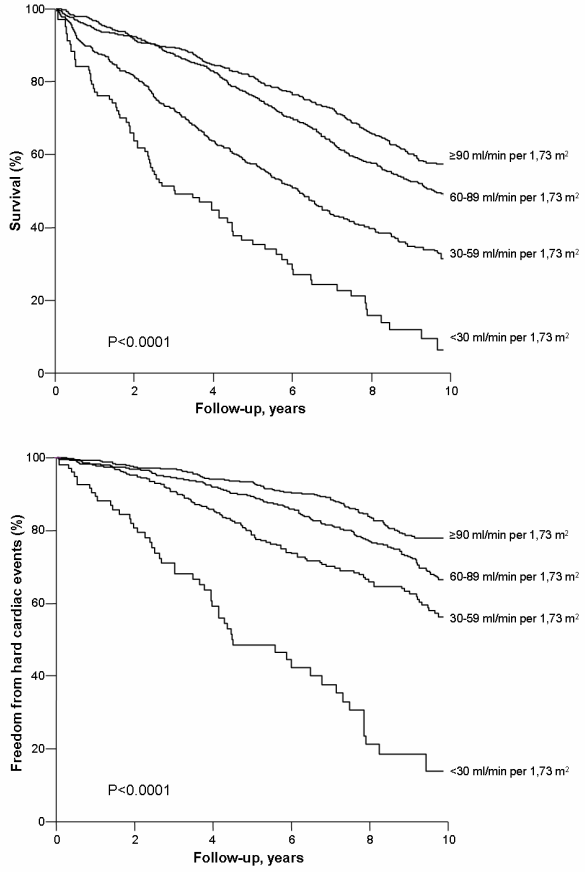

Figure 1. Kaplan-Meier curves for survival and freedom from hard cardiac events in patients with peripheral arterial disease stratified according to the level of renal function.

RESULTS

Baseline characteristics

A total of 1,940 patients were available for analysis. The mean age was 64 ± 11 years and 1385 patients (71%) were male. The mean ABI was 0.61 ± 0.19. Severe PAD (ABI was ≤0.70) was identified in 1397 patients (72%). An abnormal electrocardiogram was observed in 911 patients (47%). A total of 551 patients (28%) were using chronic statins and 515 patients (27%) were using chronic ACE-inhibitors. The mean eGFR at baseline was 78 ± 31 ml/min per 1.73 m^2. Normal renal function, mildly reduced renal function, moderately reduced renal function, severely reduced renal function and kidney failure was assessed in 31%, 42%, 22%, 3% and 2% of patients, respectively. A history of coronary artery disease, history of heart failure, diabetes and hypertension were significantly associated with declining baseline renal function (Table 1).

Follow-up

Mean time from baseline to last follow-up visit was 8 years (interquartile range 4-11 years). At 1-year follow-up, a reduction in eGFR of >25% was assessed in 211 patients (11%). Assessment of renal function at the last follow-up visit revealed a reduction in eGFR of >25% in 443 patients (23%) and progression to end-stage renal disease in 198 patients (10%). Improvement in eGFR of >25% was assessed in 293 patients (15%). All-cause mortality occurred in 889 patients (46%), cardiac death in 474 patients (24%) and non-fatal myocardial infarction in 127 patients (7%). Kaplan Meier curves demonstrate that higher decreases in baseline estimated glomerular filtration rate were associated with higher rates in all-cause mortality (p<0.001) and cardiac events (p<0.001) during follow-up (Figure 1).

ABI and outcome

Patients with lower baseline ABI values were more likely to present with a lower baseline eGFR, compared to patients with higher ABI values (Figure 2) (p<0.001). In multivariate analysis, lower ABI values were significantly associated with a higher progression rate of end-stage renal disease (Table 2). Multivariate analysis also demonstrated that lower ABI values significantly correlated with higher all-cause mortality and cardiac event rate (Table 2).

Independent predictors of mortality and cardiac events

Significant predictors for adverse long-term outcome were determined by stepwise multivariate analysis and are presented in Figure 3. Lower baseline eGFR (per 10

ml/min per 1.73 m^2) and reduction in eGFR (per 25%) during the first year of follow-up were both significantly associated with higher all-cause mortality rate (HR: 1.09, 95% CI: 1.06-1,12 and HR: 1.05, 95% CI: 1.01-1.09, respectively) and cardiac event rate (HR: 1.07, 95% CI: 1.02-1.11 and HR: 1.04, 95% CI: 1.00-1.08, respectively). Lower ABI (per 0.10 decrease) was also an independent predictor of mortality (HR: 1.08, 95% CI: 1.03-1.12) and cardiac events (HR: 1.08, 95% CI: 1.02-1.14). Importantly, chronic statin and ACE-inhibitor use was associated with a lower all-cause mortality rate (HR: 0.66, 95% CI: 0.55-0.80 and HR: 0.85, 95% CI: 0.77-0.96, respectively) and lower cardiac event rate (HR: 0.70, 95% CI: 0.56-0.90 and HR: 0.82, 95% CI: 0.69-0.97, respectively). Although in multivariate analysis the combined treatment of statins and ACE-inhibitors was associated with a decreased risk of all-cause mortality (HR: 0.79, 95% CI: 0.65-0.97) and cardiac events (HR: 0.74, 95% CI: 0.57-0.98), it was not independently associated with improved outcome in a multivariate model which included the single treatment of statin and ACE-inhibitor therapy.

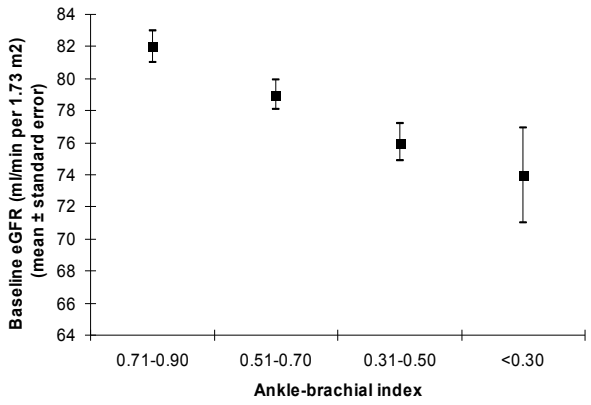

Figure 2. Baseline ankle-brachial index values in relation to baseline estimated glomerular filtration rate (eGFR) (p<0.001)

Statin and ACE-inhibitor therapy across different levels of renal function

Multivariate analysis demonstrated that chronic statin therapy was associated with a significantly lower risk of end-stage renal disease, mortality and cardiac events during follow-up across all categories of renal function (Table 3). Tests for heterogeneity revealed non-significant p-values for interaction (Table 3). ACE inhibitors were significantly associated with lower progression rate of end-stage renal disease, all-cause mortality and cardiac events in patients with moderately reduced renal function, severely reduced renal function and kidney failure, but not in patients with preserved or mildly reduced renal function (Table 3). Tests for heterogeneity further revealed that statins and ACE-inhibitors were associated with improved outcome among both patients with and without diabetes (non-significant p-values for interaction)

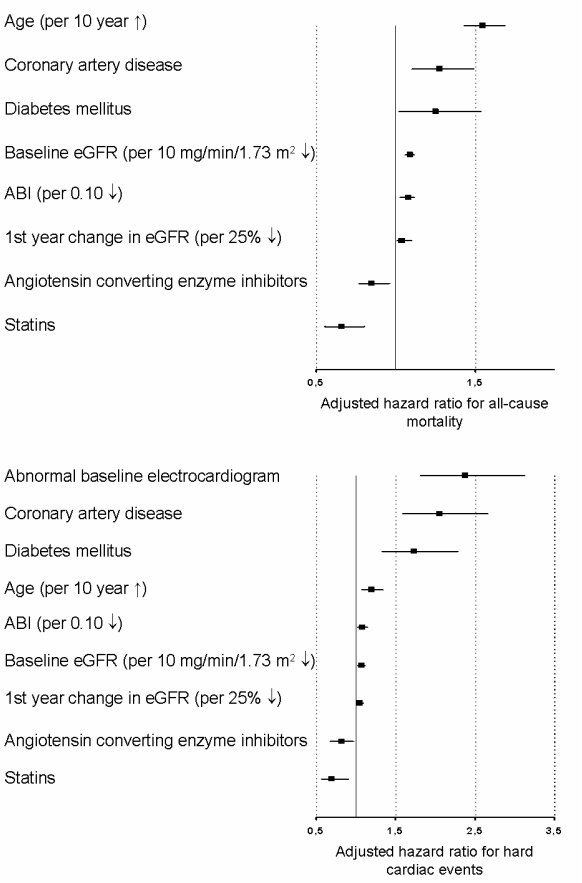

Figure 3. Multivariate model demonstrating significant predictors of all-cause mortality and cardiac events in patients with peripheral arterial disease.

DISCUSSION

The present study shows that renal dysfunction is highly prevalent among patients presenting with PAD, Mildly reduced, moderately reduced, severely reduced renal function and kidney failure were assessed in 42%, 22%, 3% and 2% of patients, respectively, perhaps reflecting the significance of generalized atherosclerosis as potential cause of renal dysfunction in patients with PAD. The mean baseline eGFR in this Dutch population of PAD patients was 78 ml/min per 1.73 m^2, which was almost similar to the results of the National Health and Nutrition Examination Survey, which found a mean eGFR of 77 ml/min per 1.73 m^2 in a United States population of PAD patients, aged 40 years and older. Many patients with PAD may present with undiagnosed

Table 2. The association between baseline ankle-brachial index values and renal and cardiovascular outcome in multivariate analysis.

	Progression to end-stage renal disease	All-cause mortality	Cardiac events
Ankle brachial index per 0.10 ↓	1.34 (1.21-1.49)	1.08 (1.03-1.12)	1.08 (1.02-1.14)
Ankle brachial index 0.71-0.90 (reference category)	1.00	1.00	1.00
Ankle brachial index 0.51-0.70	1.20 (0.73-2.00)	1.34 (0.96-1.85)	1.15 (0.95-1.40)
Ankle brachial index 0.31-0.50	1.66 (1.03-2.81)	1.62 (1.14-2.30)	1.41 (1.13-1.74)
Ankle brachial index 0.00-0.30	5.81 (3.21-9.49)	2.79 (1.75-4.44)	2.64 (2.01-3.45)

* Adjusted for age, gender, clinical risk factors, blood pressure, LDL-cholesterol, hemoglobin A1c in patients with diabetes, baseline estimated glomerular filtration rate, propensity scores for statin and angiotensin converting enzyme inhibitors, and medication including beta-blockers, calcium channel blockers, aspirin and diuretics.

Table 3. The association between medication and renal and cardiovascular outcome in patients presenting with different levels of renal function.

	Progression to end-stage renal disease	All-cause mortality	Cardiac events
Statins (all patients)	0.41 (0.28-0.63)	0.66 (0.55-0.82)	0.71 (0.56-0.91)
• Normal renal function (eGFR ≥90 ml/min per 1.73 m^2)	0.35 (0.15-0.81)	0.66 (0.48-0.91)	0.46 (0.28-0.81)
• Mildly reduced renal function (eGFR 60-89 ml/min per 1.73 m^2)	0.39 (0.16-0.94)	0.76 (0.61-0.96)	0.74 (0.60-0.93)
• Moderately reduced renal function (eGFR 30-59 ml/min per 1.73 m^2)	0.47 (0.25-0.89)	0.60 (0.45-0.79)	0.57 (0.34-0.97)
• Severely reduced renal function (eGFR 15-30 ml/min per 1.73 m^2)	0.22 (0.08-0.59)	0.42 (0.21-0.84)	0.25 (0.08-0.76)
• Kidney failure (eGFR <15 ml/min per 1.73 m^2)	0.13 (0.03-0.54)	0.03 (0.01-0.70)	0.02 (0.01-1.94)
P value for interaction	0.9	0.07	0.3
ACE-inhibitors (all patients)	0.74 (0.54-0.98)	0.84 (0.78-0.95)	0.81 (0.68-0.96)
• Normal renal function (eGFR ≥90 ml/min per 1.73 m^2)	0.96 (0.72-1.32)	1.02 (0.81-1.28)	0.80 (0.55-1.15)
• Mildly reduced renal function (eGFR 60-89 ml/min per 1.73 m^2)	1.18 (0.58-2.41)	0.95 (0.68-1.36)	0.94 (0.62-1.40)
• Moderately reduced renal function (eGFR 30-59 ml/min per 1.73 m^2)	0.67 (0.47-0.98)	0.80 (0.62-0.98)	0.76 (0.51-0.96)
• Severely reduced renal function (eGFR 15-30 ml/min per 1.73 m^2)	0.20 (0.06-0.67)	0.64 (0.39-0.95)	0.62 (0.34-0.97)
• Kidney failure (eGFR <15 ml/min per 1.73 m^2)	0.27 (0.12-0.63)	0.44 (0.18-0.94)	0.14 (0.01-0.91)
P value for interaction	0.02	0.04	0.03

Adjusted for age. gender. clinical risk factors. blood pressure. LDL-cholesterol. hemoglobin A1c in patients with diabetes. baseline estimated glomerular filtration rate. propensity scores for statin and angiotensin converting enzyme inhibitors. and medication including beta-blockers. calcium channel blockers. aspirin and diuretics. eGFR = estimated glomerular filtration rate. ACE-inhibitors = angiotensin-converting enzyme inhibitors.

renal dysfunction, which may eventually progress to chronic kidney disease or end-stage renal disease. In our population, 4% progressed to end-stage renal disease at 1-year of follow-up and 10% progressed to end-stage renal disease as assessed during the last follow-up visit.

ABI and renal outcome

Baseline characteristics demonstrated that a lower ABI value, a measure of atherosclerotic disease severity, was associated with more severe baseline renal dysfunction. The Atherosclerosis Risk in Communities Study showed that patients with an ABI of 0.90-0.99 and <0.90 were at increased risk of serum creatinine increases over a 3-year time period, compared to patients with ABI values above 1.00 [19]. The current study showed that even in patients with ABI levels ≤0.90, lower ABI values can independently predict reductions in eGFR during follow-up and can identify patients at greatest risk of renal deterioration. Another strength is the use of end-stage renal disease as clinically significant endpoint in addition to declines in eGFR. This finding supports the notion that atherosclerosis has indirect effects on the kidney because of atherosclerotic lesions in the renal artery and that atherosclerosis or atherogenic factors

induce directly intrarenal microvascular disease and renal injury [20]. Low ABI values should therefore be regarded as risk factor for developing end-stage renal disease. These high-risk patients may benefit from close renal monitoring and appropriate treatment strategies.

Statins and renal outcome

A major finding in our study was that chronic use of statins was significantly associated with a lower rate of end-stage renal disease progression across all patients with different levels of baseline renal function. The beneficial properties of statins beyond the lipid-lowering effect include atherosclerotic plaque stabilization, oxidative stress reduction and decrease in vascular inflammation [21,22]. Intensive statin therapy may even results in significant regression of atherosclerosis, as demonstrated in a recent study [23]. Given the fact that atherosclerosis is now becoming a recognized cause of renal deterioration, it seems plausible that statins can prevent renal deterioration in PAD patients, due to its pleiotropic effects. Experimental studies have suggested a preventive effect of statins on nephropathy [24,25]. A meta-analysis showed that statins can reduce proteinuria or albuminuria, especially in patients with cardiovascular disease [26]. Finally, a recent study demonstrated in 103 consecutive patients with hyperlipidemia and PAD that creatinine levels decreased after 3-4 months of treatment with simvastatin, independent of the degree of low-density lipoprotein cholesterol reduction [27].

ACE-inhibitors and renal outcome

The current study also showed that chronic ACE-inhibitor therapy was associated with a lower rate of renal deterioration, especially in patients with decreased baseline renal function. ACE-inhibitors have been shown to inhibit the atherosclerotic process and improve vascular endothelial function, peripheral blood pressure and blood flow [28-30]. Many studies have suggested that ACE-inhibitors slow or halt the progression of chronic nephropathies [31]. Patients with PAD may have a high rate of renal artery stenosis, in whom activation of the renin-angiotensin-aldosteron system serves to preserve renal blood flow and filtration rate. It should be noted that in our study population ACE-inhibitors were not prescribed to patients with bilateral renal artery stenosis, stenosis to a solitary kidney, or to patients with decompensated congestive heart failure in a sodium-depleted state, in order to minimize the risk of acute renal failure.

Combined use of statins and ACE-inhibitors

Our study failed to demonstrate an independent effect of the combined treatment of statins and ACE-inhibitors. However, animal studies have demonstrated that combining statins and ACE-inhibitors resulted in improved renal function, remarkable antiproteinuric effect and less glomerulosclerosis, tubular damage, interstitial inflammation and podocyte damage [32,33]. These results are also supported by a previous clinical study which suggested that atorvastatin in addition to ACE-inhibitors or angiotensin AT1 receptor antagonists reduce proteinuria and the rate of progression of kidney disease in patients with chronic kidney disease, proteinuria, and hypercholesterolemia [34].

Cardiovascular outcome

The prognosis of patients with PAD is characterized by a high cardiovascular event rate, due to the high prevalence of concomitant coronary artery disease. Based on previous reports in literature, patients with PAD are at 2 to 4 times increased risk of cardiovascular events, compared to patients with no PAD [35-39]. Our study showed that across the whole range of renal function, statins were associated with a lower risk of mortality and cardiac events. The beneficial effect of ACE inhibitors was noted especially in patients with decreased renal function. The Heart Protection Study provided convincing evidence that 40 mg of daily simvastatin significantly lowered the risk of vascular events in 6748 patients with PAD, when compared to placebo [11]. The HOPE study investigators showed in a subgroup of 4051 patients with PAD that ramipril significantly reduced the rate of major cardiovascular events [40]. In our study, baseline eGFR and reduction in eGFR during the first year were both independent predictors for late mortality and cardiac events. In addition to ABI values, these variables may be useful to identify patients at increased risk who may benefit from statin and ACE-inhibitor therapy.

Limitations

The main limitation of this study is that the findings must be interpreted in the context of the study design. To minimize selection bias, propensity scores were added to multivariate analysis. The causal relationship between statins and ACE-inhibitors and improved renal outcome could not be established in this observational cohort study. Randomized controlled trials would be required to establish this. Secondly, the results apply to patients referred to a university hospital which acts as a tertiary referral center for 30 affiliated hospitals. Patients admitted to our hospital may have a higher risk profile compared to patients with suspected or known PAD in the general population. Extrapolation of our results to PAD patients in the general population should therefore be done with caution. Furthermore, we used the Modification of Diet in Renal Disease equation to estimate renal function and our study may be limited by the absence of data on albuminuria and proteinuria,

which is recommended for the detection of early kidney disease. However, this equation is now widely used in clinical practice and has been recommended by the National Kidney Foundation practice guidelines as useful estimate of renal function [16,17]. Another limitation which should be mentioned is that it was not known whether patients with low ABI values may have been exposed to more intravenous contrast material during follow-up, leading to temporary or permanent renal dysfunction. However, imaging was performed with low-dose contrast material and the hospital protocol required cautious use of IV contrast material in patients with severe ABI. Finally, before implementing routine use of ACE-inhibitors in clinical practice in PAD patients with or without renal dysfunction, future studies should confirm its safety.

Conclusion

In conclusion, the current long-term prospective cohort study showed that renal dysfunction is highly prevalent among patients with PAD. Lower ABI values proved to be correlated with renal deterioration and may be used to identify patients at increased risk of end-stage renal disease. Baseline eGFR and reductions in 1-year eGFR could also identify patients at increased risk of mortality and cardiac events, in addition to ABI values. These patients may benefit from chronic statins and ACE-inhibitor therapy which was demonstrated to be associated with a lower progression rate of end-stage renal disease. In patients with PAD, statins and ACE-inhibitors were significantly associated with improved survival and freedom from cardiac events. Tests for heterogeneity revealed that the beneficial effect of statins existed across the whole range of renal function and among both patients with and without diabetes. ACE inhibitors were associated with improved renal and cardiovascular outcome, especially in patients with reduced baseline renal function.

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Chapter 9

Glycemic control, lipid lowering treatment and prognosis in diabetic patients with peripheral atherosclerotic disease

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Glycemic control, lipid lowering treatment and prognosis in diabetic patients with peripheral atherosclerotic disease

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Glycemic control may be an underestimated risk factor in diabetic patients with peripheral arterial disease. Chronic statin therapy may improve glycemic control and outcome in these patients. In an observational cohort study of 425 consecutive diabetic patients with PAD, chronic statin therapy was noted, the ankle-brachial index was measured and serial glycemic hemoglobin (HbA_{1c}) measurements were obtained. During follow-up (median 7 years), all-cause mortality and cardiac death occurred in 37% and 22%, respectively. Decreases in HbA_{1c} and HbA_{1c} variability independently predicted outcome in addition to baseline ankle-brachial index values. Patients with chronic statin therapy were more likely to have decreasing HbA_{1c} values (adjusted HR: 1.86, 95% CI: 1.27-2.74) and HbA_{1c} values less than 7% (adjusted HR 2.58, 95% CI: 1.49-4.48) during follow-up. Statins were also significantly associated with lower all-cause mortality (adjusted HR: 0.39, 95% CI: 0.26-0.61) and cardiac death rate (adjusted HR: 0.40, 95% CI: 0.24-76). Based on the results of the current observational study, we conclude that serial HbA_{1c} measurements can improve risk stratification in diabetic patients with PAD. In addition, statin therapy is associated with desirable glycemic control and improved long-term outcome.

INDIVIDUALS WITH lower extremity peripheral arterial disease (PAD) are at increased risk of all-cause and cardiovascular mortality [1-4]. Concomitant diabetes with chronic hyperglycemia may further cause significant morbidity which may require surgical intervention. PAD has therefore been recognized as a growing health burden worldwide, especially in the presence of diabetes mellitus [5,6].

Intensive blood glucose control with insulin or oral hypoglycemic medication has been demonstrated to attenuate many of the complications associated with dysglycemia. The identification of patients who fail to maintain strict glucose control is important for clinicians so that measures can be applied to prevent adverse consequences. The ankle-brachial index (ABI) is a simple and effective measurement to identify patients with PAD who are at increased risk of adverse outcome [7,8]. Repeated glycosylated hemoglobin (HbA_{1c}) measurements may improve risk stratification in addition to clinical risk factors and ABI values.

The current medical treatment of patients with PAD and diabetes is aimed at risk factor reduction, life style modifications and antiplatelet therapy [6]. Statin therapy has also been recommended by the American College of Cardiology/American Heart Association to achieve low serum low-density lipoprotein cholesterol levels [6]. Although recent studies have suggested that statins may improve insulin sensitivity in patients with the metabolic syndrome [9-14], it remains a matter of debate whether statins can improve glycemic control in patients with PAD and diabetes in order to reduce complications associated with dysglycemia and systemic atherosclerosis.

In an observational cohort study of patients with lower extremity PAD and diabetes, we sought to determine the prognostic value of repeated HbA_{1c} measurements in addition to ABI values, and we evaluated whether chronic use of statins was associated with improved glycemic control and outcome during long-term follow-up.

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METHODS

Study participants

This was a single-center observational cohort study of consecutive patients with PAD who were referred to our university clinic for ABI measurement, clinical evaluation and therapeutic management between January 1990 and September 2005. A total of 425 consecutive patients with diabetes were included in the current study. Patients eligible for the study were >18 years of age and only patients with an ABI ≤0.90 were included. Patients with a myocardial infarction in the

previous 6 months, patients with kidney failure (dialysis or estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m^2) and patients with ketonuria (>3 mmol/L) were excluded. During the first visit, patients were screened for clinical risk factors, ABI values and 12-lead electrocardiographic abnormalities. All patients had a history of diabetes which was diagnosed according to fasting plasma glucose concentrations of ≥7.0 mmol/l or according to an impaired glucose tolerance test (2 hour glucose concentration of ≥11.1 mmol/l). All patients received insulin or oral antidiabetic treatment at presentation. Insulin regimen and the dose of oral antidiabetic therapy was prescribed at the discretion of the treating physician with the aim to reduce HbA_{1c} values to less than 7% [15]. In general, insulin was prescribed when glucose levels could not be regulated by oral anti-diabetic therapy alone. The management of diabetes was primarily directed by family physicians in collaboration with internists. Chronic use of statins was recorded if patients were taking these medications for at least 1 year after the first visit. Clinical data were prospectively collected and stored into a computerized database. Risk factor reduction and life style modifications were encouraged in all patients presenting with clinical risk factors and all patients received dietary advice from a dietician.

ABI measurement

Systolic blood pressures in the right and left brachial artery, right and left dorsalis pedis artery and right and left posterior tibial artery were measured by trained technicians, using a Doppler ultrasonic instrument with an 8 MHz vascular probe (Imexdop CT+ Vascular Doppler, Miami Medical, USA). The ABI in the right and left leg was calculated by dividing the right and the left ankle pressure by the brachial pressure. The higher of the two brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Again, the higher of the dorsalis pedis and posterior tibial artery pressure was used when a discrepancy in systolic blood pressure between the two arteries was measured. If no pressure in the dorsalis pedis artery was obtained due to an absent dorsalis pedis artery, the pressure in the posterior tibial artery was used. The ABI was measured after the participants had been resting in the supine position for at least 10 minutes. Of the ABI values obtained in each leg, the lower was used in all analyses. Inter- and intra-observer agreement for the ABI was 97% and 98%, respectively.

Serial HbA_{1c} measurements

Baseline serum HbA_{1c} level was obtained during the first visit at a central laboratory using an enzyme immunoassay based on microtiter plate technology [16]. During regularly scheduled follow-up visits at 3, 6 and 9 months and every year after the initial visit, serial HbA_{1c} levels were measured to determine glycemic control over time. Absolute HbA_{1c} values and percentage changes in HbA_{1c} during follow-up were regarded as a measure of glycemic control over time. In addition, the standard deviation of the serial HbA_{1c} measurements and the absolute difference between minimum and maximum HbA_{1c} values was used as a measure of HbA_{1c} variability. Baseline HbA_{1c} measurements were obtained in all patients. In 13 patients (3%) in whom 1-year HbA_{1c} measurements were not available, 9- or 6-month HbA_{1c} measurement was used for analysis.

Study endpoints

During follow-up, primary endpoints were all-cause and cardiac mortality. Secondary endpoints were non-fatal myocardial infarction, congestive heart failure, stroke, progression to end-stage renal disease (ESRD) and ocular complications including retinopathy requiring photocoagulation, cataract extraction or blindness according to the WHO criteria [17]. Information on mortality was obtained by contacting the referring physician or by approaching the municipal civil registry. In patients who died, death certificates and autopsy reports were reviewed and general practitioners were approached to ascertain the cause of death. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias or congestive heart failure. Sudden unexpected death was also considered cardiac death. Information on secondary endpoints were obtained by follow-up visits, mailed questionnaires, telephone interviews and by reviewing the hospital records. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: elevated cardiac enzyme levels (CK level > 190 U/L and CK-MB >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/mL), typical electrocardiographic changes (new Q waves >1 mm or > 30 ms), and typical symptoms of angina. Heart failure was defined as hospitalization for cardiac decompensation with an ejection fraction ≤35%. Stroke was diagnosed when patients presented with typical symptoms for at least 1 month. ESRD was defined as an eGFR less than 15 ml/min per 1.73 m^2 or a need to start kidney replacement therapy (dialysis or renal transplantation) [18]. Ophthalmologists independent of the study made the clinical decision for photocoagulation or cataract extraction.

Statistical analysis

Continuous data (expressed as mean ± standard error of mean) were compared using the Student-t test or ANOVA techniques when appropriate. Categorical data

Table 1. Baseline characteristics of the study participants.

Characteristic	All patients (n=425)	No statins (n=267)	Statins (n=158)	p-value
Age (years)	61 ± 0.61	60 ± 0.85	62 ± 0.95	0.10
Male gender	291 (68%)	181 (68%)	110 (70%)	0.70
Angina pectoris	102 (24%)	55 (21%)	47 (30%)	0.033
Previous myocardial infarction	132 (31%)	74 (28%)	58 (37%)	0.053
Previous coronary artery bypass surgery	66 (16%)	36 (14%)	30 (19%)	0.13
Coronary artery disease (summary variable)	198 (47%)	115 (43%)	83 (53%)	0.059
History of congestive heart failure	45 (11%)	26 (10%)	19 (12%)	0.46
History of stroke or transient ischemic attack	49 (12%)	25 (9%)	24 (15%)	0.069
Hypercholesterolemia	104 (24%)	18 (7%)	86 (54%)	<0.001
Hypertension	195 (46%)	108 (40%)	87 (55%)	0.003
Cigarette smoking	127 (30%)	85 (32%)	42 (27%)	0.25
Chronic obstructive pulmonary disease	31 (7%)	21 (8%)	10 (6%)	0.56
Q waves	103 (24%)	60 (23%)	43 (27%)	0.27
Left bundle branch block	23 (5%)	17 (6%)	6 (4%)	0.26
Right bundle branch block	6 (1%)	4 (2%)	2 (1%)	0.84
Atrial fibrillation	26 (6%)	18 (7%)	8 (5%)	0.49
Aspirin	127 (30%)	53 (20%)	74 (47%)	<0.001
Angiotensin converting enzyme-inhibitor	161 (38%)	80 (30%)	81 (51%)	<0.001
Beta-blocker	135 (32%)	60 (23%)	75 (48%)	<0.001
Calcium channel blocker	123 (29%)	75 (28%)	48 (30%)	0.62
Coumarin	82 (19%)	46 (17%)	36 (23%)	0.16
Digoxin	25 (6%)	18 (7%)	7 (4%)	0.33
Diuretic	82 (19%)	45 (17%)	37 (23%)	0.13
Oral antidiabetic treatment	215 (51%)	136 (51%)	79 (50%)	0.85
Insulin treatment	210 (49%)	131 (49%)	79 (50%)	0.85
Ankle brachial index at rest	0.61 ± 0.01	0.60 ± 0.01	0.62 ± 0.02	0.44
Blood total cholesterol (mg/dL)	206 ± 6.2	198 ± 7.0	221 ± 10.7	0.057
Blood LDL-cholesterol (mg/dL)	129 ± 3.3	137 ± 4.1	116 ± 4.9	<0.001
Blood HDL-cholesterol (mg/dL)	40 ± 1.0	38 ± 1.1	43 ± 2.0	0.010
Blood triglyceride (mg/dL)	226 ± 26.5	272 ± 46	171 ± 13.5	0.009
Blood glycosylated hemoglobin (%)	8.1 ± 0.1	8.2 ± 0.2	8.1 ± 0.1	0.20
Blood glycosylated hemoglobin <7%	119 (28%)	72 (27%)	47 (30%)	0.60

Values are expressed as mean ± standard error of the mean or number with percentage

were compared using the Chi-square test. The Kaplan-Meier method with the log-rank test was used to assess differences in survival between patients with and without statins. Statins were not randomly assigned in these patients, and the impact of selection bias may profoundly distort the results of our study. Propensity analyses are reliable tools to correct for selection bias and the rationale for using propensity scores has been described previously [19]. Therefore, we calculated separate propensity scores for statins. Variables independently associated with the decision to prescribe statins and ACE inhibitors ($p<0.25$) were included in the multivariate propensity score, which was constructed using multiple logistic regression analysis. Multivariate logistic regression analysis and Cox proportional hazard regression analysis were used to evaluate whether statins were associated with improved glycemic control and a lower rate of primary and secondary endpoints. Age, clinical risk factors, ABI values, electrocardiography, baseline cholesterol levels, cardiovascular medication and propensity scores were added to all multivariate regression models. Glycemic control was assessed at 1-year of follow-up and at the last follow-up visit to assess the sustained effect of statins. Tests for heterogeneity were used to evaluate differences in the effect of statins between patients with insulin treatment and oral medication. For all tests, a p value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics

Baseline characteristics of the 425 study participants are presented in Table 1. The mean age was 61 ± 0.6 years and 291 patients (68%) were male. Mean body mass index at baseline was 25 ± 5 $kg \cdot m^{-2}$. The mean ABI was 0.61 ± 0.01. Severe PAD (ABI ≤0.70) was identified in 268 patients (63%). During the initial visit, 208 patients (49%) presented with insulin therapy and oral anti-diabetic medication was used in 217 patients (51%). A total of 158 patients (37%) received chronic statin

Table 2. Glycemic control and outcome during follow-up in patients using statins or no statins

	No statins (n=267)	Statins (n=158)	p-value
Glycemic control during 1 year of follow-up			
HbA_{1c} value at 1 year	8.7 ± 0.16	7.6 ± 0.16	<0.001
Change (%) in HbA_{1c} from baseline values	+ 4.2 ± 1.5	- 6.4 ± 1.6	<0.001
Patients with decreasing HbA_{1c}	89 (33%)	120 (76%)	<0.001
Patients with HbA_{1c} <7% at 1-year	37 (14%)	71 (45%)	<0.001
Mean HbA_{1c} during first year of follow-up	8.2 ± 0.13	7.8 ± 0.15	0.15
Standard deviation of mean HbA_{1c}	0.8 ± 0.05	0.6 ± 0.04	<0.001
Minimum HbA_{1c} level	7.3 ± 0.12	7.3 ± 0.14	0.87
Maximum HbA_{1c} level	9.1 ± 0.17	8.6 ± 0.18	0.033
Difference between minimum and maximum HbA_{1c} level	1.8 ± 0.12	1.3 ± 0.10	0.002
Glycemic control up to last follow-up visit			
HbA_{1c} value at last visit	8.2 ± 0.12	7.3 ± 0.12	<0.001
Change (%) in HbA_{1c} from baseline values	3.5 ± 1.9	-9.2 ± 1.4	<0.001
Patients with decreasing HbA_{1c}	86 (32%)	99 (63%)	<0.001
HbA_{1c} of less than 7% at last visit	40 (15%)	80 (51%)	<0.001
Mean HbA_{1c} during follow-up	8.2 ± 0.13	7.7 ± 0.14	0.023
Standard deviation of mean HbA_{1c}	0.9 ± 0.05	0.7 ± 0.05	<0.001
Minimum HbA_{1c} level	7.0 ± 0.11	6.9 ± 0.12	0.45
Maximum HbA_{1c} level	9.5 ± 0.19	8.7 ± 0.19	0.004
Difference between minimum and maximum HbA_{1c} level	2.5 ± 0.16	1.8 ± 0.14	0.002
Events during follow-up			
All-cause mortality	135 (51%)	21 (13%)	<0.001
Cardiac death	81 (30%)	13 (8%)	<0.001
Non-fatal myocardial infarction	34 (13%)	17 (11%)	0.54
Hospitalization for heart failure	25 (9%)	4 (3%)	0.007
Coronary artery bypass grafting	19 (7%)	13 (8%)	0.68
Cerebrovascular event	42 (16%)	15 (10%)	0.068
Progression towards end-stage renal disease	43 (16%)	9 (6%)	0.002
Photocoagulation for retinopathy	29 (11%)	5 (3%)	0.005
Cataract extraction	23 (9%)	9 (6%)	0.27
Blindness	1 (0.4%)	0 (0%)	0.44
Composite of end-stage renal disease and ocular complications	84 (32%)	26 (17%)	0.001
Composite of all non-fatal events	162 (61%)	71 (45%)	0.002

Values are expressed as mean ± standard error of the mean or number and percentage

therapy. In propensity analysis, important variables (p<0.001) associated with the prescription of statins were high baseline LDL-cholesterol levels and hypertension. Aspirin, angiotensin-converting enzyme inhibitors and beta-blockers were also more commonly prescribed in patients with chronic statin therapy. Mean LDL-cholesterol levels at 1-year of follow-up were lower in patients using statins, compared to patients using no statins (102 ±4.3 mg/dL vs. 130 ±6.1 mg/dL, p<0.001).The mean HbA_{1c} at baseline was 8.1 ±0.1%. A total of 119 patients (28%) presented with a baseline HbA_{1c} value of less than 7%.

Glycemic control during follow-up

At 1-year of follow-up, an elevation in HbA_{1c} was assessed in 216 patients (51%) and a lowering in 209 (49%). Figure 1 demonstrates changes in HbA_{1c} from baseline values during the first year of follow-up. HbA_{1c} decreased with 6.4% in patients using statins and increased with 4.2% in patients using no statins (p<0.001). During follow-up, 12 patients (3%) switched to a less intensive diabetic treatment strategy (6 patients switched from insulin therapy to oral medication and 6 patients discontinued oral medication due to adequate glycemic control). In statin users, a higher percentage of patients (7%) switched to less intensified treatment compared to no statin users (0.4%) (p<0.001) (Figure 1). Table 2 summarizes differences in glycemic control between patients using statins and no statins during the first year of follow-up and during overall follow-up. Absolute HbA_{1c} values at 1-year and at the last follow-up were lower in patients using statins (Table 2). The proportion of patients with decreasing HbA_{1c} values and HbA_{1c} values less than 7% during follow-up was also higher in patients using statins (Table 2). In addition, the standard deviation of the mean and the absolute difference between minimum and maximum HbA_{1c} values during follow-up was smaller in statin users, compared to non-statin users (Table 2). In multivariate analysis, patients with chronic statin therapy were more like to have decreasing HbA_{1c} values (HR: 3.48, 95% CI: 2.03-5.98) and HbA_{1c} values less than 7% (HR 4.96, 95% CI: 2.71-9.38) during the first year of follow-up. The association between statins and decreasing HbA_{1c} values (HR: 1.86, 95% CI: 1.27-2.74) and HbA_{1c} values less than 7% (HR 2.58, 95% CI: 1.49-4.48) was also

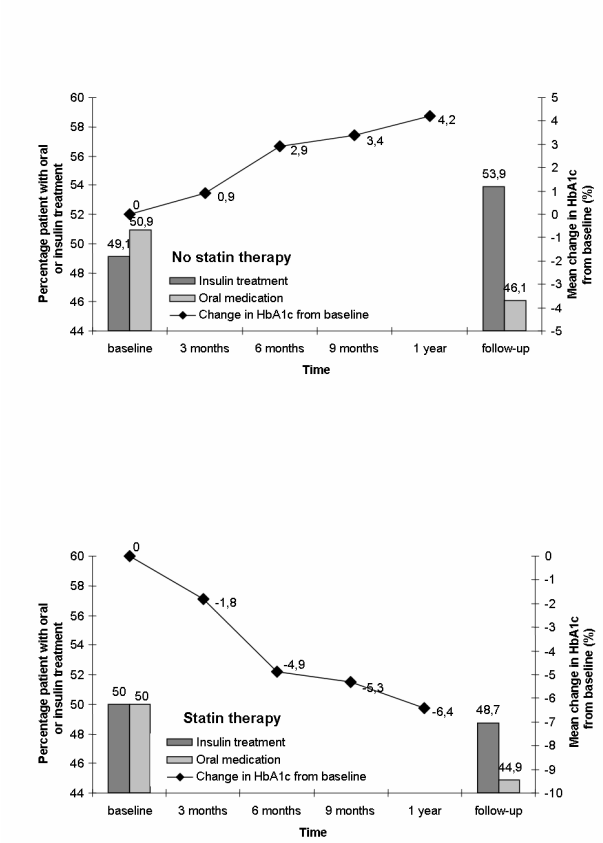

Figure 1. Change in HbA_{1c} and diabetic treatment during follow-up in diabetic patients with peripheral arterial disease according to statin use or no statin therapy.

sustained after 1-year of follow-up. During follow-up, 203 patients underwent lower extremity revascularization surgery for progressive PAD. Patients using statins were less likely to have surgery, compared to patients with no statins (41% vs. 60% respectively, p=0.021).

Study endpoints

During a median follow-up period of 6.9 ±0.2 years, all-cause mortality occurred in 156 patients (37%), cardiac death in 94 patients (22%), non-fatal cardiovascular complications in 150 patients (35%), progression to ESRD in 52 patients (12%), ocular complications in 67 patients (16%) and the composite of ESRD and ocular complications in 110 patients (26%). In Table 2, a univariate comparison between the number of events in patients with statins and no statins is presented. All-cause mortality, cardiac death, congestive heart failure, progression towards ESRD and photocoagulation for retinopathy during follow-up was significantly lower in chronic statin users, compared to no statin users. Kaplan-Meier curves also showed a significantly improved survival, freedom from cardiac death and freedom from the composite of ESRD and ocular complications in patients using statins (Figure 2). Multivariate analysis showed that statins remained significantly associated with improved outcome (Table 3). Other significant correlates of improved outcome included higher ABI values, lower HbA_{1c} values during follow-up, decreasing HbA_{1c} values during follow-up and a lower variability in HbA_{1c} during follow up (lower standard deviation of the mean HbA_{1c}). Tests for heterogeneity revealed that statins were associated with improved outcome both among patients with insulin therapy and among patients with oral anti-diabetic treatment (non-significant p-values for interaction).

DISCUSSION

The current observational study demonstrated that diabetic patients with PAD who were receiving chronic statin therapy had improved glycemic control compared to patients not using statins. Statins were also associated with lower all-cause and cardiac mortality rate and non-fatal diabetic complications, even after adjustment for clinical risk factors, baseline cholesterol levels, ABI values, cardiovascular medication and propensity scores. This study further demonstrated that patients with increasing HbA_{1c} values and higher HbA_{1c} variability over time were at increased risk of adverse outcome and that serial HbA_{1c} measurements may be useful for risk stratification in addition to clinical risk factors and baseline ABI values.

Different prevalence rates of diabetes in patients with lower extremity PAD have been reported, ranging from 8% to 18% [2,20,21]. Patients with PAD are at increased risk of developing diabetes which may partly be explained by underlying lipid abnormalities [22]. Conversely, diabetes itself may also increase the risk of developing PAD. Results from the Framingham study demonstrated that men and women with diabetes were at 4- and 9-fold increased risk, respectively, of developing PAD [23]. Moreover, the severity and duration of diabetes has also been related proportionally to the risk of developing PAD [24,25]. The coexistence of PAD and diabetes may reflect an advanced state of health impairment in which the prognosis is poor. Indeed, in the current study cohort, more than 1 out of 3 patients (37%) died during a median follow-up of 7 years. Non-fatal complications related to diabetes were also frequently observed. Cardiovascular events occurred in 35%, progression to ESRD in 12% and ocular complications in 16% of patients. Therefore, the identification of patients who are at highest risk is necessary for selection of appropriate treatment

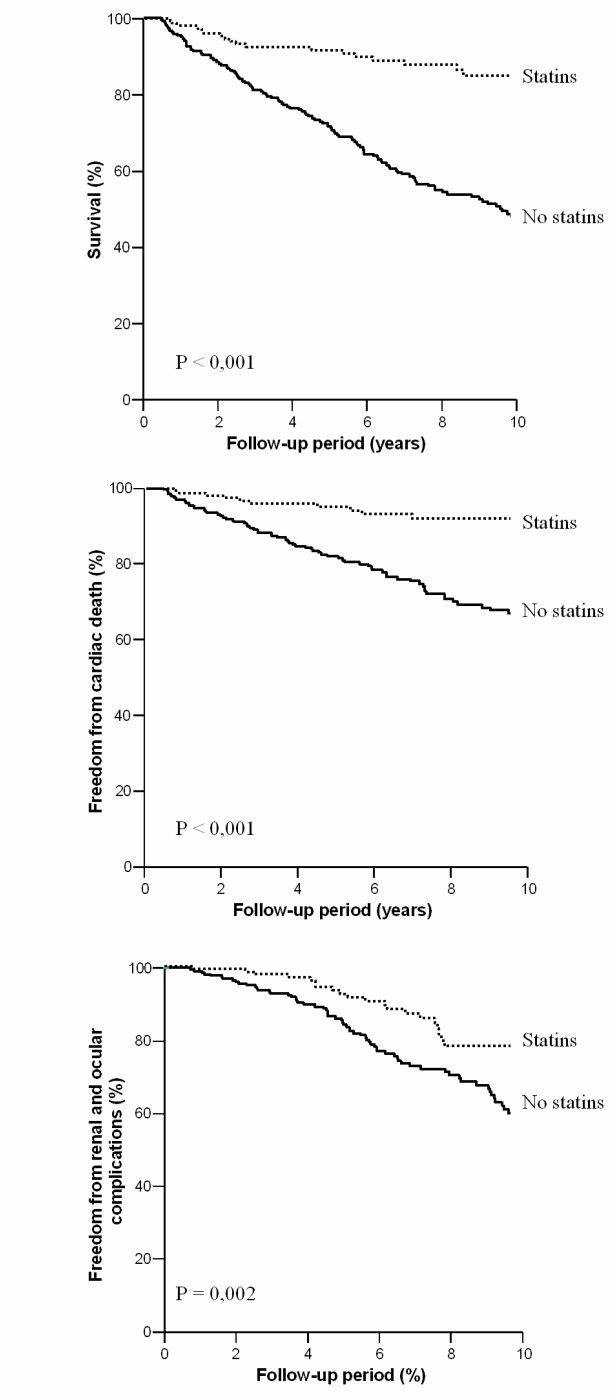

Figure 2. Kaplan-Meier curve for mortality, cardiac death and non-fatal diabetic complications (end-stage renal disease, photocoagulation for retinopathy, cataract extraction or blindness), stratified according to statin therapy.

strategies and for control of disease related complications.

Poor glycemic control and elevated HbA_{1c} values are important determinants of micro- and macrovascular complications in patients with diabetes [28]. The American College of Cardiology/American Heart Association has therefore recommended in their guidelines that all diabetic patients with PAD should be treated in order to achieve HbA_{1c} levels of less than 7% [6]. Despite the use of strict insulin treatment or oral antidiabetic medication, physicians may still be challenged to achieve these goals. In the current study population, only 28% of the patients presented with HbA_{1c} values of less than 7% at study enrolment. In most of the patients, a HbA_{1c} value of less than 7% was not achieved during follow-up. These results reflect the high rate of poor glycemic control in diabetic patients with PAD. Different factors have been associated with poor glycemic control, including diabetes disease duration, poor self-care, failure to receive diet recommendations, non-insurance and high cholesterol levels [29,30]. Especially in patients presenting with these characteristics, much benefit can be derived from appropriate patient counseling and intensive medical treatment.

Several reports in literature have suggested the beneficial properties of statins regarding insulin sensitivity, insulin secretion and insulin-mediated glucose uptake in non-diabetic and diabetic patients [10-13]. Moreover, a post-hoc analysis of the West of Scotland Coronary Prevention Study showed that patients receiving statins had a 30% reduction in the hazard of becoming diabetic [9]. Four different known effects of statins may possibly explain its effect on glucose metabolism. Firstly, dyslipidemia has been associated with the development of diabetes and statins may have effects on glucose metabolism through lipid-lowering effects [22]. Secondly, the anti-inflammatory properties of statins may reduce circulating levels of pro-inflammatory cytokines which can negatively influence the insulin receptor leading to insulin insensitivity [31]. Thirdly, it may be speculated that statins restore endothelial function and may therefore improve tissue perfusion and glucose and insulin transport [32]. Finally, the anti-oxidative properties of statins may prevent the development of endothelial dysfunction, since oxidative stress during hyperglycemia is a key element in the pathogenesis of endothelial dysfunction and diabetic complications [33].

Large studies have demonstrated that statins improve cardiovascular outcome in patients with PAD [34] and with diabetes [35]. Statin therapy has therefore been recommended in all patients with PAD [6] and diabetes [15] to achieve LDL-cholesterol levels of less than 100 mg/dL. The current results not only confirm

Table 3. Prognostic value of ankle-brachial index values, HbA_{1c} values and chronic statin therapy in diabetic patients with peripheral arterial disease, adjusted for baseline clinical variables

	All-cause mortality Hazard ratio (95% CI)	Cardiac death Hazard ratio (95% CI)	Composite of ESRD and ocular complications*** Hazard ratio (95% CI)
Ankle-brachial index (per 0.10 decrease)	1.07 (1.01-1.15) *	1.13 (1.03-1.23) *	1.05 (0.98-1.16) *
HbA_{1c} value at 1 year follow-up (per value decrease)	1.13 (0.99-1.27) **	1.17 (1.02-1.34) **	1.14 (1.02-1.27) **
% change of HbA_{1c} during 1-year follow-up (per % decrease)	1.13 (1.01-1.32) **	1.20 (1.03-1.46) **	1.21 (1.04-1.41) **
SD of mean HbA_{1c} during 1-year follow-up (per 1.0 increase)	1.50 (1.07-2.09) **	1.70 (1.16-2.48) **	1.47 (1.04-2.07) **
HbA_{1c} value at last follow-up visit (per value decrease)	1.11 (0.98-1.21) **	1.13 (1.01-1.26) **	1.15 (1.04-1.26) **
% change of HbA_{1c} during overall follow-up (per % decrease)	1.11 (1.01-1.22) **	1.15 (1.03-1.29) **	1.10 (1.01-1.22) **
SD of mean HbA_{1c} during overall follow-up (per 1.0 increase)	1.38 (1.03-1.88) **	1.64 (1.07-2.53) **	1.44 (1.04-1.99) **
Chronic statin therapy	0.39 (0.26-0.61) **	0.40 (0.24-0.76) **	0.55 (0.39-0.79) **

ESRD = end-stage renal disease; HbA_{1c} = glycosylated hemoglobin. *Adjusted for age, baseline clinical variables, electrocardiography, baseline cholesterol levels, cardiovascular medication and propensity scores **Adjusted for age, baseline clinical variables, ankle-brachial index values, electrocardiography, baseline cholesterol levels, cardiovascular medication and propensity scores. *** Ocular complications include photocoagulation for retinopathy, cataract extraction and blindness.

that statins significantly lower all-cause mortality and cardiac death rate, but they also showed that it significantly lowers the rate of diabetes-related complications, including ESRD and ocular complications. It may be hypothesized that an improvement in glucose metabolism due to chronic statin therapy may partially explain the lower rate of mortality and non-fatal diabetic complications. Lower absolute HbA_{1c} values, decreasing HbA_{1c} values and lower variability in HbA_{1c} during follow up were all independently associated with lower mortality and non-fatal diabetic complications. In addition, the severity of atherosclerosis as measured by the ABI remained an important determinant of adverse outcome. In clinical practice, serial HbA_{1c} measurements may not only be valuable to guide medical treatment, but may also allow refinement of risk stratification in addition to clinical risk factors and ABI values in order to identify patients at highest risk of adverse outcome who may benefit from aggressive lipid-lowering treatment.

Several limitations should be addressed. The main limitation of this study is that the findings must be interpreted in the context of the observational study design in which statins were not randomly assigned to the study participants. Although we have used propensity scores, it may not have compensated for all bias in the decision to prescribe statins. Secondly, potentially confounding variables such as poor health behaviors and poor adherence to a strict diabetic regimen were not obtained in this study and may have influenced the results. However, patients with statins were more likely to switch from insulin treatment to oral medication or from oral medication to only a diabetic diet, suggesting that a strict regimen of insulin therapy itself does not fully account for the improvement in HbA_{1c}. Finally, the use of HbA_{1c} as measure of glycemic control may be debated. HbA_{1c} has been proven to be a reliable measure of long-term glycemic control in patients with diabetes, however, fasting glucose and 2-hour post-glucose-load concentrations in addition to HbA_{1c} may have represented a more reliable measure of glycemic control.

Conclusion

Based on the current results, we conclude that in diabetic patients with PAD chronic statin therapy is associated with desirable glycemic control, improved survival and lower non-fatal diabetic complication rate. In addition, serial HbA_{1c} measurements may allow refinement in risk stratification in addition to clinical risk factors and ABI values to identify patients at increased risk. Despite the limitations of an observational study, the current findings suggest new clinical possibilities, which should be explored in further studies.

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Chapter 10

Perioperative myocardial inschemia during major noncardiac surgery

Submitted

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Perioperative myocardial ischemia in vascular surgery patients

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Aims. Prophylactic preoperative treatment of the culprit coronary artery lesion is not associated with improved postoperative outcome in vascular surgery patients. This study evaluates the incidence and location of perioperative ST-depression and ST-elevation as related to the culprit coronary lesion.
Methods and Results: In a prospective study of 401 consecutive vascular surgery patients, high-sensitivity C-reactive protein (HS-CRP) and white blood cell count (WBCC) were measured preoperatively. Stress echocardiography was performed to locate the culprit coronary lesion. Prolonged ST-depression and ST-elevation was recorded by 12-lead Holter monitoring starting 1 day before to 2 days after surgery. Cardiac death or Q-wave myocardial infarction were noted during follow-up (mean 2.5 years). Perioperative ST-depression occurred in 16.2% and ST-elevation in 7.5% of patients. Culprit coronary lesion-related ST-depression occurred in 89% and ST-elevation in 53% ($p<0.001$). Both ST-depression and ST-elevation were associated with long-term cardiac events (OR, 18.7 [CI, 5.2-66] and OR, 8.4 [CI, 4.6-15], respectively). Elevated HS-CRP (OR, 3.8 [CI, 2.2-6.5]) and WBCC (OR, 1.5 [CI, 1.1-2.2]) were associated with a higher incidence of ST-elevation, but not with ST-depression.
Conclusion: In contrast to perioperative ST-depression, perioperative ST-elevation often occurs in non-culprit related coronary artery territories.

THE INCIDENCE OF myocardial infarction and cardiac death in patients undergoing major vascular surgery is high with estimates ranging from 2% to 19% [1]. A perioperative myocardial infarction is the major cause of postoperative mortality in this population [2]. A perioperative myocardial infarction can be caused by prolonged subendocardial ischemia in the presence of a culprit coronary lesion and/or by acute coronary occlusion resulting in transmural ischemia [3-5]. Perioperative myocardial ischemia has been described in up to 41% of patients undergoing major vascular surgery and has been associated with increased postoperative cardiac morbidity and mortality [6]. Differences between perioperative ST-elevation ischemia and ST-depression ischemia in terms of incidence, location and prognosis are not well known.

The prediction of mortality and acute coronary events remains a challenge, due to the vulnerability of atherosclerotic plaques. According to the American College of Cardiology/ American Heart Association guidelines, clinical evaluation and non-invasive testing are the recommended risk assessment strategies [7]. Cardiac evens, however, still occur in the presence of negative stress-test results. We hypothesized that perioperative ST-depression and ST-elevation can occur at sites other than the preoperatively identified culprit coronary lesion. A disagreement in pre- and perioperatively assessed ischemia may explain why preoperative localized treatment of the coronary lesion fails to prevent perioperative ischemic events [8,9].

In this study, we defined the location of ST-depression and ST-elevation ischemia and assessed its relation to the culprit coronary lesion as identified by dobutamine stress echocardiography. We also evaluated whether both ST-depression and ST-elevation are associated with early and late cardiac events.

METHODS

Study population

The study population consisted of 401 consecutive patients undergoing elective abdominal aortic aneurysm repair (n=200), peripheral artery bypass surgery (n=128) or carotid artery surgery (n=73) at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period 2002 to 2006. The study was approved by the hospital's ethical committee and complied with the Declaration of Helsinki. All patients gave informed consent. Patients were enrolled up to 3 months prior to surgery at the outpatient clinic. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block and atrial fibrillation were excluded. Patients who participated in clinical intervention trials at or outside the Erasmus MC were also excluded. In all patients, β-blockers were considered prior to surgery to obtain perioperative heart rates of 60-65 beats per minute. All patients were screened for hypertension (blood pressure

³140/90 mmHg), diabetes mellitus (fasting glucose level ³7.0 mmol/L or use of insulin or oral glucose lowering medication), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or use of cholesterol-lowering medication) and renal failure (serum creatinine level ≥ 2.0 mg/dL (177 μmol/L)). Body mass index was calculated using the formula weight/height^2. The ankle-brachial index was calculated by dividing the right and the left ankle blood pressure by the higher of the two brachial blood pressures. Prior to surgery, blood was drawn from all patients and high-sensitivity C-reactive protein (HS-CRP) level and white blood cell count were used as markers of inflammation activity. Other laboratory tests included hemoglobin, hematocrit, glucose, glycosylated hemoglobin, urea, creatinine, cholesterol, uric acid and N-terminal pro-B-type natriuretic peptide (NT-proBNP), which were measured by commercially available tools.

Dobutamine stress echocardiography
During preoperative stress echocardiography, dobutamine hydrochloride was administered intravenously by infusion pump, starting at 10 mcg/kg/min for 3 minutes (5 mcg/kg/min for 5 minutes, followed by 10 mcg/kg/min for 5 minutes in patients with resting wall motion abnormalities), and increased by 10 mcg/kg/min every 3 minutes to a maximum of 40 mcg/kg/min. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate) was achieved. Two experienced investigators, blinded to the clinical data, performed off-line assessment of echocardiographic images, using the 17-segment 5-point scoring model. Ischemia was defined as new or worsening wall-motion abnormalities (compared to resting images of the same test) as indicated by an increase of regional wall motion score ≥1 grade(s) with stress. Myocardial segments were assigned to a coronary artery territory as follows: the anterior, anteroseptal, apical septal, apical anterior, apical lateral, and midinferoseptal segments were assigned to the left anterior descending (LAD) coronary artery; the lateral and posterior segments were assigned to the left circumflex artery (LCX); and the apical, inferior, midinferior, basal inferior, and basal inferoseptal segments were assigned to the right coronary artery (RCA).

Continuous ECG monitoring
Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts), starting 1 day before surgery up to 2 days after. Recordings were performed in the continuous 12-lead mode with a recording length of 10 seconds every minute. The frequency response was 0.05 – 150Hz. Electrocardiographic data were initially processed by a technician and analyzed by 2 experienced cardiologists who were blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the ambulatory electrocardiography recordings were analyzed for ST-segment deviations. A continuous ST segment trend was generated and all potential ischemic episodes were identified. Episodes of ischemia were defined as ST-depression or ST-elevation, lasting more than 10 minutes and shifting from baseline to more than 0.1 mV (1 mm). The baseline ST segment level was defined as the average ST segment during a stable period (duration of 20 minutes) preceding each ischemic episode. ST segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST segment change was measured 40 ms after that point. Ischemic burden was defined as ST-deviation times duration (mm*min). ST-segment changes in the precordial leads were assigned to the LAD territory, in the lateral leads (I, aVL, V5, V6) to the LCX territory and in the inferior leads (II, III, aVF) to the RCA territory. Mean heart rate prior to, during and after surgery was calculated for each patient. Heart rate variability (SDNN) was computed using time-domain analysis of short-term 5-minute recordings during the first 24-hour recording. This 24-hour recording started at the evening prior to surgery and included night and surgical period.

Troponin T release
Troponin T levels were measured on postoperative day 1, 3, 7, before discharge and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The lower limit of 0.03 ng/ml was used to define positive troponin T levels since lower levels do not meet the imprecision criteria of <10%.

Major cardiac events
Study endpoints were major cardiac events (cardiac death and non-fatal Q-wave myocardial infarction) during the perioperative period (30-day period after surgery) and during follow-up (mean: 2.5 years). During follow-up, outpatient visits were scheduled every 3 months after discharge. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure or sudden death. Q-wave myocardial infarction was diagnosed when at least the following were present: elevated cardiac enzyme levels, development of new Q waves (>1 mm or > 30 ms), and typical symptoms of angina pectoris. No patients were lost to follow-up.

Table 1. Baseline characteristics of the study population according to perioperative ST-segment changes.

Characteristic	No ST-changes (n=306)	ST-depression (n=65)	ST-elevation (n=30)
Age, years (SD)	166 ± 10	71± 8*	67 ± 11
Gender, male	227 (74.2%)	57 (87.7%)*	27 (90.0%)
Angina pectoris	47 (15.4%)	17 (26.2%)*	7 (23.3%)
Myocardial infarction	94 (30.7%)	32 (49.2%)*	21 (70.0%) †
Previous percutaneous coronary angioplasty	23 (7.8%)	1 (1.5%)	6 (20%) † ‡
Previous coronary artery bypass grafting	41 (13.4%)	14 (21.5%)	4 (13.3%)
Congestive heart failure	9 (2.9%)	5 (7.7%)	4 (13.3%) †
Diabetes	48 (15.7%)	8 (12.3%)	9 (30.0%) † ‡
Hypertension	124 (40.5%)	30 (46.2%)	12 (40.0%)
Stroke	48 (15.7%)	6 (9.2%)	3 (10.0%)
Smoking	171 (55.9%)	41 (63.1%)	16 (53.3%)
Ankle-brachial index (SD)	0.77 ± 0.28	0.72 ± 0.29	0.64 ± 0.24
High sensitivity C-reactive protein, mg/L (median, IQR)	8 (2-23)	19 (7-105)*	49 (22-198) † ‡
White blood cell count, $x10^9$/L (SD)	8.5 ±2.9	8.5 ± 2.6	10.0 ± 3.4† ‡
Ureum level, mmol/L (SD)	6.76 ± 3.21	8.27 ± 4.05	8.91 ± 6.46†
Creatinine level, umol/L (SD)	95 ± 74	101 ± 42	142 ± 157† ‡
Estimated glomerular filtration rate ml/min/1.73m^3 (SD)	85 ± 26)	74 ± 22*	74 ± 28 †
Hemoglobin, gl/L (SD)	13.9 ± 1.7	13.7 ± 1.9	13.7 ± 1.8
Hematocrit, L/L (SD)	0.41 ± 0.05	0.41 ± 0.05	0.41 ± 0.05
Glucose level, mmol/L (SD)	6.1 ± 2.1	7.2 ± 3.2*	6.6 ± 2.4
Glycosylated hemoglobin level, % (SD)	6.15 ± 1.34	6.35 ± 0.73	7.06 ± 1.71†
Low-density lipoprotein cholesterol, mmol/L (SD)	3.0 ± 1.0	3.6 ± 1.4*	3.2 ± 1.4
High-density lipoprotein cholesterol, mmol/L (SD)	1.3 ± 0.5	1.3 ± 0.9	1.0 ± 0.5
Triglycerides, mmol/L (SD)	1.9 ± 1.0	2.1 ± 0.8	2.6 ± 1.6‡
Total cholesterol, mmol/L (SD)	4.8 ± 1.2	5.6 ± 1.5*	5.3 ± 1.5
N-terminal proBNP, pmol/L (median, IQR)	20 (9-46)	82 (18-140)*	84 (15-180) †
Uric acid, mmol/L (SD)	0.34 ± 0.10	0.38 ± 0.09	0.37 ± 0.09
Angiotensin-converting enzyme inhibitor	73 (23.9%)	23 (35.4%)	5 (16.7%)
Aspirin	168 (54.9%)	33 (50.8%)	15 (50.0%)
Nitroglycerin	38 (12.4%)	14 (21.5%)	8 (26.7%) †
Statin	181 (59.2%)	20 (30.8%)*	7 (23.3%) †
Calcium channel blocker	68 (22.2%)	21 (32.3%)	12 (40.0%) †
β-Blocker	242 (79.1%)	28 (43.1%)*	16 (53.3%) †

Values are expressed as number (%), mean, standard deviation, SD) or median (interquartile range, IQR).
* P<0.05 ST depression myocardial ischemia versus no ST changes
† P<0.05 ST elevation myocardial ischemia versus no ST change
‡ P<0.05 ST elevation myocardial ischemia versus ST depression myocardial ischemia

Data analysis

Clinical, laboratory and electrocardiographic characteristics between patients with ST-segment depression and ST-elevation were compared using one-way analyses of variance for continuous characteristics and chi-square analyses for dichotomous characteristics. Non-parametric tests were used if distributions were skewed. The three patients who had both ST-elevation and ST-depression during the same recording were classified according to the ST-change with the largest ischemic burden. Multivariate logistic regression analysis was used to evaluate the association between laboratory measurements and ST-depression or ST-elevation. Multivariate logistic and Cox regression analysis was also used to evaluate the prognostic value of ST-segment changes with perioperative and long-term outcome. In multivariate analysis, adjustments were made for age, gender, smoking, hypertension and the risk factors according to the Lee risk index (coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes and renal dysfunction). Odds and hazard ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analysis was performed using SPSS 13.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Mean age of the study population was 66.8 ± 10.1 years and 77.6% was male. During continuous Holter monitoring, ST-segment changes occurred in 23.7% of

Table 2. Significant laboratory predictors of perioperative ST-segment changes in multivariate regression analysis.

Baseline predictors	ST-deviation (n=95) OR¶ (95% CI)	ST-depression (n=65) OR¶ (95% CI)	ST-elevation (n=30) OR¶ (95% CI)
*HS-CRP, per LN increase in mg/L	2.3 (1.2-4.3)	NS**	3.8 (2.2-6.5)
White blood cell count per 10^9/L increase	NS**	NS**	1.5 (1.1-2.2)
†NT-pro-BNP, per LN increase in pmol/L	2.3 (1.2-4.2)	1.4 (1.0-2.0)	3.2 (1.2-9.2)
Hemoglobin, per mmol/L decrease	1.7 (1.2-2.6)	NS**	3.3 (1.3-8.3)
Glucose level, per mmol/L increase	1.6 (1.1-2.5)	NS**	NS**
Glycosylated hemoglobin, per % increase	1.8 (1.0-3.2)	NS**	NS**
‡LDL-cholesterol, per mmol/L increase	3.8 (1.1-14.2)	1.9 (1.0-3.9)	NS**
§HDL-cholesterol, per mmol/L decrease	0.2 (0.02-0.7)	NS**	NS**
‖EGFR, per ml/min/1.73m^3 decrease	NS**	NS**	0.9 (0.8-1.0)

*High-sensitivity C-reactive protein; †N-terminal pro-B-type natriuretic peptide; ‡Low-density lipoprotein cholesterol; §High-density lipoprotein cholesterol; ‖Estimated glomerular filtration rate. Associations were adjusted for age, gender, smoking, hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes and renal dysfunction; **Non-significant.

patients. Mean duration of ST-segment change was 62.8 min (range: 10-1020 minutes), mean (SD) ST-deviation was 2.0 1.2) mm and mean ischemic burden was 432.9 (range: 15-5632 mm*min). ST-segment change in the LAD, LCX and RCA territory was observed in 12.5%, 9.5%, and 8.5% of patients. ST-depression occurred in 16.2% and ST-elevation in 7.5% of patients. Troponin T release occurred in 90 patients (22.4%).

Perioperative ischemia in relation to the culprit coronary lesion

Non-invasive testing revealed rest wall motion abnormalities in 21.7% and stress-induced wall motion abnormalities in 20.7% of patients. Stress-induced ischemia in the LAD, LCX and RCA territory was observed in 12.7%, 8.5% and 15.2% of patients. In patients with both stress-induced and perioperative ischemia, location agreement was 89% for ST-depression in contrast to 53% for ST-elevation ($p<0.001$) (Figure 1). This agreement in location for ST-depression and ST-elevation was smallest in the LCX territory (Figure 1). Prior to surgery, a percutaneous coronary angioplasty intervention was performed in 30 patients (7.5%). None of the 30 patients developed ST-depression in the stented coronary territory, while 5/30 (16.7%) developed ST-elevation in the same stented territory ($p=0.02$).

ST-elevation versus ST-depression

Baseline characteristics of patients with no ST changes, ST-depression and ST-elevation are presented in Table 1. Patients with ST-elevation had significantly higher levels of HS-CRP and white blood cell count, compared to patients with ST-depression (Table 1). In multivariate analysis, increased levels of HS-CRP and white blood cell count remained independently associated with ST-elevation, together with advanced age, previous myocardial infarction, history of heart failure, decreased hemoglobin levels and increased NT-proBNP levels (Table 2). Risk factors associated with ST-depression did not include inflammation activity but did include previous myocardial infarction, decreased ankle-brachial index and increased LDL-cholesterol and NT-proBNP levels (Table 2). Patients with ST-depression and ST-elevation had significantly higher heart rates before, during and after surgery, compared to patients with no ST changes. The highest ischemic burden, amount of troponin T release, incidence of ventricular arrhythmias and lowest variability in heart rate was observed in patients with ST-elevation (Table 3).

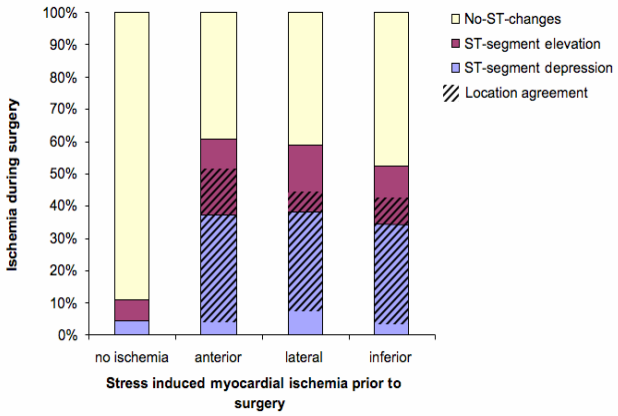

Figure 1. Myocardial ischemia during preoperative stress echocardiography in relation to perioperative myocardial ischemia during Holter electrocardiography.

Table 3. ST-depression and ST-elevation myocardial ischemia in relation to electrocardiographic variables.

Characteristic	No ST-changes (n=306)	ST-depression (n=65)	ST-elevation (n=30)
Heart rate before operation, bpm (SD)	67 ± 12	75 ± 15*	75 ± 11†
Heart rate during operation, bpm (SD)	68 ± 12	79 ± 12*	81 ± 15†
Heart rate after operation, bpm (SD)	72 ± 13	85 ± 14*	88 ± 15†
Heart rate at onset of ischemia, bpm (SD)	-	85 ± 12	92 ± 13
Peak heart rate during ischemia, bpm (SD)	-	100 ± 16	104 ± 15
Number of ischemic episodes per registration (SD)		1.9 ± 1.0	1.0 ± 1.2
Mean duration, minutes	-	143 ± 232	203 ± 258‡
Mean ST-segment deviation, mm	-	1.9 ± 0.9	2.2 ± 1.6‡
Ischemic burden, mm*min	-	512 ± 877	951 ± 1764‡
Ischemia before surgery	-	17 (26.2%)	7 (23.3%)
Ischemia during surgery	-	47 (72.3%)	18 (60.0%)
Ischemia after surgery	-	35 (53.8%)	21 (70.0%)
Non-sustained ventricular tachycardia	43 (14.1%)	21 (32.3%)*	13 (43.3)% †
Sustained ventricular tachycardia	6 (2.0%)	3 (4.6%)	7 (23.3%) † ‡
Ventricular fibrillation	0 (0%)	5 (7.7%)	4 (13.3%) †
Heart rate variability, 24 hour SDNN, ms (SD)	135 ± 45	119 ± 40	93 ± 36†
Troponin T positive	21 (6.9%)	45 (69.2%)*	24 (80.0%) †
Troponin T value, ug/L (median IQR)	0.15 (0.05-0.75)	0.19 (0.06-0.45)	0.67 (0.23-4.49) † ‡

Values are expressed as number (%), mean, standard deviation, SD) or median (interquartile range, IQR)
* P<0.05 ST depression myocardial ischemia versus no ST changes
† P<0.05 ST elevation myocardial ischemia versus no ST change
‡ P<0.05 ST elevation myocardial ischemia versus ST depression myocardial ischemia

Table 4. Association between electrocardiographic variables and cardiac events.

Characteristics	Perioperative cardiac events (n=23) OR* (95% CI)	Long-term cardiac events (n=69) HR* (95% CI)
No ST-deviation (reference)	1.0	1.0
- ST-segment depression	6.9 (2.1-22.4)	4.1 (2.3-7.2)
- ST-segment elevation	18.7 (5.2-66.2)	8.4 (4.6-15.4)
Heart rate before operation, per 10 bpm ↑	1.2 (0.9-1.7)	1.1 (1.0-1.4)
Heart rate during operation, per 10 bpm ↑	1.4 (1.0-1.9)	1.2 (1.0-1.5)
Heart rate after operation, per 10 bmp ↑	1.3 (1.1-1.7)	1.3 (1.1-1.5)
Number of ischemic episodes per registration	2.1 (1.6-2.8)	1.7 (1.5-2.0)
Ischemia duration, per hour ↑	1.3 (1.1-1.4)	1.2 (1.1-1.2)
ST-segment deviation, per mm ↑	2.3 (1.6-3.3)	1.6 (1.4-2.0)
Ischemic burden, per 1000 mm*min ↑	2.5 (1.5-4.1)	1.8 (1.4-2.4)
Ischemia before surgery	6.4 (2.1-19.3)	4.8 (2.8-8.4)
Ischemia during surgery	5.9 (2.4-14.9)	2.7 (1.6-4.3)
Ischemia after surgery	4.6 (1.8-11.8)	2.8 (1.7-4.7)
Stress echocardiography location disagreement	1.1 (0.3-3.3)	1.9 (1.1-2.9)
Heart rate variability, 24 hour SDNN, per 10 ms ↑	0.9 (0.7-1.1)	0.9 (0.7-1.0)

*Adjusted for age, gender, smoking, hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes and renal dysfunction.

Prognostic value of ST-depression and ST-elevation
In the 30-day period, major cardiac events occurred in 23 patients (6.0%). During follow-up, cardiac events occurred in 69 patients (17.2%). ST-depression during continuous ECG monitoring was associated with a 7-fold and 4-fold increased risk of perioperative and long-term cardiac events, respectively (Table 4). ST-elevation was associated with a 19-fold and 8-fold increased risk, respectively (Table 4). Higher intra- and postoperative heart rates and increased ischemic burden were also important correlates of adverse perioperative and long-term cardiac outcome (Table 4). This study confirmed that both higher doses of statins and β-blockers were associated with a lower rate of perioperative ischemia and cardiac evens (Table 5).

Table 5.The association of β-blockers and statins with perioperative ST-depression, ST-elevation and cardiac events in multivariate analysis.

Model	Perioperative ST-depression (n=65)	Perioperative ST-elevation (n=30)	Perioperative cardiac death or Q-wave myocardial infarction (n=23)	Long-term cardiac death or Q-wave myocardial infarction (n=69)
Statin dose per 10% increase of MRTD	0.85 (0.78-0.94)	0.72 (0.62-0.86)	0.60 (0.39-0.95)	0.75 (0.64-0.89)
β-Blocker dose per 10% increase of MRTD	0.67 (0.57-0.81)	0.83 (0.69-0.98)	0.72 (0.59-0.84)	0.73 (0.62-0.86)

The dose of statins and β-blocker therapy was converted to the percentage of maximum recommended therapeutic dose (MRTD) according to the FDA's Center for Drug Evaluation and Research database. The MRTD for simvastatin, pravastatin and fluvastatin was 0.67 mg/kg/day. A MRTD of 0.33 mg/kg/day was used for atorvastatin and rosuvastatin. The MRTD for atenolol and bisoprolol was 3.33 mg/kg/day, for metoprolol 6.67 mg/kg/day, for carvedilol 0.42 mg/kg/day, for propranolol 10.7 mg/kg/day, and for labetolol 40.7 mg/kg/day. Associations were adjusted for age, gender, smoking, hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes and renal dysfunction.

DISCUSSION

This study demonstrates that perioperative ST-depression occurs in 16% and ST-elevation in 8% of patients undergoing major vascular surgery. Importantly, there is a poor agreement between perioperative ST-elevation and the culprit coronary artery lesion as identified by preoperative stress testing. In addition, patients with ST-elevation were characterized by elevated inflammation activity, ischemic burden, troponin T amount, incidence of ventricular arrhythmias and the lowest heart rate variability compared to patients with ST-depression.

Perioperative ST-depression myocardial ischemia occurs mostly within the first two days after surgery and is often silent and presents without Q waves in the majority of cases [10]. ST-elevation-type ischemia has been considered relatively uncommon [10], although a high incidence of 12% of perioperative ST-elevation was observed in a study by London and colleagues [11]. This study found a high incidence of both prolonged ST-segment depression (16%) and ST-elevation ischemia (8%) in patients undergoing major vascular surgery, which were both significantly associated with early and late cardiac events. Prolonged myocardial ST-depression preceding postoperative cardiac complications has been observed in up to 85% of events [4,12]. Autopsy studies demonstrated that up to 55% of patients with fatal perioperative myocardial infarction has evidence of unstable plaques with disruption [5,13]

Several studies have investigated whether prophylactic revascularization of coronary artery lesions could prevent postoperative events. In the CARP (Coronary Artery Revascuarization Prophylaxis) randomized trial, the incidence of perioperative myocardial infarction was similar in patients allocated to prophylactic revasculization versus those allocated to optimal medical therapy (12% vs. 15% events) [8]. There was also no beneficial effect observed during long-term follow-up. The DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo Study Group)-V study confirmed these results in vascular surgery patients with extensive stress-induced ischemia [14]. In the current study, perioperative ST-elevation ischemia was poorly related to the coronary artery territory revealing wall motion abnormalities during stress testing. ST-depression ischemia, on the other hand, showed a much better agreement in location. If we assume that ST-elevation myocardial ischemia is the result of a vulnerable plaque, than this observation supports the hypothesis that vulnerable plaques can rupture at different sites in the absence of a critically narrowed coronary artery lumen. This may explain why preoperative revascularization of a coronary lesion fails to prevent perioperative cardiac events.

The positive association between HS-CRP and white blood cell count with ST-elevation supports the hypothesis that inflammation is a critical process in the development and progression of atherosclerotic vulnerable plaques in the perioperative setting. HS-CRP can directly influence vascular vulnerability by a variety of mechanisms, which include up-regulation of adhesion molecules [15,16], decreased nitric oxide production [17], increased LDL uptake by macrophages [18] and enhanced intravascular thrombosis in arterial injury [19]. Leukocytes have also been shown to play a major role in inflammatory processes and to be

pathogenic within unstable coronary plaques [20]. We also observed that decreased hemoglobin and increased NT-proBNP levels were associated with an increased risk of ST-elevation. Decreased hemoglobin levels have been recognized as an independent risk factor for major adverse cardiovascular events in community cohorts, heart failure and acute coronary syndromes [21-23]. NT-proBNP has prognostic value in patients with acute coronary syndromes and stable coronary artery disease [24,25]. Although the magnitude of NT-proBNP rises with the severity of ischemia during exercise testing [26], data linking NT-proBNP to the pathogenesis of ST-elevation are limited. More studies are needed to confirm the association between laboratory markers and the onset of ST-elevation myocardial ischemia.

It has been suggested that ST depression ischemia has a more unfavorable outcome compared to ST elevation [10]. The current study suggests the contrary. Not only was ischemic burden and amount of troponin T release higher, ventricular arrhythmias were more common and heart rate variability was lower in patients with perioperative ST-elevation. Monitoring for both ST-elevation and depression may significantly improve risk stratification in addition to clinical risk variables, laboratory markers and stress test results. Therefore, vascular surgery patients may benefit from routine ischemia screening with 12-lead electrocardiographic monitoring. This non-invasive and readily applicable procedure identifies high-risk patients who can benefit from medical risk reduction strategies, such as β-blockers and statins [7].

A limitation of this study is the high preponderance of male and Caucasian patients. In addition, the risk profile of this study population may be higher than average, since the study was performed in a University hospital which acts as tertiary referral center. The lack of coronary angiography is a limitation in the current study. However, we used stress echocardiography to identify the culprit coronary lesion, since this is the recommended method for preoperative risk stratification according to ACC/AHA guidelines. ECG monitoring was performed during a 72-hour perioperative period. Although longer than in most previous studies in this setting, a more precise estimation of the results may have been obtained by longer ECG recordings. Lastly, co-morbidities associated with perioperative cardiovascular events may have influenced our results, since statins and β-blockers were not randomized. However, we conducted multivariate analysis to adjust for known confounding factors.

In conclusion, both perioperative ST-depression and ST-elevation are common in patients undergoing major vascular surgery. The highest inflammation activity, ischemic burden, troponin T amount, incidence of ventricular arrhythmias and the lowest heart rate variability were observed in patients with ST-elevation. In contrast to perioperative ST-depression, a poor agreement was observed between perioperative ST-elevation and the culprit coronary artery lesion as identified by preoperative stress testing.

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Chapter 11

The prevalence and prognosis of unrecognized myocardial infarction and silent myocardial ischemia in patients undergoing major vascular surgery

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The prevalence and prognosis of unrecognized myocardial infarction and silent myocardial ischemia in patients undergoing major vascular surgery

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Objective(s): The aim of this study is to determine the prevalence and prognosis of unrecognized myocardial infarction (MI) and silent myocardial ischemia in vascular surgery patients.
Methods: In a cohort of 1,092 patients undergoing preoperative dobutamine stress echocardiography and non-cardiac vascular surgery, unrecognized MI was determined by rest wall motion abnormalities in the absence of a history of MI. Silent myocardial ischemia was determined by stress-induced wall motion abnormalities in the absence of angina pectoris. β-Blockers and statins were noted at baseline. During follow-up (mean: 6 ± 4 years), all-cause mortality and major cardiac events (cardiac death or non-fatal MI) were noted.
Results: The prevalence of unrecognized MI and silent myocardial ischemia was 23% and 28%, respectively. Both diabetes and heart failure were important predictors of unrecognized MI and silent myocardial ischemia. During follow-up, all-cause mortality occurred in 45% and major cardiac events in 23% of patients. In multivariate analysis, unrecognized MI and silent myocardial ischemia were significantly associated with increased risk of mortality (HR: 1.86, 95% CI: 1.53-2.25 and HR: 1.74, 95% CI: 1.46-2.06, respectively) and major cardiac events (HR: 2.15, 95% CI: 1.59-2.92, HR: 1.86, 95% CI: 1.43-2.41, respectively). In patients with unrecognized MI, β-blockers and statins were significantly associated with improved survival. Statins improved survival in patients with silent myocardial ischemia.
Conclusions: In patients undergoing major vascular surgery, unrecognized MI and silent myocardial ischemia are highly prevalent (23% and 28%) and associated with increased long-term mortality and major cardiac events.

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SINCE 1919, cardiovascular disease has been the single leading cause of death in the United States and is the underlying or contributing cause of death in about 58% of all cases [1]. Cardiac complications also remain the leading cause of morbidity and mortality in patients undergoing major vascular surgery. Perioperative cardiac complication rate in vascular surgery patients have been reported to range from 2.2% to 19.0% [2]. The high frequency of perioperative cardiac complications reflects the high prevalence of underlying coronary artery disease. Indeed, coronary angiographic abnormalities have been reported in up to 92% of patients [3]. Patients with coronary artery disease, however, may not always present with a history of myocardial infarction (MI) or with symptoms of angina pectoris [4,5]. Unfortunately, the prevalence and prognosis of these patients with asymptomatic coronary artery disease is not well known. In view of the many major vascular surgery procedures performed annually, routine screening for asymptomatic coronary artery disease may be recommended to identify high-risk patients who may benefit from medical treatment.

Dobutamine stress echocardiography is a widely used non-invasive technique for the detection of coronary artery disease. Regional wall motion abnormalities during rest signify infarcted myocardial tissue and wall motion abnormalities during stress testing signify myocardial ischemia. The current study reports the prevalence and long-term prognosis of unrecognized MI and silent myocardial ischemia in 1,092 patients who underwent preoperative dobutamine stress echocardiography and major vascular surgery. In addition, the effect of chronic β-blocker and statin therapy on survival in patients with asymptomatic coronary artery disease was evaluated.

METHODS

Patient population

A total of 1,092 patients who underwent major non-emergent non-cardiac vascular surgery at the Erasmus Medical Centre in Rotterdam, the Netherlands, were enrolled in this study from April 1990 to January 2004. In all patients, a preoperative dobutamine stress echocardiography was performed to detect the presence and extent of coronary artery disease. The study protocol was approved by the Hospital's Ethics Committee and all patients gave informed consent. Prior to surgery, patients were screened for the following cardiac risk factors: age over 70 years, angina pectoris, prior MI on the basis of history or a finding of pathologic Q waves on electrocardiography, compensated congestive heart failure or a history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction and prior stroke or transient ischemic attack. The use of cardiac medication was recorded and chronic use was ascertained if medication was documented at least one month prior to surgery and at hospital discharge.

Dobutamine stress echocardiography

Patients underwent a resting two-dimensional precordial echocardiographic examination and standard apical and parasternal views were recorded on videotaped. Dobutamine hydrochloride was administered intravenously with an infusion pump with incremental doses of 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min (stage 4) and continued for 6 minutes. The dobutamine infusion was stopped if a target heart rate was achieved (85% of a theoretic maximal heart rate; men: [220 – age] x 85%; women: [200 – age] x 85%). If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulphate (starting with 0.25 mg and increased to a cumulative maximum of 2.0 mg) was given intravenously at the end of stage 4 while the dobutamine administration was continued. During the test, a 12-lead ECG was recorded at baseline and every minute. Blood pressure was measured by sphygmomanometry every 3 minutes. Metoprolol was administered (1,0 to 5,0 mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine-atropine combination if the side effects did not revert spontaneously and quickly. Atropine was administered as an antidote if bradycardia and hypotension occurred. The criteria for stopping the test were: (1) severe new echocardiographic wall motion abnormalities in multiple locations, (2) horizontal or downsloping electrocardiographic ST depression of ≥0.2 mV measured 80 ms after the J point, or ST-segment elevation of ≥0.2 mV in the absence of Q waves, (3) symptomatic decline in systolic blood pressure of more than 40 mmHg from the resting value, or a systolic blood pressure of less than 100 mmHg, (4) hypertension (blood pressure >240/140 mmHg), (5) the occurrence of cardiac arrhythmias, (6) severe angina pectoris, and (7) intolerable adverse side effects. considered to be the result of dobutamine or atropine.

Assessment of echocardiographic images

Off-line assessment of echocardiographic images was performed by two experienced investigators without knowledge of the patient's clinical data but with knowledge of the doses of dobutamine and atropine used. From 1990 to 1993, the left ventricle was divided into 14 segments and wall motion was scored on a 4-point ordinal scale [6]. After 1993 a 16-segment 5-point score was used [7]. MI was considered in the presence of rest wall abnormalities. Myocardial ischemia was considered if new wall motion abnormalities occurred (i.e., if wall motion in any segment worsened by ≥1 grade(s) during the test, with the exception of akinesis becoming dyskinesis). For each patient, a wall motion score index (total score divided by the number of assessable segments) was calculated at rest and during peak stress. The extent of ischemia was defined as the number of segments exhibiting deteriorating wall motion during stress. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessments and a majority decision was reached. Unrecognized MI was defined as rest wall motion abnormalities in the absence of a history of MI. Silent myocardial ischemia was defined as stress-induced wall motion abnormalities in the absence of a history of angina pectoris or complaints during stress test.

Follow-up

Study endpoints were death and cardiac events (composite of cardiac death and non-fatal MI) during long-term follow-up after successful vascular surgery. Information on mortality and cause was obtained by contacting the referring physician or by approaching the municipal civil registry to determine survival status. In patients who died, death certificates and autopsy reports were reviewed and general practitioners were approached to ascertain the cause of death. Cardiac death was defined as death caused by acute MI, cardiac arrhythmias, congestive heart failure, or sudden death. Non-fatal MI was diagnosed when at least the following were present: elevated cardiac enzyme levels, development of new Q waves (>1 mm or > 30 ms), and typical symptoms of angina pectoris. No patients were lost to follow-up.

Data analysis
Continuous data were expressed as mean (± SD) and compared using the Student t test. Categorical data were compared using the Chi square test. A final set of independent and significant predictors of asymptomatic coronary artery disease was obtained by multivariate logistic regression analysis with stepwise deletion of the least significant variable. Only variables with a p-value ≤0.10 were retained in the model. The Kaplan-Meier method with the log-rank test was used to assess differences in survival between patient groups. Cox proportional hazard regression analysis was used to evaluate the long-term prognostic value of asymptomatic coronary artery disease. In multivariate analysis, adjustments were made for age, gender, diabetes, heart failure, cerebrovascular disease, hypertension and cardiovascular medication. The risk associated with a given variable was expressed by a hazard ratio (HR) with corresponding 95% confidence interval (CI). For all tests, a p-value <0.05 (two-sided) was considered significant. All analysis were performed using SPSS statistical software.

RESULTS

Baseline characteristics of the study population are presented in Table 1. A total of 371 patients (34%) presented with a history of MI, 178 patients (16%) had angina pectoris and 446 patients (41%) presented with symptomatic coronary artery disease. During stress echocardiography, the maximum dobutamine dose was 36 μg/kg/min and atropine was administered in 30%. The test was terminated for the following reasons: achievement of the target heart rate in 89%, maximal dobutamine/atropine dose in 3%, ST-segment changes in 3%, abnormal blood pressure in 1%, arrhythmias in 1%, severe angina in 1% and for other symptoms in 2%. There were no fatal complications. Rest wall motion abnormalities were observed in 533 patients (49%) and new wall motion abnormalities in 399 (37%).

Table 1. Baseline characteristics of patients undergoing major vascular surgery.

	n=1,092
Age (years)	64 ± 15
Gender (male)	848 (78%)
Length (cm)	171 ± 9
Body mass index (kg/m^2)	25 ± 4
History of angina pectoris	178 (16%)
History of myocardial infarction	371 (34%)
Coronary artery disease	446 (41%)
History of congestive heart failure	65 (6%)
Hypertension	491 (45%)
Smoking	331 (30%)
Hypercholesterolemia	205 (19%)
Diabetes Mellitus	124 (11%)
Chronic obstructive pulmonary disease	202 (18%)
Renal insufficiency	73 (7%)
Angiotensin converting enzyme inhibitor	296 (27%)
Aspirin	270 (25%)
β-blockers	289 (35%)
Calcium antagonist	296 (36%)
Coumarin	212 (19%)
Digitalis	41 (4%)
Diuretic	169 (15%)
Nitrates	241 (22%)
Statins	286 (26%)

Values are expressed as mean ± SD or number and percentage.

Prevalence and predictors of asymptomatic coronary artery disease
Unrecognized MI and silent myocardial ischemia was detected in 255 (23%), and 309 (28%) patients, respectively. The incidence of unrecognized MI and silent myocardial ischemia was significantly higher in patients with diabetes (34% and 41%, respectively) (Figure 1). The rest wall motion score index in patients with unrecognized MI was comparable to the rest wall motion score index in patients with a recognized MI (1.52 vs. 1.48, respectively, p=0.4). The wall motion score index at peak stress between patients with silent and symptomatic myocardial ischemia was comparable (1.52 vs. 1.61, respectively, p=0.1). The extent of ischemia between patients with silent and symptomatic myocardial ischemia was also comparable (4.9 vs. 4.8 segments, respectively, p=0.7). As demonstrated in Table 2, a history of heart failure and diabetes were strong predictors of unrecognized MI and silent myocardial ischemia.

Prognosis of asymptomatic coronary artery disease
During a mean follow-up of 6 ± 4 years, all-cause mortality and cardiac events occurred in 491 patients (45%) and 253 patients (23%), respectively. Kaplan-Meier analysis showed that patients with unrecognized MI (p<0.001) and silent myocardial ischemia (p<0.001) had a worse survival compared to patients with no symptoms or signs of coronary artery disease. In multivariate analysis, unrecognized MI and silent myocardial ischemia remained significantly associated with increased all-cause mortality and cardiac events (Table 3).

Table 2. Independent predictors of unrecognized myocardial infarction (a) and silent myocardial ischemia (b) in patients undergoing major vascular surgery.

a. Unrecognized myocardial infarction (n=255)

	Odds ratio	95% confidence interval	p-value
History of heart failure	7.88	2.16-28.74	0.002
Diabetes mellitus	2.28	1.34-3.88	0.002
C-index			<0.001

b. Silent myocardial ischemia (n=397)

	Odds ratio	95% confidence interval	p-value
Renal failure	1.88	1.09-3.23	0.02
History of heart failure	4.40	2.18-8.87	<0.001
Diabetes mellitus	1.83	1.20-2.79	0.005
C-index			<0.001

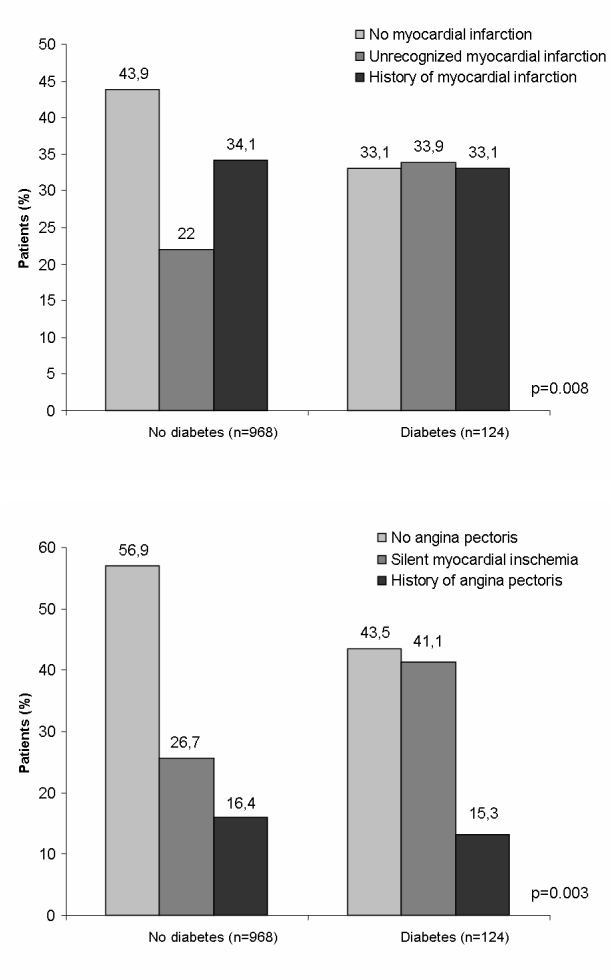

Figure 1. The prevalence of unrecognized myocardial infarction and silent myocardial ischemia in patients with and without diabetes.

Prognostic value of stress echocardiography in symptomatic coronary artery disease

Multivariate analysis revealed that rest wall motion abnormalities were associated with increased all-cause mortality (HR: 1.52, 95% CI: 1.16-1.99) and cardiac events (HR: 1.56, 95% CI: 1.09-2.23) in patients with a history of MI. Stress-induced wall motion abnormalities were associated with increased all-cause mortality (HR: 1.83, 95% CI: 1.35-2.49) and cardiac events (HR: 1.90, 95% CI: 1.27-2.83) in patients with a history of angina pectoris. Either rest or new wall motion abnormalities were associated with increased all-cause mortality (HR: 1.43, 95% CI: 1.16-1.76) and cardiac events (HR: 1.44, 95% CI: 1.08-1.88) in patients with a history of MI or angina pectoris.

Chronic β-blocker and statin therapy

Multivariate analysis showed that β-blockers were significantly associated with a lower mortality rate in subgroups of patients with unrecognized MI, compared to patients with no β-blockers (Table 4). Statins were associated with a lower mortality rate in subgroups of patients with unrecognized MI and silent myocardial ischemia, compared to patients with no statins (Table 4).

DISCUSSION

Prevalence

We found that vascular surgery patients with asymptomatic coronary artery disease are an underestimated risk group. Unrecognized MI and silent myocardial ischemia was detected in 23% and 28% of patients, respectively. The prevalence of unrecognized MI and silent myocardial ischemia was considerably higher in patients with diabetes (34% and 41%, respectively). This suggests a later clinical manifestation of coronary artery disease in patients with diabetes, compared to patients with no diabetes. Interestingly, abnormalities during cardiac testing were

Table 3. The prognostic value of unrecognized myocardial infarction and silent myocardial ischemia in patients undergoing major vascular surgery.

	Long-term mortality (n=491)	Long-term cardiac events (n=253)
No myocardial infarction (reference)	1.0	1.0
Unrecognized myocardial infarction	1.86 (1.53-2.25)	2.15 (1.59-2.92)
Recognized myocardial infarction	1.99 (1.70-2.33)	3.08 (2.42-3.92)
No myocardial ischemia (reference)	1.0	1.0
Silent myocardial ischemia	1.74 (1.46-2.06)	1.86 (1.43-2.41)
Symptomatic myocardial ischemia	1.42 (1.17-1.75)	1.80 (1.35-2.40)

Values are expressed as hazard ratio with 95% confidence interval. All associations were entered in multivariate analysis with adjustment for baseline clinical risk factors and chronic medication use.

comparable between patients with and without symptomatic disease. Thus, the absence of symptoms does not imply less coronary artery disease severity. A high prevalence of asymptomatic coronary artery disease is not uncommon in the general population. Among participants in the Framingham Study with MIs, around 25% presented with electrocardiographic abnormalities suggestive of MI without recollection of any relevant discomfort or symptoms compatible with infarction [8]. Among asymptomatic type 2 diabetic patients, 22% presented with silent myocardial ischemia as detected by cardiac stress testing [9].

Prognosis

Unrecognized MI and silent myocardial ischemia have now been recognized as clinical syndromes within the spectrum of coronary artery disease. Our results showed that the prognosis of asymptomatic coronary artery disease was as poor as the prognosis of patients with symptomatic coronary artery disease. The ultimate goal of surgery in patients with vascular disease is to improve symptoms and prognosis. Many studies have focused on the reduction of mortality and morbidity during hospital stay and their findings have resulted in helpful recommendations on perioperative care [10]. Unfortunately, guidelines on clinical management after successful hospital discharge are limited, although many patients remain at increased risk of adverse late events. Screening for asymptomatic coronary artery disease is still controversial. Stress testing may influence patient management and long-term outcome. However, when optimal medical therapy is provided routine non-invasive testing may not influence patient management [10]. The COURAGE trial, for example, demonstrated that in patients with stable coronary artery disease, percutaneous coronary intervention did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy [11].

Stress echocardiography in symptomatic coronary artery disease

Stress echocardiography has been demonstrated to be a useful method for prognostic risk assessment in patients undergoing major vascular surgery. Patients with symptomatic coronary artery disease have a high pre-test probability of coronary artery disease. According to the Bayes theorem, a normal stress test result in these patients only modestly reduces the post-test probability of coronary artery disease [12]. In this study, dobutamine stress echocardiography added independent prognostic information in patients with a history of angina or MI and with a high pre-test probability of coronary artery disease. Symptomatic patients with stress induced myocardial ischemia had a higher risk of death and hard cardiac events, whereas in patients with a normal dobutamine stress echocardiography the incidence of events was substantially lower. These findings indicate that symptomatic patients with negative dobutamine stress echocardiography findings can be exempted from further (invasive) evaluation unless a change in clinical status occurs. Those with positive findings may benefit from further cardiac evaluation with appropriate management.

Medical treatment

Since patients with asymptomatic coronary artery disease are at similar mortality risk as symptomatic patients, cardioprotective strategies should be considered in all asymptomatic patients who successfully underwent major vascular surgery. Previous studies have demonstrated that statins reduce cardiovascular events during perioperative and long-term follow-up [13,14]. β-Blockers have been demonstrated to effectively protect against the life-threatening complications of coronary artery disease in post-infarct patients [15] and in those with heart failure [16]. In the current study, a protective effect of statins was observed in both symptomatic and asymptomatic disease patients. Beta-blockers were significantly protective in patients with unrecognized or recognized MI, and non-significantly in patients with silent myocardial ischemia. It should be noted that no decisive evidence has been published in literature which demonstrates that β-blockers improve survival in patients with angina, except for its effect on symptomatic relief and blood-pressure reduction [17].

Table 4. Association between beta-blockers and long-term mortality among patients with unrecognized myocardial infarction and silent myocardial ischemia.

	Chronic β-blocker therapy	β-blockers and long-term mortality (n=491)	Chronic statin therapy	Statins and long-term mortality (n=491)
No myocardial infarction (reference)	22%	0.80 (0.45-1.41)	23%	0.43 (0.26-0.71)
Unrecognized myocardial infarction	43%	0.46 (0.27-0.81)	28%	0.44 (0.23-0.85)
Recognized myocardial infarction	47%	0.59 (0.39-0.91)	28%	0.26 (0.16-0.45)
No myocardial ischemia (reference)	22%	0.70 (0.47-1.06)	24%	0.42 (0.27-0.64)
Silent myocardial ischemia	52%	0.59 (0.33-1.05)	29%	0.32 (0.19-0.54)
Symptomatic myocardial ischemia	43%	0.52 (0.24-1.09)	28%	0.30 (0.11-0.86)

Values are expressed as hazard ratio with 95% confidence interval. All associations were entered in multivariate analysis with adjustment for baseline clinical risk factors

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Study limitations

No angiography was performed in this study. Therefore, the prevalence and prognosis of asymptomatic angiographic coronary artery stenosis cannot be described. Secondly, although physicians can be confident about the interpretation of the echocardiographic images, misinterpretation of wall motion abnormalities can still occur. However, excellent technical performance and diagnostic accuracy of dobutamine stress echocardiography for coronary artery disease have been reported previously [18]. Lastly, the data apply to patients referred to a tertiary referral center in Western Europe. These patients may have a different cardiovascular risk profile compared to patients referred to primary or secondary referral centers.

Summary

The prevalence of unrecognized MI and silent myocardial ischemia in patients undergoing major vascular surgery was 23% and 28%, respectively. Both diabetes and heart failure were important predictors of asymptomatic coronary artery disease. Abnormalities during cardiac testing were comparable between symptomatic and asymptomatic patients. The prognosis of patients with asymptomatic disease was similar to the prognosis of patients with symptomatic disease and was distinctively worse than that of patients without coronary artery disease. Not only symptomatic patients, but also patients with asymptomatic coronary artery disease may benefit from cardiovascular medication.

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Chapter 12

Impaired fasting glucose and poor glycemic control are risk factors for cardiac ischemic events in vascular surgery patients

Diabetic Medicine. In press

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Impaired glucose and elevated glycosylated hemoglobin levels in relation to cardiac ischemic events in vascular surgery patients

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Aims: Cardiac morbidity and mortality is high in patients undergoing high-risk surgery. This study evaluates whether impaired glucose and elevated glycosylated hemoglobin (HbA_{1c}) levels are associated with increased cardiac ischemic events in vascular surgery patients.
Methods: Baseline glucose and HbA_{1c} were measured in 401 vascular surgery patients. Glucose <5.6 mmol/L was normal. Fasting glucose between 5.6-7.0 mmol/L or random glucose between 5.6-11.1 mmol/L was impaired. Fasting glucose ≥7.0 or random glucose ≥11.1 mmol/L was diabetes. Perioperative ischemia was identified by 72-hour Holter monitoring. Troponin T was measured on day 1, 3, 7 and before discharge. Cardiac death or Q-wave myocardial infarction were noted at 30-day and follow-up (mean 2.5 years).
Results: Mean glucose and HbA_{1c} was 6.3 ± 2.3 mmol/L and 6.2 ± 1.3%, respectively. Ischemia, troponin release, 30-day and long-term cardiac events occurred in 27%, 22%, 6% and 17%, respectively. Multivariate analysis revealed that patients with respectively impaired glucose and diabetes were at 2.2- and 2.6-fold increased risk for ischemia, 3.8- and 3.9-fold for troponin release, 4.3- and 4.8-fold for 30-day cardiac events and 1.9- and 3.1-fold for long-term cardiac events. Patients with HbA_{1c} values >7% (n=63, 16%) were at 2.8-fold, 2.1-fold, 5.3-fold and 5.6-fold increased risk for ischemia, troponin release, 30-day and long-term cardiac events, respectively.
Conclusions: Impaired glucose and elevated HbA_{1c} levels are risk factors for cardiac ischemic events in vascular surgery patients. This finding suggests the need for aggressive glucose management in this setting and supports a vigorous screening strategy for early recognition of diabetes.

ANNUALLY, AROUND 0.2% of the Dutch population is scheduled for major non-cardiac vascular surgery [1]. Among diabetic patients undergoing major vascular surgery, cardiac complications are the leading cause of morbidity and mortality. The incidence of perioperative cardiac events in these patients ranges from 6% to 21% [2-5]. Cardiac complications in diabetes are likely the result of impaired glucose metabolism leading to endothelial dysfunction, myocardial ischemia and myocardial tissue damage [6]. Pre-diabetes represents a metabolic stage intermediate between normal glucose homeostasis and diabetes [7]. These patients exhibit a long asymptomatic period of increased glucose dysregulation and are at risk of developing type 2 diabetes [7]. Although diabetes has been recognized as an independent predictor of postoperative outcome, the prognosis of non-diabetic patients with impaired glucose levels is not well known. In addition, poor glycemic control in diabetic and non-diabetic patients may be associated with adverse cardiac outcome.

This study was conducted to elucidate the association between impaired glucose and elevated glycosylated hemoglobin (HbA_{1c}) levels with perioperative and long-term cardiac ischemic events in patients undergoing major vascular surgery.

PATIENTS AND METHODS

The study population consisted of 401 patients undergoing elective abdominal aortic aneurysm repair, peripheral artery bypass surgery or carotid artery surgery at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period 2002 to 2006. The study was approved by the hospital's ethical committee and performed with informed consent of all patients. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block and atrial fibrillation were excluded. Patients who participated in

clinical intervention trials at or outside the Erasmus Medical Center were also excluded. Patients were enrolled up to 3 months prior to surgery at the outpatient clinic. In all patients, β-blockers were considered prior to surgery to obtain perioperative heart rates of 60-65 beats per minute. Baseline characteristics were obtained and included demographic, historical, laboratory and electrocardiographic information. Body mass index was calculated using the formula weight/height^2. Renal dysfunction was defined as serum creatinine level ≥177 μmol/L (2.0 mg/dL) or if renal dialysis was required.

Baseline glucose and HbA_{1c} measurements. Baseline glucose and HbA_{1c} measurements were obtained during preoperative evaluation at a central laboratory. Blood samples were obtained using venipuncture with minimal stasis. Glucose was enzymatically determined using the Hexokinase method (Boehringer Mannheim). HbA_{1c} was determined by using an enzyme immunoassay based on microtiter plate technology. Information was obtained on history of diabetes and use of blood glucose lowering treatment. Patients were classified into three categories: glucose levels <5.6 mmol/L were normal. Fasting glucose of 5.6-7.0 mmol/L or random glucose of 5.6-11.1 mmol/L was impaired. Fasting glucose ≥ 7.0 or random glucose ≥ 11.1 mmol/L, or the use of blood glucose–lowering medication was diabetes [7].

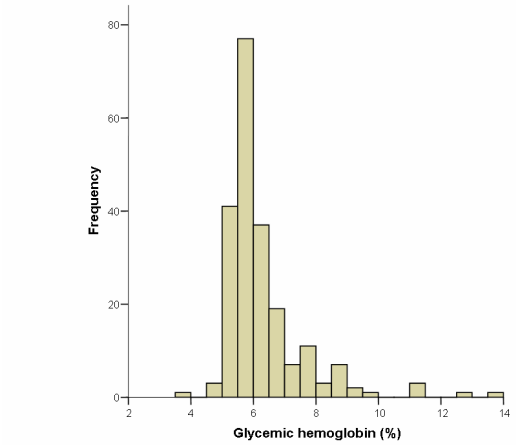

Figure 1. Histogram demonstrating baseline glucose levels in the study population.

Perioperative myocardial ischemia.
Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts), starting 1 day before surgery up to 2 days after. Recordings were performed in the continuous 12-lead mode with a recording length of 10 seconds every minute. The frequency response was 0.05 – 150Hz. Electrocardiographic data were initially processed by a technician and analyzed by 2 experienced cardiologists who were blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the ambulatory electrocardiography recordings were analyzed for ST-segment deviations. A continuous ST segment trend was generated and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST-segment changes, lasting at least one minute and shifting from baseline to more than 0.1 mV (1 mm). The baseline ST segment level was defined as the average ST segment during a stable period (duration of 20 minutes) preceding each ischemic episode. ST segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST segment change was measured 40 ms after that point.

Perioperative troponin T release.
Troponin T levels were measured on postoperative day 1, 3, 7, before discharge and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The lower limit of 0.03 ng/ml was used to define positive troponin T levels since lower levels do not meet the imprecision criteria of <10%.

Clinical cardiac outcome.
Study endpoints were major cardiac events (cardiac death and non-fatal Q-wave myocardial infarction) during the perioperative period (30-day period after surgery) and during follow-up (mean: 2.5 years). During follow-up, outpatient visits were scheduled every 3 months after discharge. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. Non-fatal myocardial infarction was diagnosed when at least the following were present: elevated cardiac enzyme levels, development of new Q waves (>1 mm or > 30 ms), and typical symptoms of angina pectoris. No patients were lost to follow-up.

Data analysis.
Characteristics of patients with normal glucose, impaired glucose and diabetes were calculated and tested for differences between groups using one-way analysis of variance for continuous characteristics and chi-square for dichotomous characteristics. Binary logistic regression analysis was used to evaluate the association of glucose and HbA_{1c} status with perioperative myocardial ischemia, troponin T release and 30-day cardiac events. Cox proportional hazard analysis was used to assess the association of glucose

Table 1. Characteristics of the study population (n=401) by glucose status.

Characteristic	No diabetes (n=332)		Diabetes (n = 69)
	Normal glucose (n =220)	Impaired glucose (n =112)	
Age, years	66 ± 11	68 ± 9	66 ± 11
Gender, male	77.3%	80.4%	72.5%
Angina pectoris	14.5%	24.1%*	20.3%
Myocardial infarction	28.2%	47.3%*	44.9%†
Previous percutaneous coronary angioplasty	5.9%	10.7%	10.1%
Previous coronary artery bypass grafting	9.5%	26.8%*	17.4%
History of congestive heart failure	0.9%	9.3%*	4.3%
Rest wall motion abnormalities	29.5%	33.0%	27.5%
Stress-induced wall motion abnormalities	25.0%	29.5%	27.5%
Hypertension	40.0%	36.6%	49.3%
Stroke	13.1%	16.1%	13.0%
Past smoking	60.9%	58.0%	43.5%†
Current smoking	31.4%	28.6%	20.3%
Renal dysfunction	1.8%	8.9%	4.3%
Body mass index (kg/m^2)	24.9 ± 3.5	25.3 ± 4.0	26.8 ± 3.6†
Ankle-brachial index	0.88 ± 0.26	0.80 ± 0.32	0.80 ± 0.28
Forced expiratory volume in 1 second, liter	2.5 ± 0.8	2.4 ± 0.8	2.4 ± 0.8
Urea level, mmol/L	6.6 ± 3.7	8.3 ± 3.9*	7.5 ± 3.6
Creatinine level, µmol/L	97 ± 83	101 ± 68	100 ± 69
Low density lipoprotein cholesterol, mmol/L	3.1 ± 1.1	3.1 ± 1.1	2.8 ± 1.0
High density lipoprotein cholesterol, mmol/L	1.3 ± 0.6	1.3 ± 0.5	1.2 ± 0.4
Total cholesterol, mmol/L	4.9 ± 1.2	5.1 ± 1.3	4.8 ± 1.3
Hemoglobin, mmol/L	8.7 ± 0.9	8.4 ± 1.2*	8.4 ± 1.3†
Hematocrit, L/L	0.42 ± 0.04	0.39 ± 0.05*	0.40 ± 0.06
High sensitivity C-reactive protein, mg/L	9.9 ± 13.8	46 ± 77*	24 ± 40‡
Uric acid, mmol/L	0.34 ± 0.09	0.35 ± 0.1	0.38 ± 0.12
N-terminal proBNP level, pmol/L, median	101	124	111
Glycosylated hemoglobin, %	5.6 ± 0.4	6.0 ± 0.8	7.9 ± 1.8 †‡

Values are presented as percentage or as mean ± standard deviation, unless otherwise notified.
* P<0.05 impaired glucose versus normal glucose
† P<0.05 diabetics versus normal glucose
‡ P<0.05 diabetics versus impaired glucose

and HbA_{1c} status with late cardiac events. In multivariate analysis, adjustments were made for age, gender, angina pectoris, myocardial infarction, congestive heart failure, hypertension, stroke, smoking, renal dysfunction and laboratory measures. Only laboratory measures of which the values were significantly different among the three groups were included (Table 1). Patients with impaired glucose levels and diabetes were compared to patients with normal glucose levels. In addition, absolute glucose and HbA_{1c} values were assessed as continuous variables. Odds and hazard ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Mean glucose level in the study population was 6.3 ± 2.3 mmol/L (Figure 1). Mean HbA_{1c} level was 6.2 ± 1.3%. The characteristics of the patients with normal glucose levels (n=220, 55%), impaired glucose (n=112, 28%) and diabetes (n=69, 17%) are presented in Table 1. Patients with impaired glucose levels had a higher prevalence of angina pectoris, myocardial infarction, coronary bypass surgery and congestive heart failure, compared to patients with normal glucose levels. Laboratory testing revealed that urea and high-sensitivity C-reactive protein were significantly higher in patients with impaired glucose levels, compared to patients with normal glucose levels (Table 1). Hemoglobin and hematocrit were significantly lower in patients with impaired glucose levels (Table 1).

Events

Perioperative myocardial ischemia during 72-hour 12-lead electrocardiographic monitoring occurred in 108 patients (27%). Perioperative troponin T release occurred in 90 patients (22%) and 30-day major cardiac events in 23 patients (6%). A total of 131 patients (33%) experienced either an episode of myocardial ischemia, troponin T release or a major cardiac event in the perioperative period. During follow-up, 85 patients

(21%) died. Cardiac death or non-fatal myocardial infarction during follow-up occurred in 69 patients (17%).

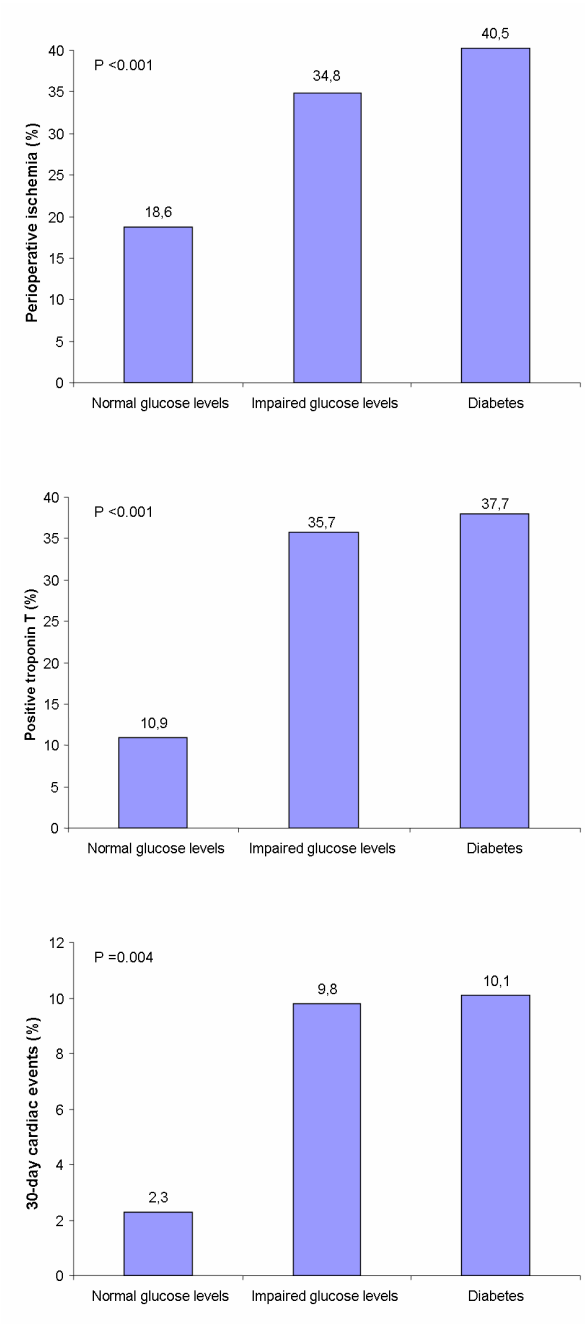

Figure 2. The incidence of myocardial ischemia (p<0.001), troponin T (p<0.001) release and 30-day cardiac events (p<0.001) in patients with different baseline glucose and glycosylated hemoglobin status.

Glucose and HbA_{1c} status in relation to events

As demonstrated in Figure 2, the lowest incidence of myocardial ischemia, troponin T release and 30-day cardiac events occurred in patients with normal glucose levels. Patients with normal baseline glucose levels had the best survival, in comparison to patients with impaired glucose or diabetes (p<0.001) (Figure 3). Multivariate analysis revealed that patients with respectively impaired glucose and diabetes, were at 2.2 and 2.6-fold increased risk for myocardial ischemia, 3.8- and 3.9-fold increased risk for troponin T release, 4.3- and 4.8-fold increased risk for 30-day cardiac events, 2.0- and 2.7-fold increased risk for long-term mortality and 1.9- and 3.1-fold increased risk for long-term cardiac events (Table 2). Patients with HbA_{1c} values above 7% (n=63, 16%) were at 2.8-fold, 2.1-fold, 5.3-fold, 3.6-fold and 5.6-fold increased risk for myocardial ischemia, troponin T release, 30-day cardiac events, long-term mortality and long-term cardiac events, respectively (Table 2). When using absolute values, higher glucose and HbA_{1c} values remained significantly associated with increased perioperative and long-term events (Table 2).

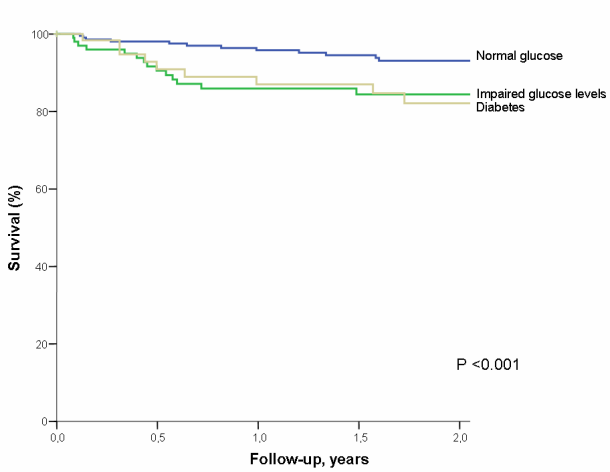

Figure 3. Kaplan-Meier curves demonstrating survival in patients with different baseline glucose and glycosylated hemoglobin status (p<0.001).

DISCUSSION

The results of this study indicate that impaired glucose is highly prevalent in vascular surgery patients (28%). Moreover, poor glycosylated hemoglobin status (HbA_{1c} >7%) was assessed in 16% of patients. Importantly, both impaired glucose and elevated HbA_{1c} levels were associated with an increased incidence of perioperative myocardial ischemia, perioperative troponin T release, and 30-day and long-term cardiac events, independent of age, gender and clinical risk factors.

Table 2. Multivariate association between glucose and glycosylated hemoglobin status at baseline with perioperative and long-term cardiac events.

Characteristic	Myocardial ischemia (n=108) OR (95%CI)	Troponin T release (n=90) OR (95%CI)	30-day cardiac events (n=23) OR (95%CI)	Composite of perioperative events (n=131) OR (95%CI)	Mortality during follow-up (n=85) HR (95% CI)	Cardiac events during follow-up (n=69) HR (95% CI)
Normal glucose levels (reference) (n=220)	1.0	1.0	1.0	1.0	1.0	1.0
- Impaired glucose (n=112)	2.2 (1.3-3.9)	3.8 (2.1-7.0)	4.3 (1.4-13.5)	2.4 (1.4-4.1)	2.0 (1.1-3.8)	1.9 (1.0-3.7)
- Diabetes (n=69)	2.6 (1.4-4.9)	3.9 (2.0-7.7)	4.8 (1.4-16.6)	3.9 (2.1-7.3)	2.7 (1.2-5.6)	3.1 (1.5-6.4)
Absolute glucose levels, per mmol/L ↑	1.3 (1.1-1.4)	1.4 (1.2-1.5)	1.2 (1.0-1.3)	1.4 (1.2-1.5)	1.2 (1.1-1.3)	1.1 (1.0-1.2)
HbA_{1c} >7% (n=63)	2.8 (1.3-6.0)	2.1 (1.1-6.5)	5.3 (1.7-16.6)	3.0 (1.4-6.5)	3.6 (1.2-11.1)	5.6 (2.1-14.6)
Absolute HbA_{1c} levels, per % ↑	1.5 (1.2-2.0)	1.3 (1.0-1.7)	1.5 (1.1-3.8)	1.5 (1.1-1.9)	1.5 (1.0-2.1)	1.4 (1.1-1.8)

Adjusted for age, gender, angina pectoris, myocardial infarction, congestive heart failure, hypertension, stroke, smoking, renal dysfunction and the laboratory variables which showed significant differences among the three groups as in Table 1. HbA_{1c} = glycosylated hemoglobin

Insulin resistance with hyperglycemia is believed to be the major underlying pathologic mechanism for the associated susceptibility to premature cardiovascular disease in pre-diabetic patients. Adipose tissue plays a crucial role in the pathogenesis of insulin resistance and is the main causative mechanism of type 2 diabetes. Metabolic disturbances associated with insulin resistance beyond hyperglycemia include dyslipidemia, hypercoagulability and inflammation. In the current study, the highest level of the inflammation marker high-sensitivity C-reactive protein was found in patients with impaired glucose levels. Inflammation probably links the metabolic and vascular pathologies [8]. Hyperglycemia also exerts direct effects on the progression of atherosclerosis by the formation of reactive advanced glycation end products that mediate vascular damage [8]. In addition, hyperglycaemia can be deleterious for the heart due to hypovolaemia, modulation of nitric oxide metabolism and oxidative stress and down regulation of ischemic preconditioning [9].

Cardiac event rate in vascular surgery patients is high [10]. The high incidence of cardiac events reflects the high prevalence of underlying coronary artery disease. Indeed, coronary angiographic abnormalities have been reported in up to 92% of patients [11]. In our contemporary study cohort, a relatively high incidence of perioperative cardiac complications was observed (6%). It should be noted that this study was conduced at a university hospital which acts as a tertiary referral center for approximately 30 affiliated hospitals. The high incidence may be related to the admission and treatment of high-risk patients, who would have been denied in other hospitals. The rate of myocardial ischemia as assessed by continuous 12-lead electrocardiographic monitoring was more than three times higher (27%) than the incidence of perioperative cardiac events. The recognition of silent perioperative ischemic episodes is important, since these directly relate to myocardial damage, infarction and cardiac death [6]. The incidence of myocardial ischemia was significantly higher in patients with impaired glucose levels (35%) and patients with diabetes (41%), compared to patients with normal glucose levels (19%).

This study demonstrated the value of glucose and HbA_{1c} levels in defining perioperative and long-term risk in vascular surgery patients. However, the management of these patients remains a challenge. Patients with impaired glucose levels do not meet the criteria for diabetes, but have impaired glucose metabolism which places them at risk for developing diabetes or cardiovascular disease. We observed that survival in patients with impaired glucose metabolism was comparable to survival in patients with diabetes. Although loss of body weight, exercise, and certain pharmacological agents can prevent the development of diabetes in patients with impaired glucose levels, the impact on cardiovascular risk has not yet been examined to date. Randomized trials have demonstrated the benefit of β-blockers and statins in the reduction of perioperative cardiac events in vascular surgery patients [12,13]. In diabetic patients, however, randomization to either metoprolol or placebo failed to demonstrate a differential effect in outcome [5]. The relatively short-term use of metoprolol in this study (from the day before surgery to a maximum of eight days after) may explain this finding, since long-term β-blocker treatment with tight heart rate are important factors in ischemic event reduction. In addition to cardiovascular medication, aggressive glucose management in these patients should improve outcome. Intensive insulin treatment to achieve normoglycemic levels (<6.1 mmol/L) reduced mortality in critically-ill patients [14] and diabetic patients undergoing cardiac surgery [15]. However, randomized trials in major vascular surgery

patients should definitely determine the role of intensified insulin therapy on cardiovascular outcome.

In conclusion, the results of this study show that impaired glucose and elevated HbA_{1c} levels are risk factors for cardiac ischemic events in vascular surgery patients. This finding suggests the need for aggressive glucose management in this setting and supports a vigorous screening strategy for early recognition of diabetes.

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Chapter 13

Association of plasma N-terminal pro-B-type natriuretic peptide with postoperative cardiac events in patients undergoing major vascular surgery

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Association of Plasma N-terminal Pro-B-type Natriuretic Peptide with Postoperative Cardiac Events in Patients Undergoing Surgery for Abdominal Aortic Aneurysm or Leg Bypass

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Postoperative cardiac events are related to myocardial ischemia and reduced left ventricular function. The utility of N-terminal Pro-B-type natriuretic peptide for preoperative cardiac risk evaluation has not been evaluated. Objective of this study was to assess whether plasma N-terminal Pro-B-type natriuretic peptide predicts postoperative cardiac events in patients undergoing major vascular surgery additional to clinical and dobutamine stress echocardiography data. We prospectively evaluated 170 consecutive patients scheduled for major non-cardiac vascular surgery by dobutamine stress echocardiography and N-terminal Pro-B-type natriuretic peptide measurements. Multivariable logistic regression analysis was performed to evaluate the predictors of cardiac death and non-fatal myocardial infarction during a follow-up of 30-days. Receiver Operating Characteristic analysis was performed to determine the optimal cut-off value of N-terminal Pro-B-type natriuretic peptide values that predicts outcome. Mean age was 59 +/- 13 years and 71% was male. The median N-terminal Pro-B-type natriuretic peptide level was 110 pg/ml (interquartile range: 42-389 pg/ml). Cardiac events occurred in 2/144 (1.4%) patients with N-terminal Pro-B-type natriuretic peptide <533 pg/ml (i.e. the optimal cut-off value to predict cardiac events), and in 11/26 (42%) of patients with N-terminal Pro-B-type natriuretic peptide ≥533 pg/ml (unadjusted odds ratio 52, 95% CI: 11-256, p<0.0001). After adjustment for cardiac risk factors and dobutamine stress echocardiography results, N-terminal Pro-B-type natriuretic peptide remained significantly associated with cardiac events (adjusted odds ratio (OR): 17, 95% CI: 3-106, p=0.002). In conclusion, in patients scheduled for major vascular surgery, elevated plasma N-terminal Pro-B-type natriuretic peptide levels are independently associated with an increased risk of postoperative cardiac events. Further studies in a larger number of patients are required to confirm these findings.

PATIENTS UNDERGOING major vascular surgery are at increased risk for postoperative cardiac complications, due to coronary heart disease (1,2). To identify high-risk patients prior to surgery, cardiac risk scores such as the revised cardiac risk index according to Lee is commonly used (3). In patients with multiple risk factors undergoing high-risk surgery, additional non-invasive stress testing is recommended according to the guidelines of the American Heart Association/American College of Cardiology (4). Stress-induced myocardial ischemia and reduced left ventricular function are major determinants of cardiac events in these patients. The aim of this study was to assess the value of NT-proBNP for predicting postoperative cardiac events, additional to clinical data and dobutamine stress echocardiography (DSE) results.

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METHODS

Study population

Patients scheduled for major non-cardiac vascular surgery at the Erasmus University Medical Center in Rotterdam, the Netherlands were prospectively included in the study from October 2003 to December 2004 after giving informed consent. The study protocol was approved by the hospital's Medical Ethics Committee. Clinical data were collected by structured interview

with patients and by reviewing medical records. Based on the revised cardiac risk index by Lee et al, a preoperative cardiac risk score was calculated by assigning one point to each of the following cardiac risk factors: high-risk type of surgery, coronary artery disease (angina pectoris or previous myocardial infarction), a history of congestive heart failure (mean time of heart failure prior to surgery: 3.5 +/-2 years), a history of cerebrovascular disease, insulin therapy for diabetes mellitus and renal dysfunction, defined by a preoperative serum creatinine level >2.0 mg/dL (177 µmol/L) (3).

Dobutamine stress echocardiography
Patients underwent a resting two-dimensional precordial echocardiographic examination and standard apical and parasternal views were recorded on videotape and a 12-lead ECG was recorded. Dobutamine hydrochloride was then administered intravenously by infusion pump, starting at 10 µg/kg/min for 3 minutes (5 µg/kg/min for 5 minutes, followed by 10 µg/kg/min for 5 minutes in patients with resting wall motion abnormalities), increasing by 10 µg/kg/min every 3 minutes to a maximum of 40 µg/kg/min. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulfate (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously while the administration of dobutamine was continued. Metoprolol was administered (1.0 to 5.0 mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine-atropine combination if the side effects did not revert spontaneously and quickly. Two experienced investigators, blinded to the clinical data, performed off-line assessment of echocardiographic images. The left ventricle was divided into 17 segments, and wall motion was scored on a 5-point scale (1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, and 5 = dyskinesis). Ischemia was defined as new or worsening wall-motion abnormalities (compared to resting images of the same test) as indicated by an increase of regional wall motion score ≥ 1 grade(s) with stress. Akinesis becoming dyskinesis was not considered an ischemic response.

Measurement of plasma N-terminal pro-B-type natriuretic peptide
The mean time of venous blood sampling prior to surgery was 21 +/-11 days and all samples were collected before DSE. The samples were centrifuged and plasma was frozen at -80°C until assay. NT-proBNP was measured with an electrochemiluminescence immunoassay kit (Elecsys 2010, Roche GmbH, Mannheim, Germany). The method is a 'sandwich'-type quantitative immunoassay based on polyclonal antibodies against epitopes in the N-terminal part of proBNP. The lower detection limit was 5 pg/ml. Intra-assay coefficients of variance at 271 pg/ml and 6436 pg/ml were 1.9% and 0.9%, respectively. Essays were performed by a laboratory technician blinded to the patient's clinical data (5).

Outcomes
Patients were monitored for cardiac events for 30 days after surgery. Twelve-lead electrocardiography, serum creatine kinase (CK) measurements (with the MB fraction), and troponin T measurements were performed immediately prior to surgery and one, three and seven days after surgery and before discharge. Serum CK and CK-MB activity were measured and troponin T was measured in heparinized plasma using a chemiluminescence immunoassay. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, or congestive heart failure. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: elevated cardiac enzyme levels (CK level > 190 U/L and CK-MB >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/mL), development of typical electrocardiographic changes (new Q waves >1 mm or > 30 ms), and typical symptoms of angina pectoris.

Statistical analysis
Continuous data with a normal distribution were expressed as mean and compared using the Student t test. Continuous data with a significant skewed distribution were expressed as median and compared using the Mann-Whitney U test. Categorical data are presented as percent frequencies and differences between proportions were compared using the chi-square test with Yates' correction. NT-proBNP levels in patients with different DSE results and different cardiac risk scores were compared for trend across ordered groups using analysis of variance (ANOVA) techniques. Receiver operating characteristic (ROC) curve analysis was performed to calculate sensitivity, specificity and area under the curve values and to select an optimal cut-off value for predicting postoperative cardiac events. Univariable logistic regression analysis was used to evaluate the association of baseline characteristics, DSE results and NT-proBNP-values with postoperative outcome. NT-proBNP level (dichotomized according to the optimal cut-off value), new wall motion abnormalities (a marker for ischemic heart disease), rest wall motion abnormalities (a marker for left ventricular

Table 1. Overall characteristics of patients with plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels higher and those with equal or lower levels than the median.

Characteristic	N-terminal pro-B-type natriuretic peptide (pg/ml)		P-value
	<533 (n=144)	≥533 (n=26)	
Age (years) (mean +/-SD)	59 +/-13	64 +/-11	0.03
Men	98 (68%)	22 (85%)	0.1
Angina pectoris	28 (19%)	17 (65%)	<0.001
Previous myocardial infarction	48 (33%)	21 (81%)	<0.001
Congestive heart failure	25 (17%)	14 (54%)	<0.001
Previous cerebrovascular event	10 (7%)	5 (19%)	0.1
Previous coronary revascularization	14 (10%)	2 (8%)	1.0
Hypertension	35 (24%)	11 (42%)	0.1
Diabetes Mellitus	20 (14%)	11 (42%)	0.001
Hypercholesterolemia	57 (40%)	13 (50%)	0.4
Current smoking	25 (17%)	7 (27%)	0.4
Renal failure	0	6 (23%)	<0.001
Aspirin	46 (32%)	10 (38%)	0.7
Angiotensin converting enzyme inhibitor	48 (33%)	15 (58%)	0.03
Beta-blocker	86 (60%)	23 (88%)	0.01
Calcium channel blocker	19 (13%)	9 (35%)	0.02
Warfarin	23 (16%)	13 (50%)	<0.001
Digoxin	9 (6%)	6 (23%)	0.02
Diuretic	33 (23%)	16 (62%)	<0.001
Nitrate	9 (6%)	7 (27%)	0.003
Statin	71 (49%)	16 (62%)	0.3
Left ventricular hypertrophy	1 (1%)	0	0.3
Q waves	32 (22%)	13 (50%)	0.007
ST-segment changes	4 (3%)	5 (19%)	0.003
Rest wall motion abnormalities	51 (35%)	22 (85%)	<0.001
New wall motion abnormalities	15 (10%)	13 (50%)	<0.001
Abdominal aortic repair	58 (40%)	9 (35%)	0.7
Lower extremity revascularization	86 (60%)	17 (65%)	0.7

dysfunction), renal failure, and diabetes mellitus, were analyzed in a final multivariable logistic model. Odds ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Patient characteristics

The study population consisted of 170 consecutive patients (71% men). Mean age was 59 +/-13 years. Abdominal aortic repair was performed in 67 patients (39%), lower extremity revascularization in 103 patients (61%). Sixteen patients (9%) had a history of previous coronary artery revascularization. No patient underwent myocardial revascularization prior to surgery as a consequence of DSE stress results. The median concentration of NT-proBNP was 110 pg/ml (interquartile range: 42-389 pg/ml). The baseline characteristics of the patients, subdivided according to a NT-proBNP level of 533 pg/ml, are listed in Table 1. Patients with NT-proBNP levels equal or above 533 pg/ml were older, had a higher incidence of angina pectoris, previous myocardial infarction, congestive heart failure, diabetes mellitus and renal failure, compared to patients with NT-proBNP levels below 533 pg/ml. Q-wave and ST-segment changes were also more common in patients with NT-proBNP levels equal or above 533 pg/ml.

DSE results

Heart rate increased from 73 +/-14 beats per minute at rest to 133 +/-17 beats per minute at peak stress. The maximum dose of dobutamine infusion was 36.8 +/-7 μg/kg/min. Atropine was administered in 52% of patients to achieve target heart rate. Stress induced myocardial ischemia occurred in 28 patients (16%). The mean number of ischemic segments in patients with stress induced myocardial ischemia was 3.2 +/-1.2. No fatal complications occurred during or immediately after the stress test.

NT-proBNP levels in relation to dobutamine stress echocardiography results

The distribution of NT-proBNP was positively skewed and the Mann-Whitney U test was used to compare NT-proBNP values in different groups. Median NT-proBNP level was higher in patients with rest wall motion abnormalities during DSE (397 pg/ml, interquartile range: 178-710 pg/ml), compared to those without (59 pg/ml, interquartile range: 34-118 pg/ml) (p<0.001). In

the 39 patients with a history of congestive heart failure, mean ejection fraction was 41% +/-15. NT-proBNP level was higher in patients with a history of CHF (median 338 pg/ml, interquartile range 85-846 pg/ml) compared to patients without a history of CHF (median 93 pg/ml, interquartile range 42-296 pg/ml) (p=0.007). In the 39 patients with a history of congestive heart failure, the mean left ventricular ejection fraction was 41% +/-15 and was inversely correlated with the level of NT-proBNP (Pearson's R correlation -0.59).

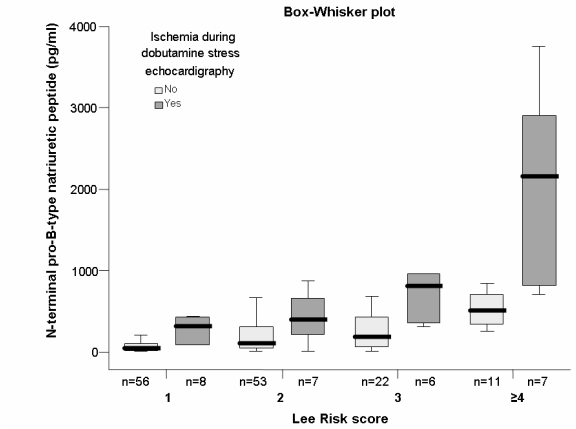

Figure 1. Correlation between median plasma N-terminal pro-B-type natriuretic peptide levels in patients with (p = 0.002) and without (0.001) new wall motion abnormalities, divided in subgroups according to the Lee risk score (high-risk type of surgery, coronary artery disease, a history of congestive heart failure, a history of cerebrovascular disease, diabetes mellitus and renal dysfunction (7). The Box-Whisker plot shows the median, upper and lower quartiles and the range of the data.

A higher median NT-proBNP level was observed in patients with new wall motion abnormalities (NWMA) during DSE (440 pg/ml, interquartile range: 195-1336 pg/ml), compared to those without (93 pg/ml, interquartile range: 42-279 pg/ml) (p=0.001). A direct relation was observed between the extent of stress induced myocardial ischemia and NT-proBNP levels, with median levels of NT-proBNP of 364, 710 and 2376 pg/ml in patients with 1-2, 3-4 and >4 ischemic segments, respectively (p for trend <0.001).

Figure 1 presents median NT-proBNP levels in patients with and without NWMA during DSE, divided in subgroups according to the cardiac risk score. In the group of patients with no NWMA during DSE, median NT-proBNP level increased from 51 pg/ml in patients with a risk score of 1 to a level of 609 pg/ml in patients with a risk score of ≥4 (p for trend: 0.001). In the group of patients with NWMA during DSE, median NT-proBNP level increased from 321 pg/ml in patients with a risk score of 1 to a level of 2148 pg/ml in patients with a risk score of ≥4 (p for trend: 0.002).

Postoperative outcome

Postoperative cardiac events occurred in 13 patients (8%) (cardiac death in 4 patients, non-fatal myocardial infarction in 9 patients). Median NT-proBNP level was higher in patients with cardiac events (939 pg/ml, interquartile range: 634-2469 pg/ml), compared to patients with no cardiac events (101 pg/ml, interquartile range: 42-304 pg/ml) (p<0.0001). Using ROC curve analysis for predicting postoperative cardiac events, a cut-off value of 533 pg/ml was identified as optimal predictor of postoperative cardiac events (area under the curve: 0.91) (Figure 2). Using this cut-off value, NT-proBNP had a sensitivity of 85% and specificity of 91%. Cardiac events were observed in 2/144 (1.4%) patients with NT-proBNP <533 pg/ml and in 11/26 (42%) patients with NT-proBNP ≥533 pg/ml (p<0.0001). Of the two patients who experienced cardiac events despite a low NT-proBNP level (533 pg/ml), one patient had a preoperative risk score of 1 and NWMA in 1 segment with no rest wall motion abnormalities during DSE; the other patient had a preoperative risk-score of 2 and only rest wall motion abnormalities with no NWMA during DSE.

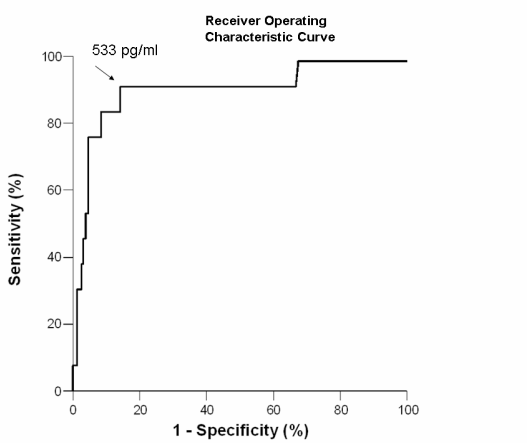

Figure 2. Receiver operating characteristic curve of plasma N-terminal pro-B-type natriuretic peptide levels to predict postoperative cardiac events. Sensitivity and 1-specificity are plotted for various NT-proBNP levels. The ideal cutoff value is indicated by the arrow.

Postoperative cardiac event rate was 1/65 (2%) in patients with a risk-score of 0-1 was, and 12/105 (11%) in patients with a risk-score greater than 1 (p=0.04). Univariable predictors of cardiac events are listed in Table 2. Each point increase on the cardiac risk score was associated with an estimated risk of 3.6 (95% CI: 2.0-6.6, p<0.0001) to develop postoperative cardiac

Table 2. Univariable association of clinical characteristics, dobutamine stress echocardiography results and plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and the composite endpoint of cardiac death or non-fatal myocardial infarction.

	OR	95% CI	P-value
Age > 70 years	1.1	0.3-4.3	0.9
Men	0.9	0.3-3.2	0.9
Angina pectoris	5.3	1.6-17.3	0.005
Previous myocardial infarction	3.7	1.1-12.5	0.04
Congestive heart failure	4.5	1.4-14.4	0.01
Previous cerebrovascular event	1.8	0.4-9.2	0.5
Previous coronary revascularization	0.8	0.1-6.5	0.8
Hypertension	2.5	0.8-7.8	0.1
Diabetes mellitus	4.7	1.5-15.3	0.01
Hypercholesterolemia	0.6	0.2-2.0	0.4
Current smoking	0.8	0.2-3.6	0.7
Renal failure	34.2	5.5-212.4	<0.0001
Abnormal electrocardiography	2.5	0.8-7.9	0.1
Q waves	3.4	1.1-10.6	0.03
ST-segment changes	4.4	1.1-18.5	0.04
Rest wall motion abnormalities	19.2	2.4-151.4	0.005
New wall motion abnormalities	25.6	6.4-101.6	<0.0001
Abdominal aortic repair	1.0	0.3-3.4	1.0
Lower extremity revascularization	1.1	0.4-3.4	0.9
NT-proBNP level per 100 pg/ml increase	1.20	1.1-1.3	<0.0001
NT-proBNP level ≥ 533 pg/ml	51.7	10.5-255.6	<0.0001

Table 3. Multivariable model to predict cardiac events in patients undergoing major vascular surgery.

	OR	95% CI	P-value
N-terminal pro-B-type natriuretic peptide ≥533 pg/ml	17.2	2.8-106.4	0.002
New wall motion abnormalities	13.0	2.0-86.9	0.009
Diabetes mellitus	4.6	0.7-30.7	0.1
Renal failure	2.0	0.1-33.8	0.6
Rest wall motion abnormalities	2.0	0.2-25.4	0.6

events. In multivariable analysis, independent predictors of cardiac events were NT-proBNP levels ≥533 pg/ml and NWMA during DSE (Table 3).

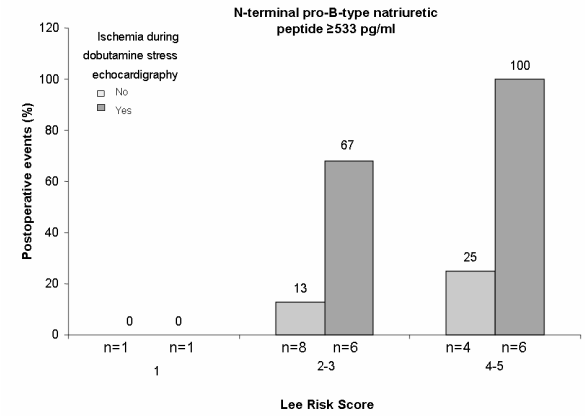

Figure 3. Postoperative cardiac events as observed in patients with and without new wall motion abnormalities (NWMA), divided in subgroups according to the risk score. The figure presents only patients with plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥63 pmol/L.

DISCUSSION

Our study showed that elevated levels of NT-proBNP are significantly associated with increased risk of postoperative cardiac events (cardiac death or non-fatal myocardial infarction) in patients undergoing major vascular surgery. The increased level of NT-proBNP was especially substantial for those with extensive stress induced myocardial ischemia during DSE. Using ROC curve analysis, NT-proBNP value of ≥533 pg/ml had the best prognostic value for postoperative cardiac events. This association between NT-proBNP and postoperative outcome was independent of clinical data, rest wall motion abnormalities, and stress-induced myocardial ischemia.

In this study, NT-proBNP levels were measured and not B-type natriuretic peptide (BNP). The half-life time of NT-proBNP is considered to be 60-120 minutes, while the half-life time of BNP is around 20 minutes (6,7). Considering the longer half-life time of NT-proBNP compared to BNP, NT-proBNP may be a superior screening marker in patients attending the out-patient preoperative clinic.

Prior to surgery, patients are screened for coronary artery disease by vascular surgeons. Initial screening is performed by using the revised cardiac risk index according to Lee (3). High-risk patients are referred to a cardiologist for additional stress testing to assess the presence and extent of coronary artery disease. As shown in this study, patients with a higher risk score have elevated NT-proBNP levels. Importantly, those patients with stress-induced ischemia also have elevated NT-proBNP levels, and the rise of NT-proBNP level is related to the magnitude of stress-induced ischemia. Therefore we speculate that NT-proBNP measurements can be used for an initial screening in patients undergoing major vascular surgery. Those patients without risk factors and a low level of NT-proBNP represent a low-risk population, in which additional testing is not warranted. Patients with elevated NT-proBNP should be referred for additional stress testing to assess the presence and extent of coronary artery disease. Postoperative cardiac events may still occur in patients without stress-induced myocardial ischemia during preoperative DSE. Elevated NT-proBNP levels may identify some patients at high risk despite absence of inducible ischemia. The reason for the independent association of NT-proBNP levels with cardiac events after controlling for DSE results is not clear. Possible explanations include the higher sensitivity for detecting ischemia, the ability to reflect the occurrence of spontaneous ischemic episodes and the objective nature of measurements as compared to DSE interpretation.

In our study, the number of patients as well as events was small. However, our results are supported by a recently published paper by Yeh et al, who also found a significant association between NT-proBNP levels and cardiac complications in patients undergoing non-cardiac surgery (8).Further studies are needed to confirm our findings in a larger population prior to recommending the use of NT-proBNP as a routine clinical investigation. Although the study has shown an additional value of NT-proBNP levels in defining risk, the management of these patients remains a challenge, since the Coronary Artery Revascularization Prophylaxic trial showed that coronary artery revascularization before elective vascular surgery does not significantly alter the long-term outcome (9). However, several studies have demonstrated the beneficial effect of perioperative beta-blocker therapy and minimal invasive surgery in reducing postoperative adverse events in high-risk patients undergoing major non-cardiac surgery (2,10,11). Patients with elevated NT-proBNP levels, with or without stress induced myocardial ischemia, are at increased risk for adverse postoperative events and may therefore benefit from these management strategies.

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Chapter 14

Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker in major vascular surgery

Heart. 2007;93:226-231

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Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery

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Objective: To assess the long-term prognostic value of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) after major vascular surgery.
Design: A single-centre prospective cohort study
Patients: 306 patients who underwent successful abdominal aortic aneurysm repair or lower extremity bypass surgery.
Interventions: Prior to surgery, baseline NT-proBNP level was measured. Patients were also evaluated for cardiac risk factors according to the Revised Cardiac Risk Index. Dobutamine stress echocardiography (DSE) was performed to detect stress-induced myocardial ischemia.
Main outcome measures: The prognostic value of NT-proBNP was evaluated for the endpoints all-cause mortality and major adverse cardiac events (MACE) during long-term follow-up.
Results: In this patient cohort (mean age: 63 years, 77% male), median NT-proBNP level was 158 ng/l (interquartile range: 58-400 ng/l). During a mean follow-up of 15 ± 6 months, 33 patients (11%) died and 30 (10%) experienced a MACE. Using receiver operating characteristic curve analysis for 6-month mortality and MACE, NT-proBNP had the greatest area under the curve, compared to cardiac risk score and DSE. In addition, a NT-proBNP level of 315 ng/l was identified as optimal cut-off value to predict 6-month mortality and MACE. After adjustment for age, cardiac risk score, DSE results and cardioprotective medication, NT-proBNP ≥315 ng/l was associated with a hazard ratio of 3.37 for all-cause mortality (95% CI: 1.28-8.87) and with a hazard ratio of 8.64 for MACE (95% CI: 2.69-27.75).
Conclusion: Preoperative NT-proBNP level is a strong predictor of late mortality and major adverse cardiac events after successful major non-cardiac vascular surgery.

ASSESSMENT OF SHORT- and long-term risk in patients undergoing major vascular surgery is regarded by the American College of Cardiology/American Heart Association as one of the most important initial steps in the evaluation and treatment of these patients [1]. Risk stratification is especially important given the substantial risk of perioperative and long-term morbidity and mortality [2-5]. To identify high-risk patients prior to surgery, several risk stratification scores have been developed and adjusted, using the patient's history and type of surgery to predict postoperative outcome [6-9]. In patients with multiple risk factors undergoing high-risk surgery, preoperative non-invasive stress testing provides additional prognostic information [10].

The natriuretic peptides are endogenous cardiac hormones that include atrial natriuretic peptide (A-type), brain natriuretic peptide (B-type or BNP), and its amino-terminal portion N-terminal pro-B-type natriuretic peptide (NT-proBNP) [11,12]. NT-proBNP is synthesized in the ventricular myocardium and released in response to ventricular wall stress [13,14]. NT-proBNP has been demonstrated to be an important diagnostic and prognostic marker in patients with heart failure [15,16]. The diagnostic and prognostic value of elevated levels of NT-proBNP has more recently been shown in patients with acute coronary syndromes and stable coronary artery disease [17,18]. It has also recently been demonstrated that elevated NT-proBNP levels predict short-term adverse cardiovascular events in patients undergoing elective non-cardiac surgical procedures [19]. Unfortunately, the long-term prognostic value of elevated baseline NT-proBNP levels along with clinical risk factors and dobutamine stress echocardiography results is not yet known.

The present prospective study was conducted to determine whether preoperative plasma NT-proBNP levels have significant long-term prognostic value in addition to conventional cardiac risk factors and dobutamine stress echocardiography in patients who underwent successful elective abdominal aortic aneurysm repair or lower extremity revascularization procedures.

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METHODS

Study population

Patients scheduled for elective abdominal aortic aneurysm repair or lower extremity bypass surgery at the Erasmus University Medical Center in Rotterdam, the Netherlands, were prospectively included in the study from October 2003 to August 2005 after giving informed consent. Patients who died (n=16), and who suffered a non-fatal myocardial infarction (n=13) during the perioperative period were excluded. Patients who underwent preoperative coronary artery revascularization were also excluded. Prior to surgery, baseline clinical data was collected by structured interviews with the patients and by reviewing the medical records. Based on the Revised Cardiac Risk Index by Lee et al [8], each of the following cardiac risk factors was obtained: history of coronary artery disease, a history of congestive heart failure, a history of cerebrovascular accident or transient ischemic attack, diabetes mellitus type I (fasting glucose level ≥7.0 mmol/l or treatment with insulin) and renal dysfunction (preoperative serum creatinine level >2.0 mg/dL (177 μmol/L) or treatment with renal dialysis). A cardiac risk score was calculated by assigning 1 point to each of these risk factors when present in the patient. Coronary artery disease was indicated if patients presented with current stable or unstable angina pectoris or if patients had a history of myocardial infarction. A preoperative electrocardiogram was obtained and evaluated. Patients were also screened for hypertension (blood pressure ≥140/90 mmHg or antihypertensive drugs), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or treatment with cholesterol lowering drugs), smoking, and cardiac medication use, including statins, β-blockers, aspirin, angiotensin-converting enzyme inhibitors and calcium channel blocking agents.

Measurement of plasma N-terminal pro-B-type natriuretic peptide

The mean time of venous blood sampling prior to surgery was 23 ± 12 days and all samples were collected before DSE. The samples were centrifuged and plasma was frozen at -80°C until assay. NT-proBNP was measured with an electrochemiluminescence immunoassay kit (Elecsys 2010, Roche GmbH, Mannheim, Germany). This 'sandwich'-type quantitative immunoassay is based on polyclonal antibodies against epitopes in the N-terminal part of proBNP. The lower detection limit was 5 ng/l. Intra-assay coefficients of variance at 271 ng/l and 6436 ng/l were 1.9% and 0.9%, respectively. Assays were performed by a laboratory technician blinded to the patient's baseline clinical data.

Dobutamine stress echocardiography

Patients underwent a resting two-dimensional precordial echocardiographic examination and standard apical and parasternal views were recorded on videotape. Dobutamine hydrochloride was then administered intravenously by infusion pump, starting at 10 μg/kg/min for 3 minutes (5 μg/kg/min for 5 minutes, followed by 10 μg/kg/min for 5 minutes in patients with resting wall motion abnormalities), and increased by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulphate (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously while the administration of dobutamine was continued. Metoprolol was administered (1.0 to 5.0 mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine-atropine combination if the side effects did not revert spontaneously and quickly. Two experienced investigators, blinded to the clinical data, performed off-line assessment of echocardiographic images. The left ventricle was divided into 17 segments, and wall motion was scored on a 5-point scale (1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, and 5 = dyskinesis). Ischemia was defined as new or worsening wall-motion abnormalities (compared to resting images of the same test) as indicated by an increase of regional wall motion score ≥ 1 grade(s) with stress. Akinesis becoming dyskinesis was not considered an ischemic response.

Outcomes

Patients were monitored for all-cause mortality and major adverse cardiac events (MACE) (cardiac death or non-fatal myocardial infarction) during long-term follow-up after their vascular surgical procedure. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, or congestive heart failure. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: 1. elevated cardiac enzyme levels (creatine kinase (CK) level > 190 U/L and CK-MB >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin

Table 1. Baseline clinical characteristics according to the median of N-terminal pro-B-type natriuretic peptide

Characteristic		NT-proBNP (ng/l)		P-value
		<158 ng/l (n=153)	≥158 ng/l (n=153)	
Age (years) (mean +/-SD)	63.0 ± 12.3	58.7 ± 12.0	67.3 ± 11.1	<0.001
Male gender	236 (77.1)	111 (72.5)	125 (81.7)	0.057
Medical history				
Current stable or unstable angina pectoris	75 (24.5)	21 (13.7)	54 (35.3)	<0.001
Previous myocardial infarction	119 (38.9)	37 (24.2)	82 (53.6)	<0.001
Coronary artery disease (summary variable)	145 (47.4)	48 (31.4)	97 (63.4)	<0.001
Previous coronary artery revascularization	37 (12.1)	10 (6.5)	27 (17.6)	0.003
History of congestive heart failure	47 (15.4)	17 (11.1)	30 (19.6)	0.076
Previous cerebrovascular event	54 (17.6)	15 (9.8)	39 (25.5)	<0.001
Diabetes mellitus type 1	55 (18.0)	23 (15.0)	32 (20.9)	0.18
Renal dysfunction	12 (3.9)	1 (0.7)	11 (7.2)	0.003
Hypertension	106 (34.6)	41 (26.8)	65 (42.5)	0.004
Hypercholesterolemia	124 (40.5)	67 (43.8)	57 (37.3)	0.24
Current smoking	105 (34.3)	46 (30.1)	59 (38.6)	0.12
Cardiac risk score	1.0 ± 0.9	0.6 ± 0.8	1.3 ± 1.0	<0.001
Electrocardiography				
Q waves	79 (25.8)	27 (17.6)	52 (34.0)	0.001
ST-segment changes	31 (10.1)	7 (4.6)	24 (15.7)	0.001
Medication				
Aspirin	129 (42.2)	56 (36.6)	73 (47.7)	0.049
Angiotensin converting enzyme inhibitor	102 (33.3)	41 (26.8)	61 (39.9)	0.015
Beta-blocker	223 (72.9)	101 (66.0)	122 (79.7)	0.007
Calcium channel blocker	54 (17.6)	20 (13.1)	34 (22.2)	0.036
Digoxin	16 (5.2)	1 (0.7)	15 (9.8)	<0.001
Statin	175 (57.2)	80 (52.3)	95 (62.1)	0.083
Abdominal aortic aneurysm repair	142 (46.4)	70 (47.1)	70 (45.8)	0.82
Lower extremity revascularization	164 (53.6)	81 (52.9)	83 (54.2)	0.82

Values are expressed in number (%) or in mean ± SD

T >0.1 ng/mL); 2. development of typical electrocardiographic changes (new Q waves >1 mm or > 30 ms); and 3. typical symptoms of angina pectoris. All patients had at least 6 months of follow-up.

Statistical analysis

Normally distributed, continuous data were expressed as mean (±SD) and compared using the Student t test. Non-normally distributed continuous data were expressed as median (25^{th} and 75^{th} percentile) and compared using the Mann-Whitney U test. Categorical data were presented as percent frequencies and differences between proportions were compared using the chi-square test with Yates' correction. To compare the predictive value of NT-proBNP, cardiac risk score and DSE results for 6-month outcome, receiver operating characteristic (ROC) curve analysis was performed and the area under the curve was calculated. The 6-month outcome was used, since all patients had a complete follow-up at this time. The optimal cut-off value of NT-proBNP for mortality and MACE at 6 months was determined and was defined as the NT-proBNP value providing the maximal sum of sensitivity and specificity. Age, cardiac risk score, DSE results, NT-proBNP values (dichotomized according to the optimal cut-off value for 6-month outcome) and cardioprotective medication (statins and β-blockers) were then entered in a multivariable Cox hazard regression model to identify independent predictors of long-term mortality and MACE. Hazard ratios are given with 95% confidence intervals. For all tests, a p value less than 0.05 (two-sided) was considered significant. All analysis was performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics

The study population consisted of 306 patients (77.1% male) with a mean age of 63.0 ± 12.3 years. Abdominal aortic aneurysm repair was performed in 142 patients (46.4%) and lower extremity revascularization in 164 patients (53.6%). The NT-proBNP level ranged from 4 to 8257 ng/l, with a mean (±SD) of 417 ± 838 ng/l, a median of 158 ng/l, and 25^{th} and 75^{th} percentile values of 58 ng/l and 400 ng/l, respectively. Baseline clinical characteristics of the patients, divided according to the median level of NT-proBNP, are presented in Table 1. Patients with NT-proBNP levels above the median were more likely to be older and to present with coronary artery disease, history of cerebrovascular events, renal dysfunction, hypertension, Q-waves and ST segment changes on electrocardiography than patients with NT-proBNP levels below the median. These patients were

also more likely to be treated with aspirin, angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers and digoxin.

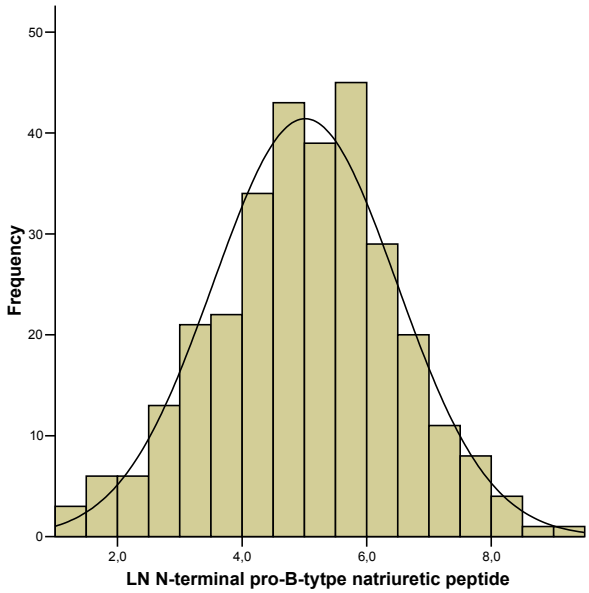


Figure 1. Histogram demonstrating the distribution of N-terminal pro-B-type natriuretic peptide level according to its natural logarithm in the study population

DSE results

The mean maximal dobutamine dose used during stress echocardiography was 36.3 ± 8 μg/kg/min. Atropine was used in 125 patients (41%). Stress induced myocardial ischemia occurred in 58 patients (19%) and the mean number of ischemic segments in patients with stress induced myocardial ischemia was 3.4 ± 1.5. No fatal complications occurred during or immediately after the stress test. The median NT-proBNP level was significantly higher in patients with a positive test (426 ng/l, IQ range: 163-1391 ng/l) compared to those with a negative stress test (120 ng/l, IQ range: 46-307 ng/l)($p<0.001$).

Outcome and ROC curve analysis

During a mean follow-up of 15 ± 6 months, all-cause mortality occurred in 33 patients (11%) and MACE in 30 (10%). NT-proBNP had a greater area under the

Figure 2. Receiver operating characteristic curves of plasma N-terminal pro-B-type natriuretic peptide against 6-month mortality and major adverse cardiac events, respectively, in 306 patients who underwent major vascular surgery.

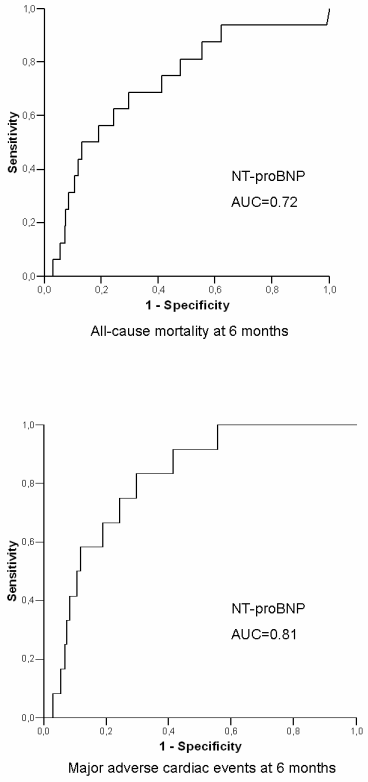
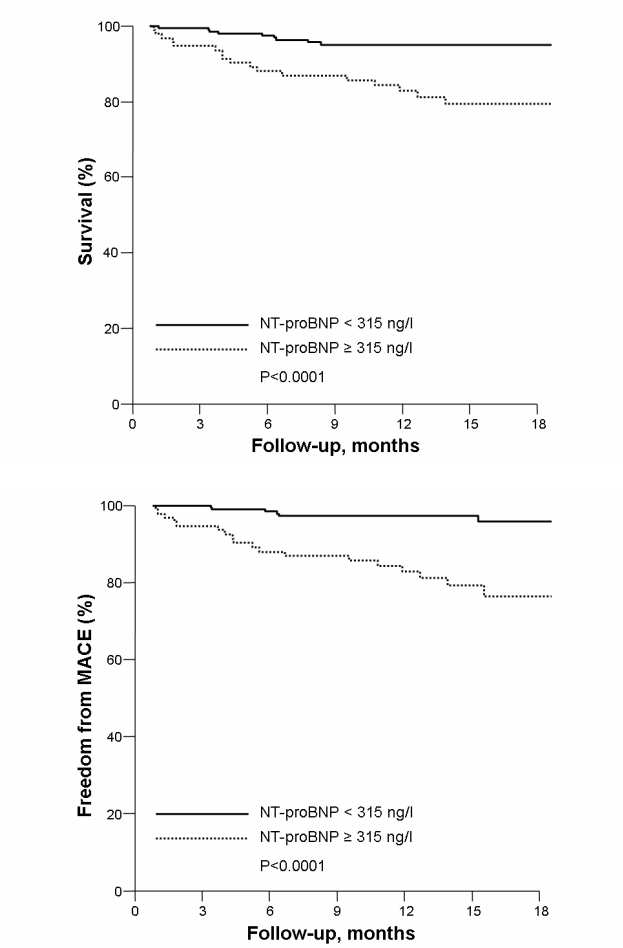


Table 2. Optimal cut-off values of N-terminal pro-B-type natriuretic peptide to predict mortality and major adverse cardiac events at 6, 12 and 18 months of follow-up.

Endpoint	Mortality number	ROC area under the curve	Optimal cutoff value of N-terminal pro-B-type natriuretic peptide (ng/l)	Sensitivity	Specificity
Mortality within 6 months	16	0.72	315	69%	70%
Mortality within 12 months	24	0.72	303	67%	70%
Mortality within 18 months	26	0.74	228	73%	67%
Cardiac events within 6 months	12	0.81	315	83%	70%
Cardiac events within 12 months	20	0.80	205	90%	60%
Cardiac events within 18 months	24	0.80	206	88%	66%

ROC curve for the endpoint 6-month mortality (AUC=0.72), compared to the cardiac risk score (AUC=0.64) and DSE (AUC=0.66). (Figure 1). Also for MACE, the area under the curve was greater for NT-proBNP (AUC=0.81) compared to cardiac risk score (AUC=0.65) and DSE (AUC=0.66). (Figure 2). A NT-proBNP level of 315 ng/l was identified as the optimal cut-off value to predict both mortality and cardiac events at 6 months follow-up. Using this cut-off value, the sensitivity and specificity for 6-month mortality was 69% and 70%, respectively. Sensitivity and specificity for 6-month MACE was 83% and 70%, respectively.

Figure 3. Kaplan-Meier curves showing the cumulative incidence of death and major adverse cardiac events during follow-up, according to N-terminal pro-B-type natriuretic peptide level.



Prognostic value of NT-proBNP

Kaplan-Meier survival curves demonstrate that patients with NT-proBNP level ≥315 ng/l had a lower survival and freedom of MACE compared to patients with NT-proBNP levels <315 ng/l (Figure 2). Independent predictors of all-cause mortality and MACE were identified by Cox hazard regression analysis, which demonstrated that NT-proBNP was the strongest predictor for all-cause mortality and for MACE (Figure 3). The adjusted hazard ratio for all-cause mortality in patients with baseline NT-proBNP levels ≥315 ng/l was 3.37 (95% CI: 1.28-8.87, p=0.014). The adjusted hazard ratio for MACE in patients with baseline NT-proBNP levels ≥315ng/ml was 8.64 (95% CI; 2.69-27.75, p<0.001). Notably, β-blockers and statin therapy were significantly associated with an improved long-term outcome (Figure 3).

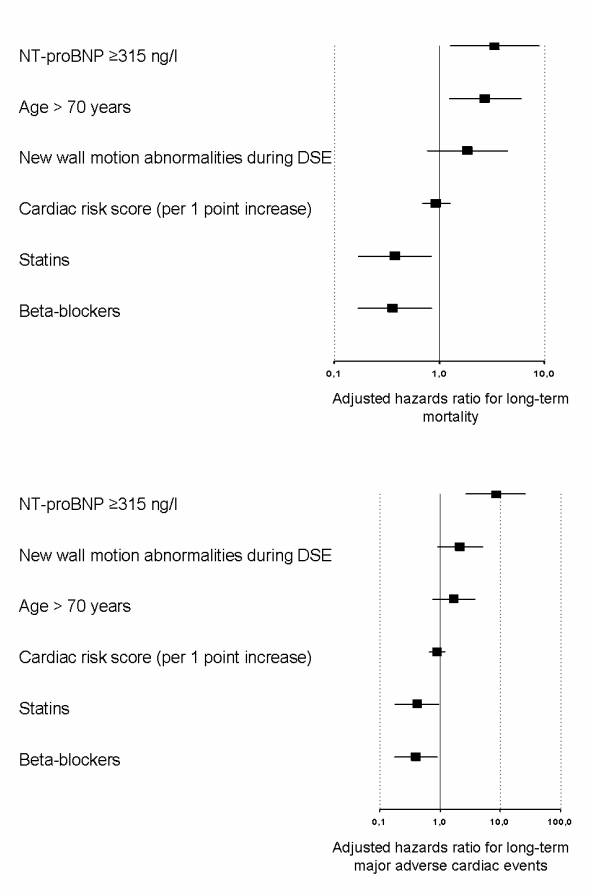
DISCUSSION

This study demonstrates that a single measurement of NT-proBNP, obtained prior to surgery, provides powerful information for use in risk stratification in patients undergoing abdominal aortic aneurysm repair or lower extremity bypass surgery. Patients with higher NT-proBNP levels were more likely to present with older age, coronary artery disease, previous coronary artery bypass grafting, history of cerebrovascular events, renal dysfunction, hypertension and Q-waves and ST segment changes on electrocardiography, compared to those with lower NT-proBNP levels. This finding suggests that high baseline NT-proBNP levels due to activation of the cardiac neurohormonal system may be a unifying feature in patients at high risk for late mortality or major adverse cardiac events.

NT-proBNP as a prognostic marker in non-surgical patients

NT proBNP is the physiologically inactive 1-76 amino acid fragment that is secreted along with the 32 amino acid brain natriuretic peptide after cleavage from the pro-hormone pro-BNP [11-14]. Considering the longer half life and better in vitro stability, NT-proBNP may be a superior target for assay in comparison to BNP [11-14]. The long-term prognostic value of NT-proBNP has been evaluated in non-surgical patients with congestive heart failure, demonstrating that higher levels of NT-proBNP were associated with adverse outcome [20-22]. In our study cohort, only 15% of the study cohort presented with a history of congestive heart failure, however, a history of coronary artery disease was much more frequently observed (47%). Recent studies have demonstrated the prognostic value of NT-proBNP in non-surgical patients with acute and stable coronary

Figure 4. Multivariate Cox regression model showing independent predictors of all-cause mortality and major adverse cardiac events.



artery disease. In a sub-study of the Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV trial with 6,809 patients with non-ST-segment elevation acute coronary syndromes, NT-proBNP was the strongest predictor of death at 1-year, among other biochemical and clinical markers [23]. The prognostic value of NT-proBNP was also proved in a group of patients presenting with a full range of severities of acute coronary syndromes (from unstable angina pectoris, through non-ST segment elevation myocardial infarction, to ST-segment elevation myocardial infarction [24]. In 755 patients with symptoms suggestive of an acute coronary syndrome and no ST-segment elevation, Jernberg and colleagues demonstrated that NT-proBNP levels were independently associated with long-term prognosis [25]. Finally, NT-proBNP has been proven to provide long-term prognostic information above and beyond that provided by conventional cardiac risk factors and the degree of left ventricular systolic dysfunction in1034 patients referred for angiography because of symptoms or signs of coronary heart disease [26].

NT-proBNP as promising prognostic marker in major vascular surgery

The substantial postoperative mortality rate in patients undergoing major vascular surgery has led researchers and physicians to find strategies that identify high risk patients [2-5]. In the investigated study cohort, more than 1 out of 10 patients died from all causes during a mean follow-up of 15 months, with the exclusion of patients who died in the perioperative period. The Revised Cardiac Risk Index has currently been considered as the best available cardiac risk index in non-cardiac surgery [8]. This index uses the patient's history to predict major cardiac complications. Stress induced myocardial ischemia during DSE has also been shown to be a strong predictor of early and late cardiac events [27,28]. The American College of Cardiology/American Heart Association guidelines on perioperative cardiovascular evaluation for non-cardiac surgery recommends preoperative clinical evaluation to identify high risk patients and recommends further cardiac stress testing in selected patients [1].

Few data are available whether NT-proBNP levels provide additional prognostic information in vascular surgery patients. A recently published study including 190 patients undergoing elective non-cardiac surgery demonstrated that a NT-proBNP level greater than 450 ng/l was predictive of perioperative cardiac complications [19]. Although there is no consensus of what normal NT-proBNP values are, we have identified 315 ng/l as optimal cut-off values to predict 6-month mortality and MACE, using ROC curve analysis. Our study extends currently available information about the value of NT-proBNP as risk marker and suggests that NT-proBNP may be a superior long-term prognostic marker compared to conventional cardiac risk scores and DSE. Measurement of plasma NT-proBNP concentration is an objective, convenient and inexpensive test. For the purpose of optimal risk stratification and for the targeting of treatment strategies, our results suggest that NT-proBNP should be incorporated in the management of major vascular surgery patients.

Conclusion

Patients undergoing major vascular surgery are at increased risk of late cardiac morbidity and mortality. The present study demonstrates that elevated preoperative plasma NT-proBNP level is associated with an increased risk of late all-cause mortality and MACE after successful major vascular surgery, independent of cardiac risk factors and DSE results. Using ROC curve analysis, a level of 315 ng/ml of NT-

proBNP was identified as optimal cut-off values to predict 6-month mortality and MACE. NT-proBNP levels above these cut-off values may be a promising marker of long-term prognosis and should be incorporated in preoperative risk stratification.

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Conflict of interest: The authors of this manuscript have no conflicts of interest to declare.

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Chapter 15

Baseline plasma N-terminal pro-B-type natriuretic peptide level is associated with the extent of stress induced myocardial ischemia during dobutamine stress echocardiography

Coronary Artery Disease. 2006;17:255-259

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Baseline plasma N-terminal pro-B-type natriuretic peptide is associated with the extent of stress induced myocardial ischemia during dobutamine stress echocardiography

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Objective: To determine the relation between baseline plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and the presence and extent of myocardial ischemia during dobutamine stress echocardiography (DSE).
Methods: NT-proBNP was measured in 170 consecutive patients prior to DSE. Rest wall motion abnormalities (RWMAs) and new wall motion abnormalities (NWMAs) were scored using a 5-point, 17-segment model. Kruskal-Wallis tests were applied to study differences in NT-proBNP levels between patients with normal DSE, RWMAs but no NWMAs, and NWMAs, and (in patients with NWMAs) between those with 1-2, 3-4 and >4 ischemic segments. Univariate and multivariate regression analyses were used to determine the value of NT-proBNP in predicting NWMAs.
Results: The median NT-proBNP level was 13 pmol/L (interquartile range: 5-46 pmol/L). Median NT-proBNP was 7, 38 and 52 pmol/L in patients with normal DSE, with RWMAs but no NWMAs, and with NWMAs, respectively ($p<0001$). Among patients with NWMAs, median NT-proBNP was associated with the number of ischemic segments: 43, 84 and 281 pmol/L in patients with 1-2, 3-4 and >4 ischemic segments, respectively ($p<0.001$). Elevated NT-proBNP levels were significantly associated with NWMAs (OR per 10 pmol/L: 1.13, 95% CI: 1.1-1.2) in a multivariate analysis of clinical baseline variables and RWMAs.
Conclusion: Elevated baseline levels of NT-proBNP are associated with the presence and extent of myocardial ischemia during DSE, independent of the presence of RWMAs.

PLASMA N-TERMINAL PRO-TYPE natriuretic peptide (NT-proBNP) is a neurohormone, synthesized in the ventricular myocardium and released in response to ventricular wall stress [1-3]. NT-proBNP is produced as a prohormone that is enzymatically cleaved into brain-type natriuretic peptide and NT-proBNP [4]. NT-proBNP is a strong marker for the diagnosis, severity and prognosis of patients with heart failure [5,6]. More recently, NT-proBNP was shown to have prognostic value in patients with acute coronary syndromes [7-11]. Limited information is available on the association between NT-proBNP levels and the presence and extent of stress induced myocardial ischemia. Dobutamine stress echocardiography (DSE) is a widely used non-invasive technique for the diagnosis and prognosis of coronary artery disease [12]. Patients who experience transient new wall motion abnormalities (NWMAs) during DSE, a specific marker of myocardial ischemia, may also experience transient ischemic episodes during daily life.

We conducted a prospective study to assess the relation between pre-test NT-proBNP levels and the presence and extent of stress induced myocardial ischemia in patients undergoing DSE.

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METHODS

Study population

The study included consecutive patients with suspected or known coronary artery disease who were referred for DSE at the Thorax-center, Rotterdam, the Netherlands between October 2003 and December 2004. Patients with severe valvular heart disease or hypertrophic or dilated cardiomyopathy were excluded. The hospital's

Medical Ethical Committee approved the study protocol. Based on hospital records and personal interviews at the time of stress testing, a medical history was recorded, including clinical risk factors, medications, prior history of myocardial infarction, angina pectoris, congestive heart failure, coronary artery revascularization, stroke and transient ischemic attacks, and a baseline 12-leaed electrocardiogram was obtained. We have chosen to include the 6 patients with renal failure into our analysis in multivariate analysis, we have adjusted for renal failure. Patients were characterized as having diabetes mellitus if they were treated with insulin or if they had a pre-test fasting plasma glucose level ≥126 mg/dL (≥7.0 mmol/L). Hypercholesterolemia was recorded if patients presented with a plasma cholesterol level of ≥212 mg/dL (≥5.5 mmol/L) or if patients were taking lipid-lowering agents. Hypertension was recorded if patients presented with a blood pressure of 140/90 mmHg or higher or if patients received antihypertensive medication. Smoking included only current smoking. Renal failure was recorded if patients presented with a serum creatinine level ≥2.0 mg/dL (≥177 μmol/L) or in those who required dialysis

Table 1. Baseline characteristics of 170 patients.

Characteristic	Number (%), or Mean (+/- SD)
Demographics	
Age (years)	59 +/-13
Male gender	120 (71%)
Cardiovascular history	
Angina pectoris	45 (26%)
Previous myocardial infarction	69 (41%)
History of congestive heart failure	39 (23%)
Previous coronary artery revascularization	16 (9%)
History of cerebrovascular accident	15 (9%)
Clinical risk factors	
Diabetes Mellitus	31 (18%)
Hypercholesterolemia	70 (41%)
Hypertension	46 (27%)
Smoking	32 (19%)
Renal failure	6 (4%)
Abnormal baseline electrocardiogram*	70 (41%)
Cardiac medication use	
Aspirin	56 (33%)
ACE-inhibitor	63 (37%)
Beta-blocker	109 (64%)
Calcium channel blocker	28 (16%)
Diuretic	49 (29%)
Nitrate	16 (9%)
Statin	87 (51%)

* Abnormal ECG = electrocardiography with one or more of the following: Q-waves consistent with a previous myocardial infarction, ST segment changes, left bundle branch block and right bundle branch block. ACE-inhibitor = Angiotensin converting enzyme-inhibitor

Measurement of plasma N-terminal pro-B-type natriuretic peptide

Immediately before the performance of DSE, a heparinized venous blood sample was collected for measurement of NT-proBNP level. Venous blood samples were centrifuged and plasma was frozen at -80°C until assay. NT-proBNP was measured with an electrochemiluminescence immunoassay kit (Elecsys 2010, Roche GmbH, Mannheim, Germany). The method is a 'sandwich'-type quantitative immunoassay based on polyclonal antibodies against epitopes in the N-terminal part of proBNP. The lower detection limit was 0.6 pmol/l. Intra-assay coefficients of variance at 32 pmol/L and 761 pmol/L were 1.9% and 0.9%, respectively. A reference value of NT-proBNP was determined in 100 control patients prior to the start of the study. In these patients the median (IQ-range) NT-proBNP level was 2.3 (1.4-4.4) pmol/L in males and 4.4 (3.2-6.1) pmol/L in females. Essays were performed by a laboratory technician blinded to the patient's clinical and stress test data [13].

Dobutamine stress echocardiography

Patients underwent a resting two-dimensional echocardiographic examination from the standard apical and parasternal views. Images were digitally stored and were also recorded on videotape. A 12-lead ECG was recorded. Dobutamine hydrochloride was then administered intravenously by infusion pump, starting at 5 μg/kg/min for 3 minutes, followed by 10 μg/kg/min for 3 minutes and increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min (stage 5). The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate (men: (220 – age) x 85%; women: (200 – age) x 85%) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulphate (starting with 0.25 mg, increased to a cumulative maximum of 2.0 mg) was given intravenously at the end of stage 5 while the dobutamine administration was continued. During the test, a 12-lead ECG was recorded every minute. Blood pressure was measured by sphygmomanometry every 3 minutes. Metoprolol was administered to reverse the side effects of the administration of dobutamine or the dobutamine-atropine combination if the side effects did not revert spontaneously and quickly. The criteria for stopping the test were: (1) severe new echocardiographic wall motion abnormalities in multiple locations, (2) horizontal or down-sloping electrocardiographic ST depression of ≥0.2 mV measured 80 ms after the J point, or ST-segment elevation of ≥0.2 mV in the absence of Q waves, (3) symptomatic decline in systolic blood pressure of more than 40 mmHg from the resting value, or a systolic blood pressure of less than 100 mmHg, (4) hypertension (blood pressure >240/140 mmHg), (5) severe angina pectoris, and (6) intolerable adverse

Table 2. Median plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in relation to patient characteristics

	Median NT-proBNP level (Interquartile range)		p-value
Characteristic	+	-	
Age > 70 years	12 (4-40)	25 (11-59)	0.04
Male gender	17 (5-51)	11 (4-29)	0.1
Angina pectoris	52 (23-84)	10 (4-26)	<0.001
Previous myocardial infarction	39 (13-81)	10 (4-22)	<0.001
History of congestive heart failure	40 (10-100)	11 (5-36)	0.007
History of cerebrovascular accident	33 (15-67)	12 (5-43)	0.08
Diabetes Mellitus	38 (8-81)	12 (5-37)	0.2
Hypertension	29 (10-62)	11 (4-38)	0.03
Smoking	23 (4-49)	12 (5-46)	0.5
Hypercholesterolemia	13 (5-51)	13 (5-40)	0.9
Renal failure	172 (64-254)	12 (5-49)	0.04
Electrocardiography			
ST segment changes	53 (30-92)	12 (5-38)	0.004
Q-waves	37 (10-80)	11 (5-33)	<0.001
Left bundle branch block	51 (11-59)	12 (5-40)	0.2
Right bundle branch block	27 (7-46)	13 (5-46)	0.5

effects considered to be the result of dobutamine or atropine.

Wall motion analysis

Off-line assessment of echocardiographic images was performed by two experienced investigators without knowledge of the patient's clinical data (D.P., J.J.B., and S.E.K.). The left ventricle was divided into 17 segments and wall motion was scored on a 5-point scale (a score of 1 indicating normal, 2 mild hypokinesis, 3 severe hypokinesis, 4 akinesis, and 5 dyskinesis). For each patient, a wall motion score index (total score divided by the number of segments scored) was calculated at rest and at peak heart rate. NWMA during the stress test were considered diagnostic for ischemia. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessments, and a majority decision was reached.

Statistical analysis

Continuous data were expressed as mean (+/- SD) or median (+/- interquartile range) (in skewed distributions), and compared using the Student t test or the Mann-Whitney U test, when appropriate. Patients were divided into three groups according to DSE results: group 1 normal DSE, group 2 RWMAs but no NWMAs, and group 3 NWMAs. Patients with NWMA were further divided into patients with 1-2 ischemic segments, 3-4 ischemic segments and >4 ischemic segments. NT-proBNP values in patients with a normal DSE, with RWMAs but no NWMAs, and with NWMAs were compared using the Kruskal-Wallis test. Kruskal-Wallis test was also used to compare NT-proBNP values in patients with 1-2, 3-4 and >4 ischemic segments. Receiver Operating Curve analysis was used to determine the optimal cutoff value of NT-proBNP to predict NWMAs. Univariable logistic regression analysis was used to evaluate the crude value of NT-proBNP in predicting stress induced myocardial ischemia. NT-proBNP level and clinical risk factors identified as confounders (significant univariate predictors of stress induced myocardial ischemia) were included in a final multivariable logistic model. Odds ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Patient characteristics

Inclusion criteria were fulfilled in 170 patients. Baseline characteristics are presented in Table 1. The median NT-proBNP level for all patients was 13 pmol/L (interquartile range: 5-46 pmol/L). The following clinical parameters were associated with increased levels of NT-proBNP: age above 70 years, angina pectoris, previous myocardial infarction, congestive heart failure, hypertension, renal failure, ST segment changes, and Q-waves on baseline electrocardiogram (Table 2).

DSE results

Heart rate increased from 73 +/-14 beats per minute at rest to 133 +/-17 beats per minute at peak stress. The maximum dose of dobutamine infusion was 36.8 +/-7 µg/kg/min. Atropine was administered in 52% of patients to achieve target heart rate. No fatal complications occurred during or immediately after the stress test. DSE was normal in 97 patients (57%). RWMAs but no NWMAs were detected in 45 patients

(26%). NWMAs occurred in 28 patients (16%). The mean number of ischemic segments in patients with stress induced myocardial ischemia was 3.2 +/-1.2.

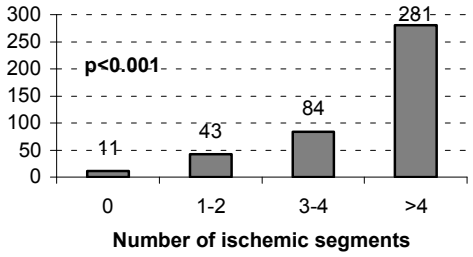


Figure 1. Median plasma N-terminal pro-B-type natriuretic peptide levels (NT-proBNP) in relation to the number of ischemic segments during dobutamine stress echocardiography.

NT-proBNP levels and DSE results

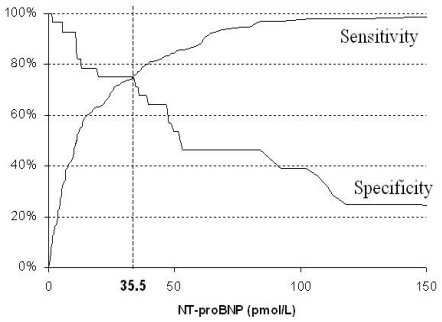
The median NT-proBNP level was 7 pmol/L (interquartile range: 4-14) in patients with a normal DSE, 38 pmol/L (interquartile range: 19-61) in patients with RWMAs but no NWMAs, and 52 pmol/L (interquartile range: 23-157) in patients with NWMAs ($p<0.001$). In the group of patients with NWMA, NT-proBNP levels correlated with the extent (number of segments) of stress induced myocardial ischemia (Figure 1): the median level of NT-proBNP was 43 pmol/L (interquartile range: 11-52), 84 pmol/L (interquartile range 20-185) and 281 pmol/L (interquartile range: 114-302), in patients with 1-2 (n=10), 3-4 (n=14) and >4 (n=4) ischemic segments, respectively ($p<0.001$).

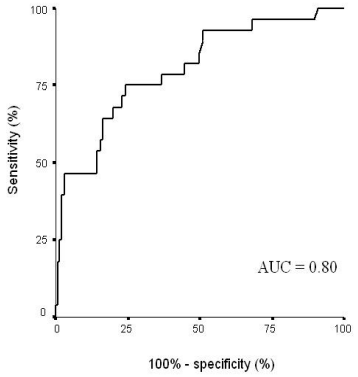
The optimal cut-off value of NT-proBNP to predict stress induced myocardial ischemia was 36 pmol/L, using Receiver Operating Curve analysis (area under the curve 0.80) (Figure 2). A cutoff value of 36 pmol/L was associated with a sensitivity and specificity of 76%. Univariate associations of clinical parameters and NT-proBNP levels with stress induced myocardial ischemia are presented in Table 3. After adjusting for RWMA and clinical risk factors, elevated NT-proBNP levels were independently associated with stress induced myocardial ischemia (OR for every 10 pmol/L increase of NT-proBNP level: 1.13, 95% CI: 1.09-1.17) (Table 4).

DISCUSSION

The present study was conducted to evaluate the relation between baseline levels of NT-proBNP and the extent of stress induced myocardial ischemia during DSE. The level of NT-proBNP was related to the presence and extent of myocardial ischemia, manifested as NWMAs. An elevated baseline NT-proBNP level was

Figure 2. ROC curve analysis demonstrates that the optimal cutoff value of plasma N-terminal pro-B-type natriuretic peptide levels (NT-proBNP) for predicting new wall motion abnormalities was 36 pmol/L (dashed line crossing at intersection of sensitivity and specificity) (A). The area under the curve (AUC) was 0.80 (B). The x-axis (NT-proBNP values) presents individual values and does not represent a linear or logarithmic scale.





independently associated with stress induced myocardial ischemia after adjustment for clinical data and RWMA. To our knowledge, this is the first study to demonstrate an independent association between baseline NT-proBNP levels and dobutamine stress induced myocardial ischemia.

The human brain natriuretic peptide (BNP) gene, located on chromosome 1, encodes the prohormone proBNP, which is split into the 32 amino-acid BNP and the 76 amino-acid NT-proBNP [4]. NT-proBNP is synthesized predominantly in the left ventricular myocardium and released in response to ventricular wall stress, i.e. ventricular dilatation and pressure overload [3,4]. The synthesis and release of natriuretic peptides in patients with coronary artery disease may be triggered

Table 3. Univariate predictors of stress induced myocardial ischemia.

	OR	95% CI	p-value
NT-proBNP level per 10 pmol/L increase	1.15	1.1-1.2	<0.001
Age >70 years	2.0	0.8-.4.9	0.1
Male gender	2.9	0.9-8.9	0.06
Angina pectoris	2.6	1.1-5.9	0.03
History of myocardial infarction	2.7	1.2-6.2	0.02
History of congestive heart failure	2.6	0.9-7.8	0.07
History of cerebrovascular accident	1.8	0.5-6.0	0.4
Hypertension	1.3	0.6-3.2	0.5
Smoking	1.2	0.5-3.2	0.7
Hypercholesterolemia	0.6	0.3-1.5	0.3
Diabetes Mellitus	1.3	0.5-3.6	0.6
Renal failure	11.6	2.0-66.8	0.006
Abnormal ECG*	3.7	1.5-8.7	0.003

* Abnormal ECG = electrocardiography with one or more of the following: Q-waves consistent with a previous myocardial infarction, ST segment changes, left bundle branch block and right bundle branch block

Table 4. Multivariate model to predict stress induced myocardial ischemia.

	OR	95% CI	p-value
NT-proBNP level per 10 pmol/L increase	1.13	1.1-1.2	0.02
Age >70 years	2.2	0.8-6.3	0.1
Male gender	2.0	0.5-7.5	0.3
Angina pectoris	1.1	0.3-3.3	0.9
History of myocardial infarction	0.8	0.2-2.8	0.7
History of congestive heart failure	1.1	0.3-4.5	0.9
Renal failure	1.0	0.1-12.0	1.0
Abnormal baseline ECG*	1.5	0.4-5.3	0.5
Rest wall motion abnormalities	2.4	0.8-7.4	0.1

Abnormal ECG = electrocardiography with one or more of the following: Q-waves consistent with a previous myocardial infarction, ST segment changes, left bundle branch block and right bundle branch block. NT-proBNP = plasma N-terminal pro-B-type natriuretic peptide.

by the effects of ventricular wall stress secondary to chronic or repetitive ischemia or by ischemia itself. It has been demonstrated in an experimental rat model of acute myocardial infarction, that ventricular BNP mRNA expression and tissue concentrations of BNP were increased in the non-infarcted region as well as in the infarcted region [14]. Another published study, using myocardial biopsies from patients with coronary artery disease, has demonstrated an association between BNP mRNA expression in ischemic myocardium and plasma BNP levels, even in the absence of left ventricular dysfunction as evaluated by ventriculography [15].

Ndrepepa et al. studied patients with angina pectoris and acute myocardial infarction, and found a positive association between the level of NT-proBNP and the severity of angiographic coronary artery disease [16]. Sabatine et al. measured NT-proBNP levels before and after exercise testing with nuclear perfusion imaging, and it showed that NT-proBNP levels rose immediately in patients with exercise induced transient myocardial ischemia and that the magnitude of NT-proBNP rise was associated with the severity of ischemia [17]. It was unclear from their study whether baseline levels were independently associated with myocardial ischemia. DSE is an established method for diagnosis of coronary artery disease [12,18,19]. Elevated NT-proBNP levels before stress testing suggest that patients with inducible ischemia during DSE often sustain spontaneous ischemic episodes prior to stress testing. A low level of NT-proBNP was associated with a low incidence of ischemia. On the contrary, a high level was associated with a high incidence of ischemia. NT-proBNP levels may potentially be useful in determining the probability of an abnormal test and perhaps exempting patients with low or high probability of myocardial ischemia from stress testing. Considering the longer half-life time of NT-proBNP compared to BNP, NT-proBNP may be a superior screening marker in patients scheduled for stress testing. Nevertheless, more studies are needed to confirm this conclusion prior to recommending this approach in clinical practice.

In conclusion, patients with stress induced myocardial ischemia during DSE had higher baseline levels of NT-

proBNP than patients without ischemia. NT-proBNP level was a significant predictor of stress induced myocardial ischemia, independent of clinical risk factors and RWMA. In addition, the extent of stress induced myocardial ischemia was positively correlated to the level of NT-proBNP. Levels of NT-proBNP could stratify patients with regard to the probability of having inducible ischemia.

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Chapter 16

Baseline natriuretic peptide levels in relation to myocardial ischemia, troponin T release and heart rate variability in patients undergoing major vascular surgery

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Baseline natriuretic peptide levels in relation to myocardial ischemia, troponin T release and heart rate variability in patients undergoing major vascular surgery

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Background: This study was conducted to determine the association between baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) and myocardial ischemia, troponin T release and heart rate variability (HRV) in patients undergoing major vascular surgery.
Methods: In a prospective study, 182 vascular surgery patients were evaluated by clinical risk factors, dobutamine stress echocardiography and baseline NT-proBNP levels. Myocardial ischemia was detected by continuous 12-lead electrocardiographic monitoring starting 1 day before to 2 days after surgery. Troponin T (>0.03 ng/ml) was measured on day 1, 3, and 7 postoperatively and before discharge. HRV was measured at the day prior to surgery.
Results: The median NT-proBNP level was 184 ng/L (interquartile range: 79-483 ng/L). Myocardial ischemia was detected in 21% and troponin T release in 17% of patients. After adjustment for clinical risk factors and stress echocardiography results, higher NT-proBNP levels (per 1 ng/L increase in the natural logarithm of NT-proBNP) were associated with a higher incidence of myocardial ischemia (OR: 1.59, 95% CI: 1.21-2.08, p<0.001) and troponin T release (OR: 1.76, 95% CI: 1.33-2.34, p<0.001). The optimal cut-off value of NT-proBNP to predict ischemia and/or troponin T release was 270 ng/L (area under the curve: 0.70). Higher baseline NT-proBNP levels were also associated with a larger ischemic burden at electrocardiographic monitoring (r=0.22, p=0.03). However, no significant correlation was found between NT-proBNP and preoperative HRV (r=-0.024, p=0.78).
Conclusion: Elevated baseline NT-proBNP levels are significantly associated with perioperative myocardial ischemia and troponin T release, but not with preoperative HRV in patients undergoing major vascular surgery.

NATRIURETIC PEPTIDES are endogenous cardiac hormones that include atrial natriuretic peptide (A-type), brain natriuretic peptide (B-type or BNP), and its amino-terminal portion N-terminal pro-B-type natriuretic peptide (NT-proBNP) [1,2]. NT-proBNP is synthesized in the ventricular myocardium and released in response to ventricular wall stress [3,4]. NT-proBNP has been demonstrated to be an important diagnostic and prognostic marker in patients with heart failure [5,6]. The diagnostic and prognostic value of elevated levels of NT-proBNP has more recently been shown in patients with acute coronary syndromes and stable coronary artery disease [7,8]. In the search for safe, inexpensive and accurate preoperative screening, natriuretic peptides have emerged as promising preoperative risk measures. Three studies published last year have consistently demonstrated that elevated natriuretic peptide levels predict short-term adverse cardiovascular events in patients undergoing elective non-cardiac surgery [9,10,11]. The prognostic value of preoperative natriuretic peptides was also sustained for long-term events, as demonstrated in a study involving 335 patients who were followed for a mean duration of 14 months [12].
Patients who experience perioperative myocardial ischemia detected during continuous 12-lead electrocardiographic monitoring or who have troponin T release are considered to be at increased risk for adverse postoperative cardiac events [13,14]. In addition, reduced heart rate variability has also been associated with a worse prognosis in patients with myocardial infarction, congestive heart failure, or in patients undergoing major surgery [15,16]. A positive association of elevated baseline natriuretic peptides with increased perioperative myocardial ischemia and decreased preoperative heart rate variability may strengthen the evidence that natriuretic peptides can be used as a preoperative risk marker. The primary objective of this study was to determine whether baseline NT-proBNP levels are associated with myocardial ischemia as assessed by continuous 12-lead electrocardiographic monitoring and troponin T release in patients undergoing major vascular surgery. The

secondary objective was to assess the association between baseline NT-proBNP levels and preoperative heart rate variability.

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METHODS

Study population

Patients scheduled for elective abdominal aortic aneurysm repair, lower extremity bypass surgery or carotid artery surgery at the Erasmus University Medical Center in Rotterdam, the Netherlands, were prospectively included in the study from January 2004 to December 2006 after giving informed consent. Patients with severe valvular heart disease or hypertrophic or dilated cardiomyopathy were excluded. Patients who participated in clinical intervention trials at or outside the Erasmus Medical Center were also excluded (i.e. the DECREASE III trial). All patients agreed on participation in the study after given informed consent and the Institutional Review Board approved the protocol. Baseline clinical data were collected by structured interviews with the patients and by reviewing the medical records. Based on the Revised Cardiac Risk Index by Lee et al [17], patients were screened for each of the following cardiac risk factors: history of coronary artery disease, congestive heart failure, cerebrovascular accident or transient ischemic attack, diabetes mellitus (fasting glucose level ≥7.0 mmol/l or treatment with insulin) and renal dysfunction (preoperative serum creatinine level >2.0 mg/dL (177 µmol/L) or treatment with renal dialysis). Coronary artery disease was defined as patients presented with current stable or unstable angina pectoris or if patients had a history of myocardial infarction. A preoperative electrocardiogram was obtained and evaluated. Patients were also screened for hypertension (blood pressure ≥140/90 mmHg or antihypertensive drugs), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or treatment with cholesterol lowering drugs), smoking, and cardiac medication use, including statins, β-blockers, aspirin, angiotensin-converting enzyme inhibitors and calcium channel blocking agents.

Measurement of baseline N-terminal pro-B-type natriuretic peptide

The mean time of venous blood sampling prior to surgery was 22 ± 11 days and all samples were collected before dobutamine stress echocardiography. The samples were centrifuged and plasma was frozen at -80°C until assay. NT-proBNP was measured with an electrochemiluminescence immunoassay kit (Elecsys 2010, Roche GmbH, Mannheim, Germany). This 'sandwich'-type quantitative immunoassay is based on polyclonal antibodies against epitopes in the N-terminal part of proBNP. The lower detection limit was 5 ng/l. Intra-assay coefficients of variance at 271 ng/l and 6436 ng/l were 1.9% and 0.9%, respectively.

Dobutamine stress echocardiography

Dobutamine stress echocardiography was performed prior to surgery. Patients underwent a resting two-dimensional precordial echocardiographic examination and standard apical and parasternal views were recorded on videotape. Dobutamine hydrochloride was then administered intravenously by infusion pump, starting at 10 µg/kg/min for 3 minutes (5 µg/kg/min for 5 minutes, followed by 10 µg/kg/min for 5 minutes in patients with resting wall motion abnormalities), and increased by 10 µg/kg/min every 3 minutes to a maximum of 40 µg/kg/min. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulfate (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously while the administration of dobutamine was continued. Metoprolol was administered (1.0 to 5.0 mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine-atropine combination if the side effects did not revert spontaneously and quickly. Two experienced investigators performed off-line assessment of echocardiographic images. The left ventricle was divided into 17 segments, and wall motion was scored on a 5-point scale (1=normal, 2=mild hypokinesis, 3=severe hypokinesis, 4=akinesis and 5=dyskinesis). Ischemia was defined as new or worsening wall-motion abnormalities (compared to resting images of the same test) as indicated by an increase of regional wall motion score ≥ 1 grade(s) with stress. Akinesis becoming dyskinesis was not considered an ischemic response.

Myocardial ischemia during 12-lead electrocardiography

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts), starting 1 day before surgery up to 2 days after. Recordings were performed in the continuous 12-lead mode with a recording length of 10 seconds every minute. The frequency response was 0.05 – 150Hz. Electrocardiographic data were initially

processed by a technician and analyzed by two experienced investigators, who were blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the ambulatory ECG recordings were analyzed for ST-segment deviations. A continuous ST segment trend was generated and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST-segment changes, lasting at least one minute and shifting from baseline to more than 0.1 mV (1 mm). The baseline ST segment level was defined as the average ST segment during a stable period (duration of 20 minutes) preceding each ischemic episode. ST segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST segment change was measured 40 ms after that point. The ischemic burden (mm*min) was defined as maximum ST segment deviation multiplied by ischemia duration.

Troponin T measurement
In all patients, troponine T levels were measured on postoperative day 1, 3, 7, before hospital discharge and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Troponin T level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany). A value of >0.03 ng/ml was used to define positive troponin T levels.

Table 1. Baseline characteristics of the study population.

	n=182
Age (years)	66 ± 11
Male gender	147 (81%)
Current stable angina pectoris	34 (19%)
History of myocardial infarction	52 (29%)
Previous coronary artery revascularization	23 (13%)
History of congestive heart failure	11 (65)
History of cerebrovascular event	50 (28%)
Renal failure	9 (5%)
Diabetes mellitus	28 (15%)
Hypertension	76 (42%)
Hypercholesterolemia	70 (39%)
Current or past smoking	91 (50%)
Aspirin	101 (56%)
Angiotensin-converting enzyme inhibitors	46 (25%)
Beta-blockers	152 (84%)
Calcium channel blockers	37 (20%)
Digoxin	2 (1%)
Statins	109 (60%)
Preoperative heart rate	67 ± 10
Rest wall motion abnormalities	45 (25%)
Stress induced new wall motion abnormalities	31 (17%)
Abdominal aortic aneurysm repair	91 (50%)
Lower extremity revascularization	57 (31%)
Carotid artery surgery	34 (19%)

Values are given in number (%), or in mean ± standard deviation

Heart rate variability
Heart rate variability was computed for each subject using time-domain analysis of short-term 5-minute recordings in the preoperative period. Consecutive 5-minute recordings of 2-hour periods were standardly obtained at the evening before surgery. The average heart rate variability of the 5-minute recordings during the 2-hour period was calculated. We used standard time domain measures including the standard deviation of the normal-to-normal (NN) intervals (SDNN) and the square root of the mean squared differences of successive NN intervals (rMSSD).

Perioperative management
Prior to surgery, patients with beta-blockers were asked about medication adherence. Beta-blockers were withheld if patients presented with a systolic blood pressure <100 mmHg or with a heart rate <50 bpm. Beta-blockers were administered orally. In patients not able to take their medication orally, beta-blockers were administered by naso-gastric tube or by intravenous line. All patients received standard perioperative pain management. Surgical procedures were classified as abdominal aortic aneurysm repair (91 patients, 50%), lower extremity revascularization (57 patients, 31%) and carotid artery surgery (34 patients, 19%).

Follow-up
Study endpoints were hard cardiac events (cardiac death and non-fatal myocardial infarction) during follow-up. Outpatient visits were scheduled every 3 months after discharge. Cardiac death was defined as any death with a cardiovascular cause, including those deaths following a cardiac procedure, cardiac arrest, myocardial infarction, pulmonary embolus, stroke, hemorrhage, or sudden deaths due to unknown causes. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: elevated cardiac enzyme levels (troponin T >0.1 ng/ml), development of typical electrocardiographic changes (new Q waves >1 mm or > 30 ms), and typical symptoms of angina pectoris. No patients were lost to follow-up.

Statistical analysis
Continuous data are expressed as mean (± SD) and compared by using the Student t test. Categorical data are presented as percentages and analyzed using the chi-square test with Yates' correction. Baseline natriuretic peptide levels were abnormally distributed and converted to its natural logarithm. Binary logistic regression analysis was used to study the association between natriuretic peptides and myocardial ischemia and troponin T release. Receiver operating curve characteristic analysis was used to assess the optimal cutoff value of NT-proBNP in predicting the composite

Table 2. Univariate and multivariate analysis of the association between baseline N-terminal pro-B-type natriuretic peptide and perioperative myocardial ischemia as detected by continuous 12-lead electrocardiographic monitoring, troponin T release and early and late hard cardiac events.

	Number of events	Odds/Hazard Ratio per 1 ng/l increase in the natural logarithm of baseline NT-proBNP (95% CI)	
		Univariate	Multivariate*
Perioperative myocardial ischemia	38 (21%)	1.59 (1.21-2.08)	1.49 (1.12-1.98)
Troponin T release	31 (17%)	1.76 (1.33-2.34)	1.63 (1.22-2.19)
Hard cardiac events during follow-up	11 (6%)	1.68 (1.10-2.55)	1.59 (1.03-2.50)

Adjusted for age, gender, coronary artery disease, history of congestive heart failure, history of cerebrovascular events, diabetes mellitus, renal failure, hypertension, dobutamine stress echocardiography results and cardiovascular medication.

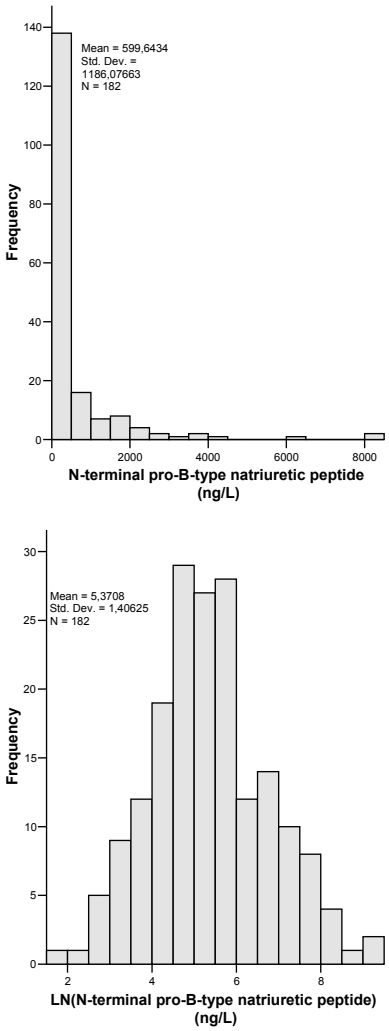

Figure 1. A histogram showing the distribution of N-terminal pro-B-type natriuretic peptide levels and its natural logarithm in the study population

of myocardial ischemia and troponin T release. Cox regression analysis was use to study the association between natriuretic peptides and long-term events. The Pearson coefficient was used to estimate the correlation between baseline natriuretic peptides and preoperative heart rate variability. In multivariate analysis, adjustments were made for age, gender, cardiac risk factors according to the Revised Cardiac Risk Index (coronary artery disease, history of congestive heart failure, cerebrovascular disease, diabetes mellitus and renal failure), dobutamine stress test results, hypertension and cardiovascular medication. Odds and hazard ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics

Inclusion criteria were fulfilled in 182 patients. Baseline characteristics are presented in Table 1. The mean age of the study population was 66 ± 11 years and 81% was male. The distribution of baseline NT-proBNP levels and its natural logarithm are presented in Figure 1. The median NT-proBNP level was 184 ng/L (interquartile range: 79-483 ng/L). Dobutamine stress echocardiography revealed rest wall motion abnormalities in 25% and stress induced wall motion abnormalities in 17% of the patients. No fatal complications occurred during or immediately after the stress test.

NT-proBNP in relation to myocardial ischemia and troponin T release

Myocardial ischemia during continuous 12-lead electrocardiographic registration was assessed in 38 participants (21%). A total of 77 periods of myocardial ischemia were detected. The number of ischemic events per patient ranged from 1 to 5. The median duration of ischemic events was 43 minutes (range 5-1130 minutes)

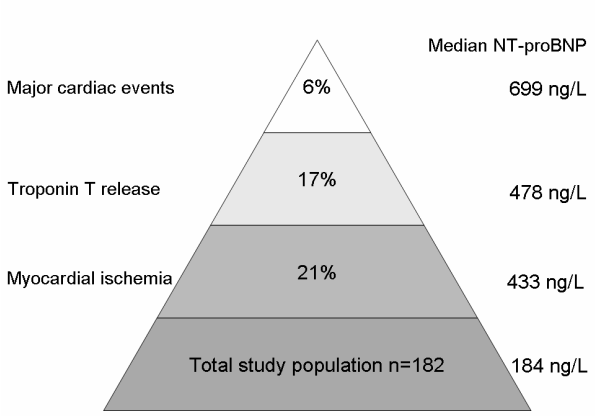

Figure 2. The incidence of myocardial ischemia, troponin T release and late hard cardiac events and the median N-terminal pro-B-type natriuretic peptide level.

and the median ST-segment deviation was 1.5 mm (range 1.0-5.6 mm). In patients with ischemia, median ischemic burden was 72 mm*min (range: 7-5508 mm*min). Troponin T levels >0.03 ng/ml were measured in 31 patients (17%). Troponin T values ranged from 0.03 to 8.2 ng/ml. Figure 2 demonstrates the median NT-proBNP level in patients with myocardial ischemia, troponin T release and late cardiac events.

As demonstrated in Figure 3, higher baseline NT-proBNP levels were associated with an increased incidence of myocardial ischemia and troponin T release. The optimal cut-off value to predict the composite of myocardial ischemia and troponin T release as determined by receiver operating characteristic analysis was 270 ng/L (area under the curve: 0.70) (Figure 4).

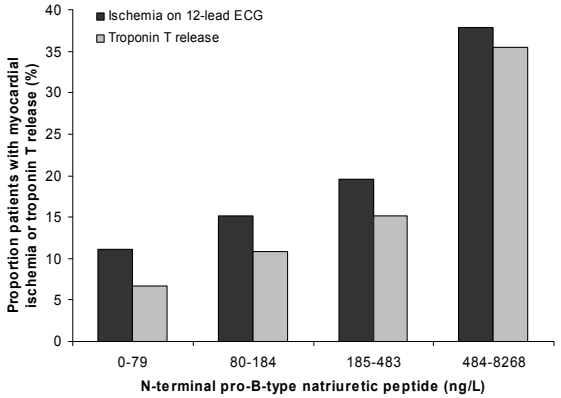

Figure 3. The proportion of patients with perioperative myocardial ischemia detected by continuous 12-lead electrocardiographic monitoring and troponin T release in relation to baseline N-terminal pro-B-type natriuretic peptide levels, according to the quartiles.

Interestingly, in the 38 patients with myocardial ischemia, higher NT-proBNP levels correlated significantly with a larger ischemic burden at 12-lead ECG monitoring (r=0.22, p=0.03). In multivariate analysis, higher baseline NT-proBNP levels remained significantly associated with a higher incidence of myocardial ischemia and troponin T release (Table 2).

During follow-up, hard cardiac events occurred in 11 patients (6%). Higher baseline NT-proBNP levels were significantly associated with a higher incidence of hard cardiac events, irrespective of clinical variables and dobutamine stress echocardiography results (Table 2).

NT-proBNP and preoperative heart rate variability

Mean SDNN and rMSSD prior to surgery was 47 ± 26 and 37 ± 34 ms respectively. No correlation was found between baseline NT-proBNP levels and preoperative SDNN (r=-0.024, p=0.78) and rMSSD (r=0.14, p=0.1) (Figure 5). Also in a subgroup of patients without rest wall motion abnormalities and new wall motion abnormalities (n=130), no correlation was found between baseline NT-proBNP levels and preoperative SDNN (r=-0.009, p=0.9) and rMSSD (r=0.12, p=0.08).

DISCUSSION

In this study of patients undergoing major vascular surgery, we found that increased levels of preoperative NT-proBNP significantly correlated with an increased incidence of perioperative myocardial ischemia during continuous 12-lead electrocardiographic monitoring and with increased troponin T release. This association was independent of baseline clinical variables and independent of preoperative dobutamine stress echocardiography results. No association was observed between baseline NT-proBNP levels and preoperative heart rate variability.

NT-proBNP and perioperative myocardial ischemia

Natriuretic peptides are released from the ventricle and play a valuable role in the regulation of body fluid and blood pressure. Ventricular wall stress causes synthesis and release of natriuretic peptides and explains the elevated levels in patients with left ventricular dysfunction. The reason of elevated natriuretic peptides in patients with ischemic heart disease has not been completely understood. In an experimental rat model of acute myocardial infarction, ventricular BNP mRNA expression and tissue concentrations of BNP were increased both in the non-infarcted as well as in the infarcted region [188]. Another study obtained myocardial biopsies from patients with coronary artery disease and demonstrated an association between BNP

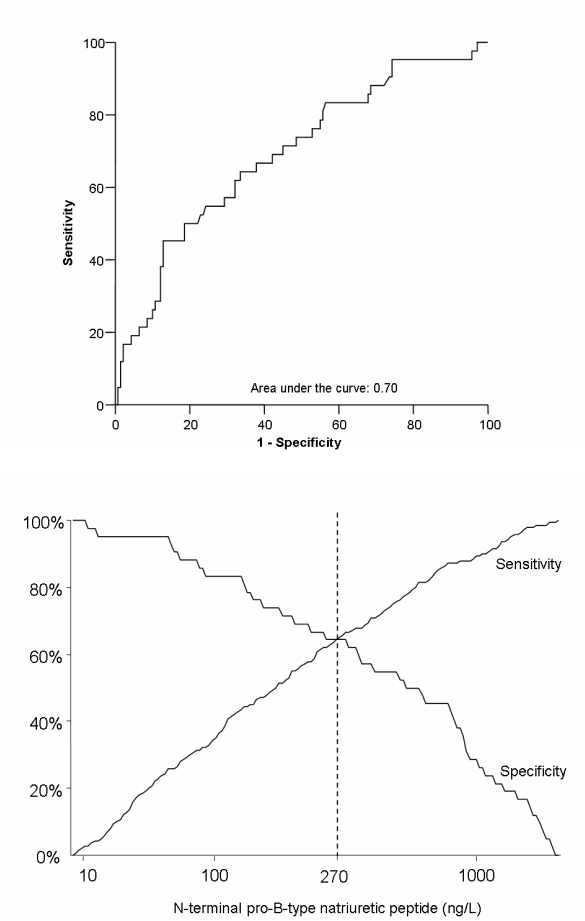

Figure 4. Receiver operating curve analysis demonstrating the optimal cutoff value of plasma N-terminal pro-B-type natriuretic peptide levels for predicting the composite of perioperative myocardial ischemia and troponin T release.

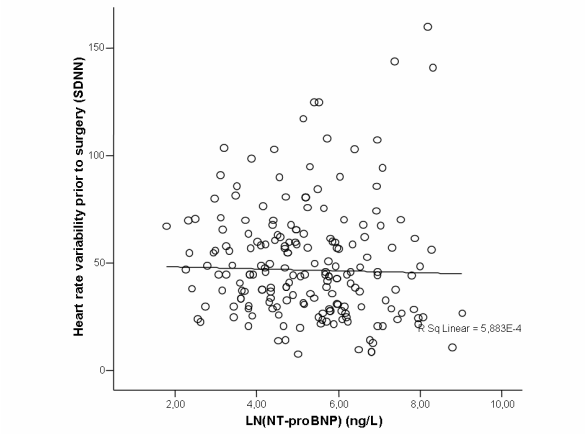

Figure 5. A scatter plot demonstrating the correlation between the natural logarithm of baseline plasma N-terminal pro-B-type natriuretic peptide level and preoperative heart rate variability (SDNN).

mRNA expression in ischemic myocardium and plasma BNP levels, even in the absence of left ventricular dysfunction as evaluated by ventriculography [19]. Ndrepepa and colleagues found a positive association between the level of NT-proBNP and the severity of angiographic coronary artery disease in patients with angina pectoris and acute myocardial infarction [20]. It has been hypothesized that ventricular wall stress secondary to chronic or repetitive ischemia triggers the synthesis and release of natriuretic peptides. Sabatine and colleagues measured NT-proBNP levels before and after exercise testing with nuclear perfusion imaging, and showed that NT-proBNP levels rose immediately in patients with exercise induced transient myocardial ischemia and that the magnitude of NT-proBNP rise was associated with the severity of ischemia [21]. The current study supports the notion that natriuretic peptide levels are associated with myocardial ischemia, irrespective of baseline rest wall motion abnormalities, and that elevations in natriuretic peptides may reflect early silent or symptomatic ischemic heart disease.

NT-proBNP and heart rate variability

Heart rate variability, a commonly used measure of cardiac autonomic dysfunction, mostly reflects vagal tone. Reduced heart rate variability in patients following a myocardial infarction or congestive heart failure has consistently been shown to be predictive of sudden, arrhythmic, cardiovascular and non-cardiovascular mortality. Also in patients undergoing major non-cardiac surgery at high risk of coronary artery disease, depressed heart rate variability before induction of anesthesia has been found to be an independent predictor of one-year mortality [16]. It has been hypothesized that natriuretic peptides are released as an early response to cardiac autonomic dysfunction, before the onset of clinically detectable cardiac dysfunction. In an histological study of a dissected bovine heart, BNP and ANP immunoreactivities frequently occur in the atrioventricular bundle and are co-localized in Purkinje fibres, suggesting that natriuretic peptides may act in an autocrine and/or paracrine way in the conduction system [22]. It also has been reported that exogenous administration of BNP in a rat model can modulate autonomic nervous activity [23]. However, the relation between NT-proBNP and the severity of autonomic dysfunction remains poorly understood. A previously published study found in 32 consecutive patients with type 2 diabetes that increased levels of plasma BNP correlated with cardiac reflex parasympathetic dysfunction [24]. A significant association between BNP and heart rate variability could not be established, which may have been due to the small sample size. In the current study involving 182 patients, an association between NT-proBNP and heart rate variability could

also not be established in the total population as well as in the population of patients without resting and stress induced echocardiographic abnormalities. Therefore, in our opinion, it seems not likely that decreased heart rate variability contributes significantly to the synthesis and release of NT-proBNP.

Clinical implications

Risk stratification identifies patients at risk for perioperative and long-term mortality who benefit from primary and secondary prevention strategies, such as risk factor reduction, life-style modification and optimal medical treatment with β-blockers and statins. Natriuretic peptides are promising markers for risk assessment in patients undergoing major vascular surgery. Currently, preoperative risk stratification is based on a set of clinical risk factors that allows an estimate of the weighted risk of perioperative cardiac complications. According to the American College of Cardiology/American Heart Association guidelines, preoperative cardiac exercise or pharmacological stress testing is recommended in all patients at increased cardiac risk based on clinical risk profile, functional capacity and type of surgery [25]. Extensive screening increases costs and delays surgery. The optimal algorithm that includes NT-proBNP for preoperative risk stratification still has to be developed. Although the current study was not designed to elucidate the biological mechanism between elevated NT-proBNP levels and cardiovascular events, the results showed that NT-proBNP levels are associated with important correlates of adverse cardiovascular outcome. Ultimately, the utility of NT-proBNP lies in its ability to guide and improve perioperative medical management.

Study limitations

Several limitations should be noted when interpreting the results of the study. The results apply to patients undergoing major vascular surgery, and our findings may not be generalized to patients undergoing general or low-risk surgery. For troponin T release, we used a lower cut-off level of 0.03 ng/ml to define positive troponin T levels. Lower troponin T levels were not used, since they do not meet the imprecision criteria (coefficient of variation) of <10%. Therefore, the results may have been biased to the detection of higher troponin T release.

Conclusion

On the basis of this observational study, increased preoperative NT-proBNP levels in patients scheduled for major vascular surgery are associated with an increased incidence of perioperative myocardial ischemia during 12-lead electrocardiographic monitoring and increased troponin T release, independent of clinical risk factors and dobutamine stress echocardiography results. These findings support the evidence that natriuretic peptides can be used as prognostic marker in patients undergoing major vascular surgery. Although it has been hypothesized that NT-proBNP may be elevated in patients with cardiac autonomic dysfunction, this study could not establish an association between baseline NT-proBNP levels and preoperative heart rate variability.

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Chapter 17

Plasma natriuretic peptides reflect left ventricular function and functional status after mitral valve repair

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Plasma natriuretic peptide levels reflect changes in heart failure symptoms, left ventricular size and function after surgical mitral valve repair

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Background and aim: N-terminal pro-B-type natriuretic peptide (NT-proBNP) has diagnostic and prognostic value in patients with heart failure. The present prospective study was designed to assess whether changes in NT-proBNP levels after surgical mitral valve repair reflect changes in heart failure symptoms and changes in left atrial size, left ventricular size and left ventricular function.
Methods: The study population consisted of 22 patients (mean age: 62.8 ± 14.2 years, 68% male) undergoing surgical mitral valve repair. Serial NT-proBNP measurements, transthoracic echocardiography and New York Heart Association (NYHA) class assessment were performed before and 6 months after surgery.
Results: All patients underwent successful mitral valve repair and no patients died during follow-up. The decrease in NT-proBNP level was associated with the reduction in left atrial dimension ($r=0.72$, $p<0.001$), left ventricular end-systolic dimension ($r=0.63$, $p=0.002$), left ventricular end-diastolic dimension ($r=0.46$, $p=0.031$), and the increase in fractional shortening ($r=-0.63$, $p=0.002$). Finally, patients with decreasing NT-proBNP levels revealed a significant improvement in heart failure symptoms (NYHA class).
Conclusion: Changes in NT-proBNP after surgical mitral valve repair reflect changes in heart failure symptoms and changes in left atrial and ventricular dimensions and function.

THE NATRIURETIC PEPTIDES are endogenous cardiac hormones that include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and its amino-terminal portion N-terminal pro-B-type natriuretic peptide (NT-proBNP) [1,2]. The BNP peptides are synthesized in the ventricular myocardium and released in response to ventricular wall stress [3,4]. In the clinical setting, both BNP and NT-proBNP have been demonstrated to provide important diagnostic and prognostic information in patients with heart failure [5-8].
Recently, elevated plasma BNP levels have been demonstrated in patients with chronic valvular disease [9-11]. In patients with chronic mitral regurgitation, the severity of regurgitation was directly related to the BNP levels [9-11]. The effect of mitral valve repair on BNP levels however, has not been studied. Accordingly, the topic of the current study was to evaluate the change in BNP levels after surgical correction of severe mitral regurgitation and to relate the findings to left ventricular reverse remodeling and improvement in clinical status after surgery.

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MATERIALS AND METHODS

Study population

Between July 2005 and September 2005, 22 consecutive patients undergoing mitral valve repair for severe mitral regurgitation were prospectively enrolled. All patients gave informed consent to participate in the study and the study was conducted in accordance with the Declaration of Helsinki. Patients with mitral valve stenosis (mitral valve area <1.5 cm^2) or aortic valve disease (severe aortic stenosis or regurgitation) were not included.
Mitral regurgitation was related to cardiomyopathy in 11 patients, and to degenerative disease in 11 patients.

Assessment of symptoms and follow-up

Clinical evaluation and assessment of symptoms using NYHA class was conducted by the patient's referring cardiologist and was confirmed by an independent cardiothoracic surgeon at the time of hospital admission. A clinical follow-up was performed at 6 months after mitral valve repair to evaluate the change in NYHA class. During the 6-month follow-up period, adverse events including non-fatal myocardial infarction, repeat mitral valve surgery, cerebrovascular events, renal

dysfunction and hospitalization for heart failure were noted.

Echocardiography

Prior to surgery, transthoracic echocardiography was performed in all patients. The patients were imaged in the left lateral decubitus position by using a commercially available system (Vingmed Vivid Seven, General Electric – Vingmed, Milwaukee, WI, USA). Using a 3.5 MHz transducer, images were obtained at a depth of 16 cm in the parasternal (long- and short-axis images) and apical views (2- and 4-chamber images). From parasternal M-mode acquisitions, the left atrial diameter and left ventricular dimensions (end-systolic and end-diastolic diameter) were determined and the fractional shortening was calculated. The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images. Mitral regurgitation was characterized as mild = 1+ (jet area/left atrial area <10%), moderate = 2+ (jet area/left atrial area 10-20%), moderately severe = 3+ (jet area/left atrial area 20-45%), and severe = 4+ (jet area/left atrial area >45%) [12]. Immediately after surgery, transesophageal echocardiography was performed to assess residual mitral valve regurgitation. A transthoracic echocardiogram was repeated at 6 months follow-up to assess left atrial and ventricular dimensions, fractional shortening, the presence of residual mitral valve regurgitation, the transmitral diastolic gradient, the length of leaflet coaptation and the mitral valve area. Two experienced cardiologists who were blinded to the BNP levels and clinical data analyzed the echocardiographic data.

NT-proBNP measurement

Venous blood samples were collected on the day before and 6 months after surgery with the patient at rest and in semi-supine position. The samples were collected in chilled ethylene-diamine-tetra-acetic acid vacutainers and were immediately placed on ice. After centrifugation, the plasma samples were stored at -80°C until assay. Plasma NT-proBNP concentrations was measured with an electrochemiluminescence immunoassay kit (Elecsys 2010, Roche GmbH, Mannheim, Germany). The method is a 'sandwich'-type quantitative immunoassay based on polyclonal antibodies against epitopes in the N-terminal part of pro-BNP [13]. Assays were performed by a laboratory technician blinded to the patient's clinical data.

Table 1. Baseline clinical characteristics of the study population divided into patients with increasing and decreasing N-terminal pro-B-type natriuretic peptide levels.

	Overall (n=22)	Decreasing NT-proBNP levels (n=10)	Increasing NT-proBNP levels (n=12)	p value
Clinical variables				
Age (yrs)	62.8 ± 14.2	63.3 ± 13.5	62.4 ± 15.3	0.89
Male gender	15 (68.2)	7 (70.0)	8 (66.7)	1.00
Hypertension	4 (18.2)	3 (30.0)	1 (8.3)	0.29
Diabetes mellitus	3 (13.6)	2 (20.0)	1 (8.3)	0.57
Chronic obstructive pulmonary disease	4 (18.2)	1 (10.0)	3 (25.0)	0.59
Peripheral arterial disease	3 (13.6)	3 (30.0)	0 (0)	0.078
History of stroke	0 (0)	0 (0)	0 (0)	-
New York Heart Association class	2.9 ± 1.0	3.3 ± 0.9	2.8 ± 0.8	0.23
Medication				
Angiotensin-converting enzyme inhibitors	10 (45.5)	6 (60.0)	4 (33.3)	0.39
Beta-blockers	8 (36.4)	5 (50.0)	3 (25.0)	0.38
Diuretics	9 (40.9)	4 (40.0)	5 (41.7)	1.00
Reason of mitral regurgitation				
Degenerative disease	11 (50.0)	5 (50.0)	6 (50.0)	1.00
Cardiomyopathy	11 (50.0)	5 (50.0)	6 (50.0)	0.17
Echocardiographic measurements				
Mitral regurgitation, grade	3.6 ± 0.5	3.7 ± 0.5	3.6 ± 0.5	0.54
Left atrial dimension (cm)	4.9 ± 0.7	5.2 ±0.6	4.7 ± 0.7	0.040
Left ventricular end-systolic dimension (cm)	4.5 ± 0.8	4.7 ± 1.0	4.3 ± 0.6	0.21
Left ventricular end-diastolic dimension (cm)	6.1 ± 0.8	6.3 ± 0.7	5.9 ± 0.9	0.27
Fractional shortening (%)	26.8 ± 7.3	25.4 ± 8.3	28.0 ± 6.6	0.42
Baseline LN NT-proBNP level (ng/l)	6.2 ± 1.5	6.6 ± 1.4	5.8 ± 1.5	0.18

Values are expressed in mean ± standard deviation or in number (%). NT-proBNP denotes N-terminal pro-B-type natriuretic peptide

Statistical analysis
The change in NT-proBNP levels from baseline to 6 months follow-up was calculated and expressed as percentage values. Changes in left atrial dimension, left ventricular end-systolic and end-diastolic dimensions and fractional shortening were also calculated and expressed as percentage values. Continuous data were expressed as mean (± SD) or median (interquartile range) when the distributions were skewed and compared using the Student t-test or the Mann-Whitney U-test when appropriate. Categorical data were compared using the Fisher's exact test. Group comparisons were performed with analysis of variance (ANOVA) techniques. The Pearson correlation coefficient was used to assess the association between changes in NT-proBNP levels and changes in echocardiographic variables. For all tests, a p value <0.05 was considered significant. All analysis was performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics
The baseline characteristics of the 22 patients (mean age 62.8 ± 14.2 years, 68% male) are summarized in Table 1. Eight patients (36%) were in NYHA class II, 5 (23%) in class III and 9 (41%) in class IV (mean NYHA class 3.1 ± 0.9). Prior to surgery, all patients presented with severe mitral valve regurgitation (grade 3 to 4+), with a mean regurgitation grade of 3.6 ± 0.5. Mean left atrial dimension was 4.9 ± 0.7 cm, mean left ventricular end-systolic dimension 4.5 ± 0.8 cm, mean left ventricular end-diastolic dimension 6.1 ± 0.8 cm and mean fractional shortening 26.8 ± 7.3%. Median NT-proBNP level at baseline was 418 ng/l (interquartile range: 204-1258 ng/l).

Surgical results and follow-up
Mean length of hospital stay was 9.8 ± 4.3 days. Transesophageal echocardiography immediately after surgery demonstrated competent valves with minimal residual mitral valve regurgitation in all patients (mitral regurgitation grade 0 in 13 patients, 59% and grade 1 in 9 patients, 41%). All patients survived the 6-month follow-up period and no patients were lost to follow-up. During hospital stay and follow-up, none of the patients required repeat mitral valve surgery. Adverse events, including nonfatal myocardial infarction, cerebrovascular events, hospitalization for heart failure or endocarditis were not observed. Two patients (9%) developed renal dysfunction in the postoperative period which was successfully treated with a short period of renal dialysis. None of the patients presented with renal dysfunction at 6 months follow-up. Median NT-proBNP level at 6 months follow-up was 426 ng/l (interquartile range 196-1172 ng/l). In 10 patients (45%), NT-proBNP levels decreased >10% and in 12 patients (55%) NT-proBNP level remained unchanged or increased >10% as compared to baseline values.
The patient population was subsequently divided into patients with a decrease in plasma NT-proBNP level versus patients with unchanged/increased NT-proBNP plasma levels (Table 1). Baseline characteristics were comparable between the 2 groups, including baseline NT-proBNP levels. Only left atrial dimension was somewhat larger in patients with decreasing NT-proBNP levels after surgery as compared to those with increasing NT-proBNP levels (p=0.04).

Changes in NT-proBNP levels and symptoms
NYHA class deteriorated in 3 patients (14%), remained unchanged in 5 (23%) and improved in 14 (64%). The 10 patients with decreased NT-proBNP levels exhibited a mean improvement in NYHA class of 2.0 ± 1.1, whereas the 12 patients with unchanged/increased NT-proBNP levels revealed a small but significant worsening in NYHA class (0.3 ± 0.9, p<0.001 versus baseline).

Changes in NT-proBNP levels and echocardiographic variables
The transthoracic echocardiogram at 6 months follow-up revealed a mean mitral regurgitation grade of 0.5 ± 0.7, mean length of leaflet coaptation of 0.9 ± 0.2 cm, mean mitral valve area of 2.6 ± 0.9 cm^2, and mean transmitral diastolic gradient of 3.3 ± 1.2 mmHg. At follow-up, mean left atrial dimension was 4.4 ± 0.5 cm, mean left ventricular end-systolic dimension 4.2 ± 0.9 cm, mean left ventricular end-diastolic dimension 5.8 ± 0.6 cm, and mean fractional shortening 28.0 ± 10.7%. The 10 patients with decreased NT-proBNP levels demonstrated significant reverse left ventricular remodeling, with a reduction in left ventricular end-systolic dimension from 4.7 ± 1.0 cm to 3.8 ± 0.9 cm (p=0.042), a reduction in left ventricular end-diastolic dimension from 6.5 ± 0.8 cm to 5.7 ± 0.6 cm (p=0.036) and a reduction in left atrial dimension from 5.3 ± 0.6 cm to 4.3 ± 0.5 cm (p=0.001). Conversely, reverse left ventricular remodeling was not observed in the 12 patients with unchanged/increased NT-proBNP levels. Mean left ventricular end-systolic dimension was 4.3 ± 0.6 cm at baseline versus 4.5 ± 0.7 cm (p=0.43) at follow-up, and mean left ventricular end-diastolic dimension was 5.9 ± 0.9 cm at baseline versus 5.8 ± 0.6 cm at follow-up (p=0.66). Mean left atrial dimension did also not change (4.7 ± 0.7 cm versus 4.5 ± 0.6 cm, p=0.67). Scatter plots demonstrating the correlation between changes in NT-proBNP level and changes in echocardiographic variables during the 6-month follow-

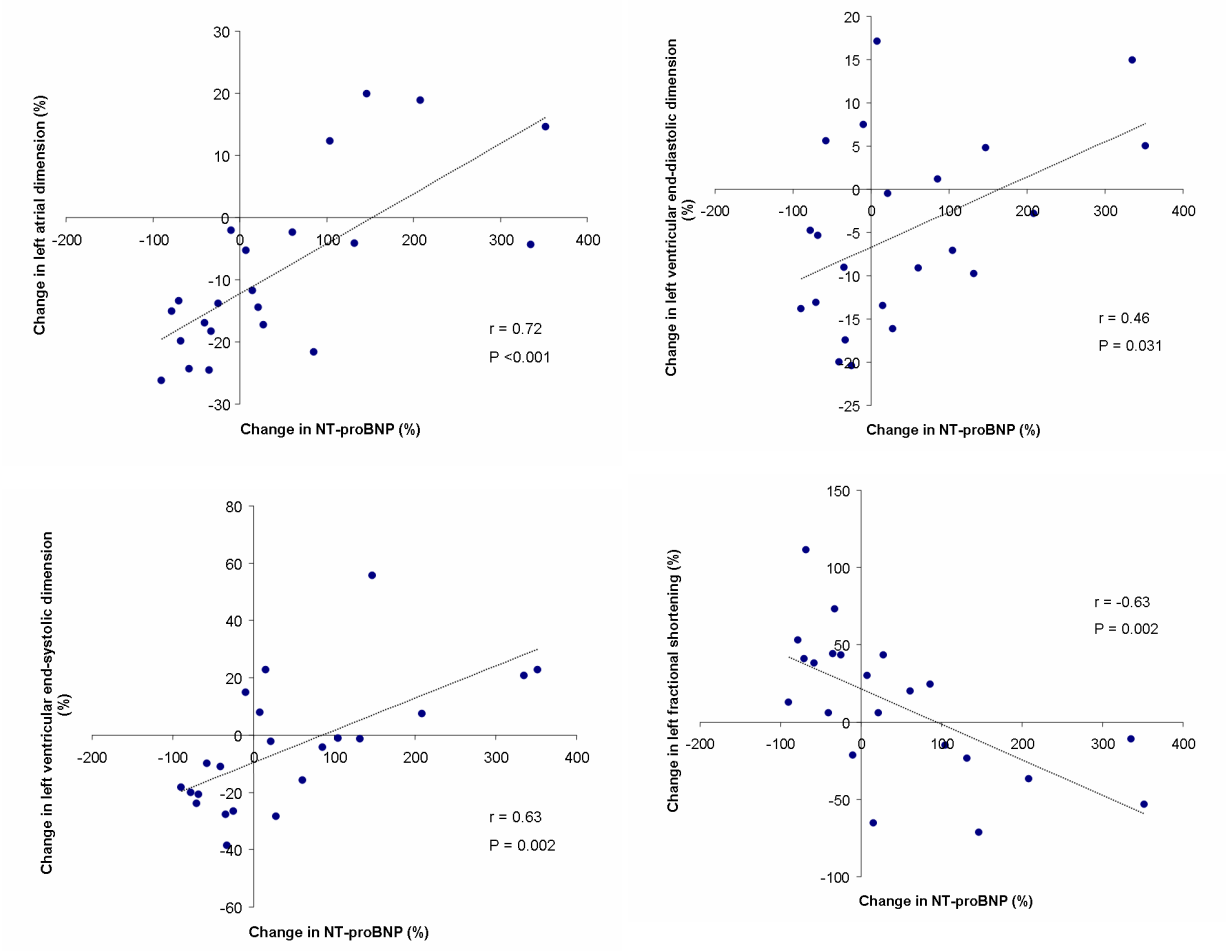

Figure 1. Scatter plots demonstrating the correlation between changes in plasma N-terminal pro-B-type natriuretic peptide level (NT-proBNP) and changes in echocardiographic variables (A. left atrial dimension; B. left ventricular end-systolic dimension; C. left ventricular end-diastolic dimension; D. fractional shortening) during the 6-month follow-up period after mitral valve surgery. Of note, negative changes in left atrial dimension, left ventricular end-systolic dimension and left ventricular end-diastolic dimension indicate reductions in dimensions (reverse remodeling), whereas positive changes indicate ongoing dilatation. A positive change in fractional shortening indicates an increase in systolic function, whereas a negative change in fractional shortening indicates a decrease in systolic function. Negative changes in NT-proBNP indicate a reduction in plasma levels after surgery, whereas positive changes indicate an increase in plasma levels after surgery.

up period after mitral valve surgery are presented in Figure 1. Decreases in NT-proBNP levels at follow-up were significantly correlated with reductions in left atrial dimension ($r=0.72$, $p<0.001$), left ventricular end-systolic dimension ($r=0.63$, $p=0.002$), and left ventricular end-diastolic dimension ($r=0.46$, $p=0.031$), indicating reverse remodeling; conversely, increases in NT-proBNP levels were related to increases in the different dimensions, indicating ongoing dilatation. Moreover, decreases in NT-proBNP levels at follow-up were significantly correlated with improved fractional shorting ($r=-0.63$, $p=0.002$), indicating improved systolic function.

COMMENTS

BNP has been used extensively in the diagnosis and prognosis of patients with heart failure [5-8]. More recently, Sutton and colleagues demonstrated in 49 patients with mitral regurgitation and preserved left ventricular ejection fraction that plasma levels of BNP and NT-proBNP levels were directly related to the severity of mitral valve regurgitation [11]. In addition, Detaint et al evaluated 124 patients with chronic mitral regurgitation and demonstrated that BNP levels were correlated with long-term outcome [14]. In particular, higher BNP levels independently predicted mortality and the combined endpoint of mortality and heart

failure. Moreover, the authors demonstrated that BNP levels in chronic mitral regurgitation were related to left atrial volumes, left ventricular end-systolic volume index, atrial fibrillation and heart failure symptoms. These findings indicate that the BNP plasma level reflects the hemodynamic, ventricular and atrial consequences of mitral regurgitation and that it may be a useful parameter to predict outcome in patients treated conservatively.

In the present study, NT-proBNP was assessed in patients with severe mitral regurgitation and re-assessed after surgical correction of regurgitation. The patient population consisted of patients with severe mitral valve regurgitation (grade 3 to 4+), left ventricular dilatation (left ventricular end-diastolic dimension 6.1± 0.8 cm) and reduced left ventricular function (fractional shortening 26.8 ± 7.3%), with a mean NYHA class of 3.1 ± 0.9.

All patients underwent successful surgical correction and demonstrated competent mitral valves without or minimal regurgitation on echocardiography at 6-months follow-up.

The current study is the first to report the association between NT-proBNP changes and echocardiographic outcome after surgical repair for mitral regurgitation. The changes in NT-proBNP levels were directly related to changes in left atrial dimension, left ventricular dimensions and systolic function (as indicated by the fractional shortening, see Figure 1).

In particular, the patients with a decrease in NT-proBNP levels exhibited a reduction in left atrial size, with reverse left ventricular remodeling. On the contrary, the patients with an increase in NT-proBNP levels did not exhibit this reverse remodeling and left atrial size did also not decrease after surgery. In addition, the patients with a reduction in NT-proBNP levels demonstrated an improvement in symptoms (reduction in NYHA class), whereas patients with an increase in NT-proBNP did not show a change in symptoms.

The findings confirm the use of NT-proBNP to assess clinical status. In addition to the heart failure population, NT-proBNP may be of use to reflect clinical status after mitral valve surgery, with a decrease in NT-proBNP indicating an improvement in symptoms and reverse left ventricular remodeling; conversely, an increase in NT-proBNP should alert the clinician, since it was associated with absence of reverse remodeling and absence of improvement in symptoms.

The main limitations of the current study are the small sample size and the relatively short follow-up; accordingly, larger studies with longer follow-up are needed to confirm the present results. In addition, patients with mitral regurgitation with different etiologies were included, and findings need confirmation in homogenous populations. Also, the patients in the current study had moderate left ventricular dysfunction, and additional studies in patients with severe left ventricular dysfunction are needed.

Conclusion

In conclusion, changes in NT-proBNP after surgical mitral valve repair reflect changes in heart failure symptoms and changes in left ventricular dimensions. Changes in NT-proBNP levels may guide therapy after mitral valve surgery.

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Chapter 18

Ischemic heart disease in renal transplant candidates: towards non-invasive approaches for preoperative risk stratification

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Ischemic heart disease in renal transplant candidates: towards non-invasive approaches for preoperative risk stratification

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IN PATIENTS WITH END-STAGE renal failure, coronary artery disease is the leading cause of morbidity and mortality. It has been shown in a prospective randomized study that prophylactic coronary artery revascularization in renal transplant candidates with diabetes and without symptoms of coronary artery disease reduces the incidence of cardiac events. [1] The detection of coronary artery disease prior to renal transplantation has therefore been an important goal in transplant programs. The American Society of Transplantation reported guidelines for the pre-transplant evaluation of renal transplant candidates. [2] They included the use of non-invasive cardiac stress testing, however, it remained unclear which test to use due to the lack of firm support for a single test.

In this issue of the European Journal of Echocardiography, Sharma et al evaluated the diagnostic accuracy and prognostic value of dobutamine stress echocardiography (DSE) and elevated baseline plasma cardiac troponin T levels in a study population of 118 consecutive patients with end-stage renal disease. They used coronary angiography for stress test validation and found DSE to be an accurate technique for detecting coronary artery disease (sensitivity of 88%, specificity of 94%). Also, elevated troponin T levels in addition to an abnormal stress test could not improve the sensitivity of the test, however, this was an important marker for the prognosis in renal transplant candidates (cardiac troponin T level >0.08 ng/mL for predicting mortality: sensitivity 75%, specificity of 76%).

Previously published studies evaluating the diagnostic accuracy of DSE for detecting coronary artery disease reported sensitivities of 52-95% and specificities of 71-86%.[3,4] In addition, the result of the DSE has been shown to be an independent predictor of prognosis in patients with end-stage renal disease. [5-7] The accuracy of these studies may have been limited by small sample sizes, low event rates and the lack of adjustment for clinical risk factors, but a meta-analysis of 12 studies assessed the prognostic utility of DSE and thallium scintigraphy in patients with end-stage renal disease and confirmed that abnormal test results were associated with a higher risk for cardiac events.[8] Inducible ischemia was associated with a six-fold increased risk of myocardial infarction and an almost four-fold increased risk of cardiac death. Fixed defects (rest wall motion abnormalities) were also significantly associated with an increased risk of cardiac death.

Cardiac isoforms of troponin I and troponin T are sensitive and specific markers of myocardial injury, have been accepted as a standard biomarker for the diagnosis of acute myocardial infarction and unstable angina pectoris, and identify patients at increased risk for subsequent cardiac events. Elevated troponin levels in asymptomatic patients with renal disease have been well-documented [9] and there is substantial evidence that cardiac troponins predict cardiac complications in patients with end-stage renal disease. [10-12] Dierkes et al studied 102 patients with end-stage renal disease on haemodialysis without clinical evidence of acute coronary artery disease and they found a strong association of elevated troponin T levels and all-cause mortality (cardiac troponin T level >0.10 ng/mL: sensitivity 83%).[10] In a large study cohort of 244 haemodialysis patients, Ooi et al found that higher plasma cardiac troponin T levels and increasing cardiac troponin T concentrations over time predicted all-cause mortality. [11] The association between increases in cardiac troponin T concentrations and mortality was confirmed in a large study cohort of 733 patients with end-stage renal disease, conducted by Apple et al. [12]

Although the underlying pathophysiological mechanism is still not clearly elucidated, elevated troponin levels may be a marker of subclinical myocyte damage secondary to clinically silent myocardial necrosis. [13] The sensitivity of troponin T to predict angiographic coronary artery disease in patients has been demonstrated in patients with a normal renal function; however, future studies are still needed to confirm this in patients with end-stage renal failure. [14] It may be difficult to detect elevated plasma cardiac troponin T levels in asymptomatic patients with

coronary artery disease, not only because of the transient release of cardiac troponin T during transient myocardial ischemia, but also because cardiac troponins are susceptible to various biochemical modifications, including phosphorylation, oxidation and proteolysis. [13] In addition, dialysis may affect serum levels of cardiac troponins. [15] Serial troponin measurements may enhance the detection rate of plasma cardiac troponin levels and the value of cardiac troponins to predict coronary artery disease.

Coronary angiography is an effective method for detecting CAD and essential for the performance of percutaneous transluminal coronary angiography and revascularization surgery, however, it is invasive, expensive and potentially nephrotoxic. Dissimilarities in sensitivity and specificity for DSE and myocardial scintigraphy to detect anatomic evidence of coronary artery disease have been reported in patients with end-stage renal failure, and the use of invasive coronary angiography might still be necessary to rule out significant coronary artery disease. [16] Coronary angiography in comparison to non-invasive stress testing might have stronger prognostic value in patients with end-stage renal disease. [16] However, the good negative predictive value of non-invasive stress testing suggests that patients with no stress-induced myocardial ischemia do not need further coronary angiography. In addition, the risk of contrast-associated nephropathy is an important concern in these patients. Coronary angiography should only be performed in patients with end-stage renal disease, when coronary artery revascularization is considered a reasonable option.

Recently, interest has focused on coronary CT scanning as non-invasive method for diagnosing coronary artery disease. Coronary calcification detected by coronary CT scanning has been shown to be associated with silent myocardial ischemia as assessed with myocardial perfusion studies and to detect coronary artery disease in symptomatic patients. [17] Coronary calcification is frequently observed in patients with end-stage renal failure and coronary CT may be a promising tool to improve cardiac risk stratification in these population.

Traditionally, coronary artery disease in patients with end-stage renal disease has been treated conservatively, but these patients may gain from an aggressive treatment strategy, including mechanical coronary revascularization for clinically significant coronary artery disease. Manske et al randomly assigned 26 asymptomatic diabetic renal transplant candidates to medical treatment or coronary revascularization and demonstrated that revascularization significantly decreased the frequency of cardiac events during follow-up. [1] Retrospective studies also suggest that mechanical coronary revascularization is associated with improved outcomes, compared to medical therapy alone in patients with end-stage renal disease. [18] Prophylactic mechanical coronary artery revascularization before surgery may only be recommended in patients with advanced left main coronary artery disease or unstable cardiac symptoms. However, many physicians are reluctant to perform mechanical coronary revascularization procedures in patients with end-stage renal disease because of the poor outcomes compared to patients with normal renal function. The Coronary Artery Revascularization Prophylaxis trial showed that long-term outcome after elective major vascular surgery was not significantly altered by coronary artery revascularization before surgery in 510 patients with stable coronary artery disease randomly assigned to either revascularization of no revascularization. [19] Large, prospective, randomized, controlled trials are needed to prove a survival benefit of preoperative coronary artery revascularization in renal transplant candidates with stable coronary artery disease. Besides surgical strategies, attention should also be focused on medical treatment strategies for cardiovascular disease, which may be under-utilized in patients with severe chronic kidney disease.

Appropriate preoperative evaluation of renal transplant candidates is not only mandated to identify those at increased cardiac risk, but also because the number of available organs is limited and early death of a recipient can be prevented by pre-transplant coronary intervention. Dobutamine stress echocardiography is widely recognized as an accurate diagnostic method for use in the general population and several studies have proved its diagnostic and prognostic value in patients with end-stage renal disease. Dobutamine stress testing has substituted exercise stress testing, because a substantial number of patients do not reach 85% of their maximum heart rate during exercise stress testing. It furthermore avoids the potentially nephrotoxic influence of contrast material as observed during nuclear imaging techniques. The ideal algorithm, incorporating risk factors, laboratory results, non-invasive stress testing, coronary angiography and preoperative coronary revascularization for the work-up of renal transplant patients still has to be validated.

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Chapter 19

The impact of glomerular filtration rate on minor troponin T release for cardiac risk stratification in major vascular surgery

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Impact of Glomerular Filtration Rate on Minor Troponin T Elevations for Risk Assessment in Patients Undergoing Operation for Abdominal Aortic Aneurysm or Lower Extremity Arterial Obstruction

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Debate surrounds the impact of renal function on the prognostic value of minor troponin T release in vascular surgery patients. Objective of this study was to assess the long-term prognostic value of minor degrees of troponin T release in patients undergoing major vascular surgery, especially in those with concomitant renal dysfunction. Survivors of major non-cardiac vascular surgery (n=558) were preoperatively screened for cardiac risk factors and renal function. Serial troponin T was measured on day 1, 3, and 7 after surgery, using a threshold of 0.03 ng/ml. All-cause mortality and major adverse cardiac events (MACE) were noted during follow-up (mean: 3.5 ± 2.0 years). Minor (0.03-0.09 ng/ml) and major (≥0.1 ng/ml) release of troponin T was observed in 5% and 8%, respectively. During follow-up, 21% of the patients died and 15% experienced MACE. After adjustment for estimated glomerular filtration rate, patients with minor and major troponin T release were both at comparable increased risk for late mortality (HR: 3.43, 95% CI: 1.79-6.58, HR: 3.72, 95% CI: 2.37-5.85, respectively), and MACE (HR: 5.47, 95% CI: 2.60-11.48, HR: 6.32, 95% CI: 3.82-10.48, respectively), compared to patients with troponin T release <0.03 ng/ml. Tests for heterogeneity revealed that both minor and major troponin T release have prognostic value across the entire spectrum of renal function. In conclusion, marginal elevations of troponin T strongly predict late mortality and MACE after major vascular surgery, irrespective of renal function. A currently underestimated high-risk subgroup of patients may be identified by using a lower troponin T threshold level.

THE PRESENT STUDY was conducted to investigate whether minor (0.03-0.09 ng/ml) and major (≥0.1 ng/ml) elevations of perioperative troponin T level have significant prognostic value in patients undergoing successful elective abdominal aortic aneurysm repair or lower extremity revascularization procedures. The impact of renal function on the prognostic value of minor troponin T release was also evaluated.

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METHODS

The study population consisted of consecutive adult patients undergoing and surviving elective abdominal aortic aneurysm repair or lower extremity bypass surgery at the Erasmus Medical Centre in Rotterdam, the Netherlands between January 2000 and January 2006. For the assessment of long-term prognosis, we have excluded patients who died during surgery or before hospital discharge. All patients gave informed consent. Preoperative evaluation was performed according to the ACC/AHA guidelines on perioperative cardiovascular evaluation for non-cardiac surgery [1]. Prior to surgery, patients were screened for cardiac risk factors, including hypertension (blood pressure ≥140/90 mmHg or treatment with antihypertensive drugs), diabetes mellitus (fasting glucose level ≥126 mg/dl (≥7.0 mmol/l) or treatment with antidiabetic drugs) and hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or treatment with cholesterol lowering drugs). A detailed cardiac history was obtained and coronary artery disease was indicated by a previous myocardial infarction, by a previous coronary intervention, or by the presence of angina pectoris. Patients were also screened for a history of stroke, congestive heart failure and chronic obstructive pulmonary disease. Preoperative serum creatinine levels were obtained and the last single serum creatinine measurement was used when multiple measurements were performed before surgery. The Modification of Diet in Renal Disease study has

provided a useful estimate of the glomerular filtration rate (eGFR) in adults, which has been recommended by the National Kidney Foundation practice guidelines for chronic kidney disease [2,3]. eGFR was calculated by the following equation: glomerular filtration rate (ml/min/1.73 m^2) = 186 x (serum creatinine level)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.210 if African-American) [2,3]. A total of 275 patients (49%) underwent elective abdominal aortic aneurysm repair and 283 patients (51%) underwent lower extremity bypass surgery.

Serial cardiac troponin T levels measurements were obtained in all patients on postoperative day 1, 3 and 7 and before discharge by an electrochemiluminescence immunoassay on the Elecsys 2010 immunoanalyzer (Roche Diagnostics, Mannheim, Germany). If one of these measurements was elevated, measurements were repeated on every day until the level returned to normal values. Absolute troponin T levels were noted and the highest of the serial troponin T measurements was used for analysis. We used the recommended lower limit of 0.03 ng/ml, since lower troponin T levels do not meet the imprecision criteria (coefficient of variation) of <10% [4].

During follow-up, the end-points of the study were mortality from all causes and major adverse cardiac events (cardiac death or non-fatal myocardial infarction, MACE). Survival status was obtained by approaching the municipal civil registries. The cause of death was determined by reviewing autopsy reports, death certificates and by approaching the referring physician. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, or congestive heart failure. Sudden unexpected death was included as cardiac death. Clinical information was obtained by regularly scheduled outpatient visits, by telephone interviews, by reviewing hospital records and by approaching the referring physician. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: elevated cardiac enzyme levels (creatine kinase (CK) level > 190 U/L and CK-MB fraction >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/ml), development of typical electrocardiographic changes (new Q waves >1 mm or > 30 ms), and typical symptoms of angina pectoris.

Continuous data were expressed as mean (± SD) and compared using the Student t test or using analysis of variance techniques. Categorical data were compared using the Chi-square test. Troponin T release was divided in minor release (between 0.03-0.09 ng/ml) and major release (≥0.10 ng/ml). Renal function was classified according to non-standard cut-off values: normal renal function (eGFR ≥75.0 ml/min per 1.73 m^2), mild dysfunction (eGFR 60.0-74.9 ml/min per 1.73 m^2), moderate dysfunction (eGFR 45.0-59.9 ml/min per 1.73 m^2) and severe dysfunction (eGFR <45.0 ml/min per 1.73 m^2). The Kaplan-Meier method with the log-rank test was used to compare survival between different groups of patients. Multivariate Cox proportional hazard regression analysis was used to evaluate the long-term prognostic value of perioperative troponin T elevations, independent of eGFR, demographics, cardiac risk factors according to the Revised Cardiac Risk Index (coronary artery disease, history of congestive heart failure, history of cerebrovascular disease, and diabetes mellitus) [5] and cardioprotective medication. Tests for heterogeneity were used to reveal a possible interaction between troponin T release and eGFR. For all tests, a p value <0.05 (2-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

Table 1. Clinical characteristics of the study cohort according to different troponin T elevations

Characteristic	All	Troponin T levels			P-value
	n=558	<0.03 ng/ml n=487	0.03-0.09 ng/ml n=25	≥0.10 ng/ml n=46	
Age (years) (mean +/-SD)	66.6 ± 10.7	66.1 ± 10.9	68.6 ± 10.2	70.7 ± 7.8	0.014
Male gender	428 (76.7)	373 (76.6)	19 (76.0)	36 (78.3)	0.96
Angina pectoris	100 (17.9)	81 (16.6)	6 (24.0)	13 (28.3)	0.10
Previous myocardial infarction	192 (34.4)	157 (32.2)	11 (44.0)	24 (52.2)	0.014
Previous CABG[a]	89 (15.9)	72 (14.8)	4 (16.0)	13 (28.3)	0.058
Coronary artery disease (summary)	239 (42.8)	197 (40.5)	15 (60.0)	27 (58.7)	0.012
History of congestive heart failure	22 (3.9)	18 (3.7)	3 (12.0)	1 (2.2)	0.093
Previous cerebrovascular event	70 (12.5)	61 (12.5)	4 (16.0)	5 (10.9)	0.82
Diabetes mellitus type 1	78 (14.0)	65 (13.3)	5 (20)	8 (17.4)	0.51
Hypertension	232 (41.6)	198 (40.7)	11 (44.0)	23 (50.0)	0.46
Hypercholesterolemia	172 (30.8)	150 (30.8)	6 (24.0)	16 (34.8)	0.64
Current smoking	326 (58.4)	293 (60.2)	13 (52.0)	20 (43.5)	0.072
Abdominal aortic aneurysm repair	275 (49.3)	229 (47.0)	20 (80.0)	26 (56.5)	<0.001
Lower extremity revascularization	283 (50.7)	258 (53.0)	5 (20.0)	20 (43.5)	0.003
Serum creatinine (mg/dl)	1.21 ± 1.08	1.13 ± 0.89	1.58 ± 1.58	1.93 ± 2.00	<0.001
eGFR[b] (ml/min per 1.73 $m^{2)}$	80 ± 31	82 ± 31	67 ± 33	61 ± 32	<0.001

[a]coronary artery bypass grafting; [b]estimated glomerular filtration rate. Values are expressed in mean ± SD or number (%).

RESULTS

The study population was predominantly male and mean age was 67 ± 11 years (Table 1). Mean eGFR was 80 ± 31 ml/min/1.73 m^2. Normal renal function was assessed in 318 patients (57%), mild renal dysfunction in 105 patients (19%), moderate renal dysfunction in 68 patients (12%) and severe renal dysfunction in 67 patients (12%). Minor troponin T elevation was observed in 25 patients (5%) and major troponin T elevations in 46 patients (8%).

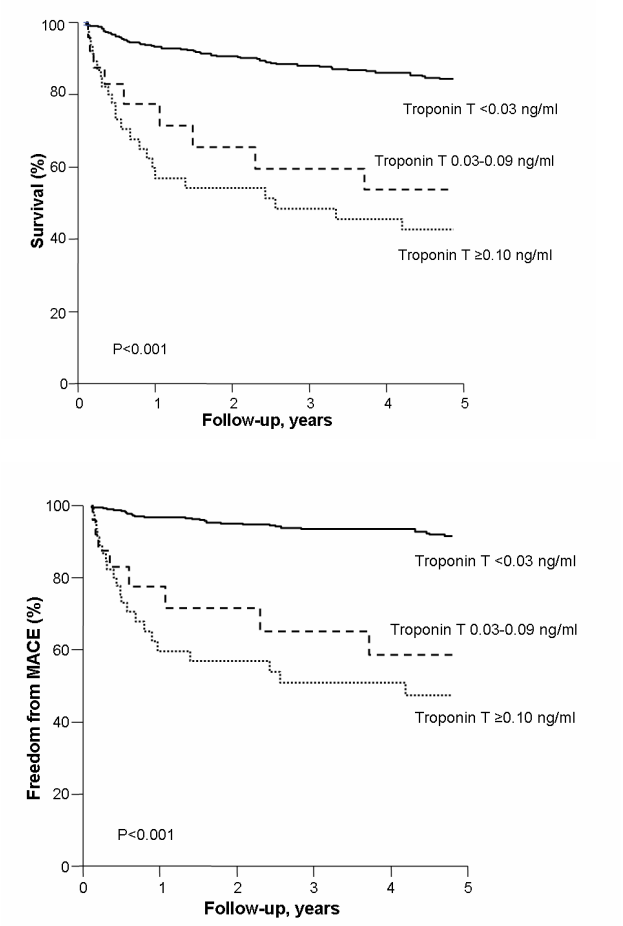

Figure 1. Survival and freedom from major adverse cardiac events (MACE) in 558 patients who survived major non-cardiac vascular surgery according to perioperative troponin T release.

During a mean follow-up time of 4 ± 2 years, 116 patients (21%) died. MACE were observed in 82 patients (15%) (cardiac death in 62 patients and non-fatal myocardial infarction in 20). Kaplan-Meier curves stratified according to the level of troponin T release revealed that patients with minor and major troponin T release had a significantly decreased survival and MACE free survival, compared to patients with troponin T release <0.03 ng/ml ($p<0.001$ and $p<0.001$, respectively) (Figure 1). A decreased survival and MACE free survival was also observed in patients with more severe renal dysfunction ($p<0.001$ and $p<0.001$, respectively) (Figure 2). Multivariate analysis with adjustment for clinical characteristics and eGFR revealed that patients with minor (HR: 3.43, 95% CI: 1.79-6.58, $p<0.001$) and major troponin T release (HR: 3.72, 95% CI: 2.37-5.85, $p<0.001$) were both at comparable increased risk for late mortality compared to patients with troponin T release <0.03 ng/ml. Patients with minor (HR: 5.47, 95% CI: 2.60-11.48, $p<0.001$) and major troponin T release (HR: 6.32, 95% CI: 3.82-10.48, $p<0.001$) were also at increased risk for MACE, compared to patient with troponin T release <0.03 ng/ml.

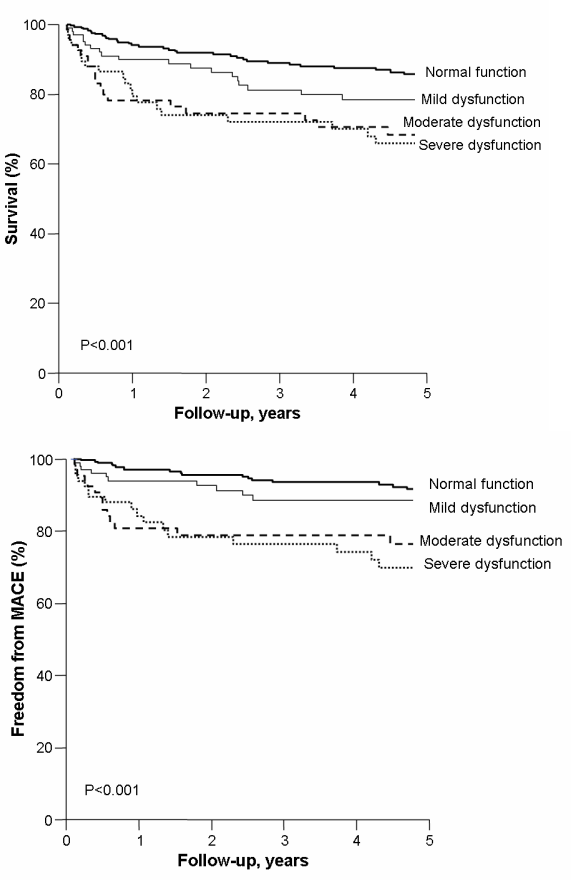

Figure 2. Survival and freedom from major adverse cardiac events (MACE) in 558 patients who survived major non-cardiac vascular surgery according to renal function.

In a subgroup analysis of patients with moderate or severe renal dysfunction (n=135), minor and major troponin T release remained significantly associated with late mortality (HR: 4.27, 95% CI: 1.75-10.40, p<0.001, and HR: 5.54, 95% CI: 2.92-10.52, p<0.001) and MACE (HR: 8.09, 95% CI: 2.72-24.05, p<0.001, and HR: 7.05, 95% CI: 3.44-14.47, p<0.001). Moreover, tests for heterogeneity revealed no evidence for a differential effect of troponin T release in patients with different eGFR (p=0.19 for the endpoint all-cause mortality and p=0.79 for the endpoint MACE), indicating that minor and major elevations of troponin T predicted the risk of late mortality and MACE across the entire spectrum of renal function.

DISCUSSION

The troponin complex is a group of 3 proteins (troponin T, troponin I and troponin C) that act together through the tropomyosin complex to regulate muscle contraction. Cardiac troponin T levels are detectable in 3 to 12 hours after myocardial injury, and the concentration is in direct proportion to the extent of myocardial injury [6]. Because of its high cardiac specificity, we have used troponin T as biomarker for myocardial damage instead of troponin I, troponin C, or creatine kinase and its MB subfraction. No consensus exists about optimal threshold levels of troponin T.

The ACC/ESC task force expressed in their consensus document that all elevated values of troponin T in the setting of documented myocardial ischemia should be considered myocardial infarction, using a upper value which corresponds to the 99th percentile of a reference group [7]. In our study, the Roche elecsys 2010 immunoanalyzer, which does not cross-react with skeletal troponin, allowed a lower limit of 0.03 ng/ml with an acceptable imprecision (coefficient of variation) of ≤10%. The prognostic usefulness of small troponin T elevations has been studied previously among patients who presented to the emergency department with suspected myocardial ischemia. Hendrikson and colleagues showed that patients with small elevations of troponin T between 0.01 and 0.09 ng/ml were at significantly increased risk of death, myocardial infarction and coronary revascularization, compared to patients with undetectable troponin T release [8]. In patients who underwent major vascular procedures, Landesberg and colleagues demonstrated that at low cut-off levels, elevations in cardiac troponins (troponin I >0.6 ng/ml and/or troponin T >0.03 ng/ml) independently predicted increased risk of long-term mortality [9]. In this study, it was less clear whether a subgroup of patients with small troponin T elevations were at increased risk of late cardiac events and whether renal function interfered with the prognostic value of troponin T.

The current study showed that after adjustment for eGFR, minor elevations in troponin T between 0.03 and 0.09 ng/ml were strongly associated with adverse outcome. The hazard ratio for late all-cause mortality in patients with troponin T release between 0.03 and 0.09 ng/ml was comparable to the hazard ratio of patients with troponin T release of 0.10 ng/ml or more. Tests of heterogeneity confirmed that both minor and major elevations of troponin T predicted the risk of late mortality across the entire spectrum of renal function.

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Chapter 20

Perioperative medical management of ischemic heart disease in patients undergoing non-cardiac surgery

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Perioperative medical management of ischemic heart disease in patients undergoing non-cardiac surgery

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Purpose of review Cardiovascular disease is the leading cause of death after anesthesia and surgery. The preoperative identification of patients with underlying coronary artery disease is important to initiate appropriate treatment strategies in order to reduce the risk of perioperative complications. The current review will discuss new insights in the field of perioperative medicine that can be applied to clinical practice or stimulate further investigation.
Recent findings Recent findings in the past year have developed preoperative risk stratification in terms of simplicity, safety, accuracy and cost-effectiveness. Natriuretic peptides have been demonstrated to be promising new preoperative risk markers. Although recommended in high-risk patients, non-invasive cardiac stress testing may be safely omitted in patients at intermediate risk. The anti-ischemic properties of beta-blockers have been well described. In clinical practice however, adequate beta-blocker dosage, tight perioperative heart rate control and continuation of beta-blockers after surgery may be important factors too. Statins have emerged as promising drugs with perioperative cardioprotective properties. However, before recommending routine administration of statin therapy, more clinical trials are needed.
Summary New perceptions in perioperative medical management and novel developments in surgical and anaesthesiologic techniques continue to improve the cardiovascular outcome of patents undergoing major non-cardiac surgery.

DURING THE LAST FEW decades, tremendous efforts have been made to decrease cardiac morbidity and mortality associated with non-cardiac surgery. Firstly, preoperative evaluation of the surgical patient has been refined to identify those at increased risk of adverse cardiac events. In addition to medical history and physical examination, preoperative electrocardiography and functional testing have been demonstrated to be effective tools in predicting cardiac outcome after surgery. Secondly, developments in surgical and anesthesiological techniques, i.e. endovascular surgery and loco-regional anesthesia, have improved postoperative outcome considerably. Thirdly, several cardiovascular drugs have been shown to reduce the incidence of cardiovascular events after major non-cardiac surgery. Consensus guidelines now recommend beta-blocker therapy in high-risk patients undergoing major non-cardiac surgery. More recently, evidence suggests that statins have cardioprotective properties that can be useful in surgical patients at increased perioperative risk. The current review will discuss new insights in the field of perioperative medicine that can be applied to clinical practice or stimulate further scientific investigation.

Ischemic heart disease; a continuing problem in major surgery

It has been estimated that 71.3 million people in the United States suffered from cardiovascular disease and that 13.2 million people suffered from coronary heart disease (history of angina pectoris or myocardial infarction) in the year 2003 [1**]. Since 1919, cardiovascular disease has been the single leading cause of death in the United States. It is the underlying or contributing cause of death in about 58% of all cases. In the 30 million patients undergoing non-cardiac surgery in the United States annually, cardiac complications also remain the leading cause of perioperative morbidity and mortality. A pooled analysis of several large studies found an incidence of 2.5% for the composite endpoint of perioperative myocardial infarction or cardiac death in unselected patients over the age of 40 (range: 2.0% to 3.7%) [2]. These complications were higher in vascular surgery patients who had an incidence of 6.2% for cardiac events (range: 2.2% to 19.0%) [3]. The high frequency of perioperative complications reflects the high prevalence of underlying coronary artery disease. According to the World Health Organization, the global epidemic of cardiovascular disease will not only increase, but will also shift from developed to developing nations. It is further estimated that in the second half of the 21st century, more than one in four individuals will be 65 years of age or older. In the past,

major surgery was rarely performed on patients in their eighties or nineties. Nowadays, many major surgical interventions are performed in this very elderly population. A recent study performed in 1351 patients undergoing non-cardiac surgery showed that the rate of cardiac events increased with advanced age, independent of other clinical variables, in those patients with myocardial perfusion abnormalities during stress scintigraphy [4*]. With the growing elderly population, with the increasing incidence of cardiovascular disease and with the availability of more advanced surgical techniques to a higher-risk patient population, underlying ischemic heart disease in surgical patients continues to demand our attention.

Towards simple, safe, inexpensive and accurate preoperative screening

The first step in perioperative medical management is to identify the patient at increased risk of cardiovascular events. Based on a set of clinical risk factors that allows an estimate of the weighted risk of perioperative cardiac complications, several risk indices have been developed, including the Goldman cardiac risk index [5], the Detsky modified multifactorial risk index [6] and Eagle's risk score [7]. It was shown that some of these existing risk indices, including the Goldman risk index, the modified Detsky index, the American Society of Anesthesiologists index and the Canadian Cardiovascular Society index, performed better than chance, but that no index was significantly superior to the other [8]. However, after the revision of the Goldman risk index by Lee and colleagues, the predictive value of this risk index improved substantially [9]. This index identifies 6 predictors of major cardiac complications: 1) high-risk surgery, 2) ischemic heart disease, 3) congestive heart failure, 4) cerebrovascular disease, 5) diabetes and 6) renal failure. Based on the presence of 0, 1, 2, or ≥3 of these predictors, the rate of major cardiac complications was estimated to be 0.4%, 0.9%, 7% and 11%, respectively. Clinicians and researchers have applied this revised cardiac risk index to a large extent. Moreover, it was demonstrated that the risk index could be improved substantially by adding the type of surgical procedure. Boersma and colleagues validated the Lee risk index in a large cohort (n=108.593) of patients undergoing all types of non-cardiac surgical procedures and demonstrated a substantial improvement by adding the surgical risk of the various surgical procedures (C-statistic improved form 0.63 to 0.85) [10].

A simple evaluation based on clinical risk factors and type of surgery is the cornerstone of rational preoperative cardiac risk assessment that can guide subsequent cardiac evaluation (Figure 1). According to the American College of Cardiology/American Heart Association guidelines, preoperative cardiac exercise or pharmacological stress testing is recommended in all patients at increased cardiac risk based on clinical risk profile, functional capacity and type of surgery [12]. A few studies have compared the prognostic accuracy of various non-invasive tests used for preoperative cardiac risk assessment. Among ambulatory and exercise electrocardiography, myocardial perfusion scintigraphy, radionuclide ventriculography and dobutamine or dipyridamole stress echocardiography, stress echocardiography has been favored consistently as test of choice [13,14,15,16]. In addition to the detection of stress induced myocardial ischemia, resting echocardiography detects valvular heart disease or left ventricular dysfunction. This may be important since heart murmurs are frequently observed during the preoperative evaluation [17*] and aortic stenosis is associated with a fivefold increased risk of perioperative cardiac events [18].

Accurate screening with all available techniques may be risky, may increase costs, may delay surgery and may not influence perioperative management. This situation has led to commentaries that emphasis should be shifted from risk stratification to risk modification [19*]. Indeed, the DECREASE-II study questioned the value of cardiac testing in patients at intermediate risk, since only a minority of these patients experience stress-induced myocardial ischemia. The recently published results showed that cardiac testing could safely be omitted in these patients, provided that beta-blockers aiming at tight heart rate control are prescribed [20**]. The study further showed that no testing brought surgery almost 3 weeks forward [20**].

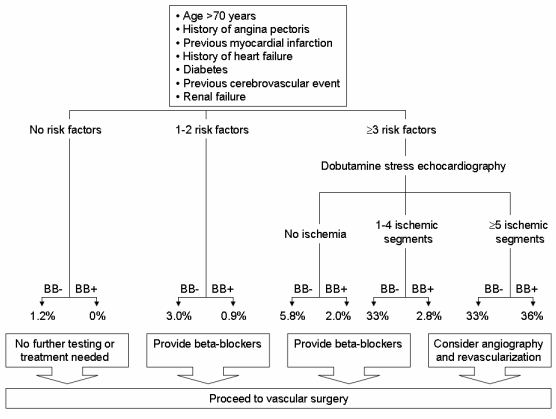

Figure 1. Risk evaluation and cardiac complications in patients undergoing major vascular surgery. BB = beta-blockers. The proportions are the incidence of cardiac death or myocardial infarction. Derived from Boersma and colleagues [11].

New laboratory markers in risk stratification

In the search for simple, safe, inexpensive and accurate preoperative screening, blood serum markers have emerged as promising preoperative risk measures. The use of absolute serum creatinine levels and serum glucose levels can refine risk stratification and can guide further management [21,22]. A promising marker that has been investigated more recently is the natriuretic peptide. Natriuretic peptides are endogenous cardiac hormones that include atrial natriuretic peptide (A-type), brain natriuretic peptide (B-type or BNP), and its amino-terminal portion N-terminal pro-B-type natriuretic peptide (NT-proBNP) [23,24]. NT-proBNP is synthesized in the ventricular myocardium and released in response to ventricular wall stress [25,26]. NT-proBNP has been demonstrated to be an important diagnostic and prognostic marker in patients with heart failure [27,28]. The diagnostic and prognostic value of elevated levels of NT-proBNP has more recently been shown in patients with acute coronary syndromes and stable coronary artery disease [29,30]. Three studies published last year have consistently demonstrated that elevated natriuretic peptide levels predict short-term adverse cardiovascular events in patients undergoing elective non-cardiac surgery [31,32*, 33*]. Optimal cut-off values as determined with receiver operating curve characteristics analysis in the three studies were 450 ng/l and 533 ng/l for N-terminal pro-B-type natriuretic peptide and 189 ng/l for brain natriuretic peptide. The prognostic value of preoperative natriuretic peptides was also sustained for long-term events, as demonstrated in a study involving 335 patients who were followed for a mean duration of 14 months (Figure 2) [34*]. The optimal cut-off value to predict late events was 319 ng/l [34*]. Natriuretic peptide measurements are objective, easily obtainable and inexpensive and are therefore promising markers for routine first-line cardiac risk assessment.

The controversy surrounding perioperative beta-blocker therapy

The application of appropriate cardiac risk reduction strategies is one of the most important steps in perioperative medical management. Numerous clinical trials have shown that perioperative use of beta-blockers can reduce the incidence of postoperative myocardial ischemia, myocardial infarction and cardiac mortality [35,36,37,38,39,40]. Randomized trials have demonstrated that perioperative ischemia as detected by continuous 12-lead electrocardiographic monitoring was significantly reduced by beta-blocker therapy [35,36,37]. Two randomized trials have demonstrated that beta-blockers were also effective for the prevention

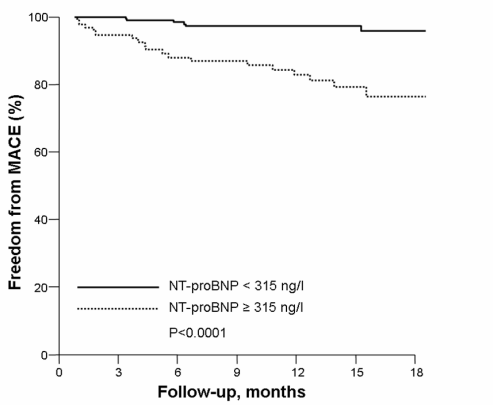

Figure 2. An increase in preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) level can predict long-term major adverse cardiac events (MACE) after major vascular surgery. Derived from Feringa and colleagues [34*].

of cardiac death and myocardial infarction in the perioperative period [39,40]. The first trial evaluated the effect of atenolol in 200 high-risk patients undergoing non-cardiac surgery and demonstrated no difference in perioperative mortality, but a significantly lower mortality rate at 6 months after discharge (0% versus 8%, $p<0.001$), over the first year (3% versus 14%, $p=0.005$) and over 2 years of follow-up (10% versus 21%, $p=0.2$) [39]. The second trial showed in 112 high-risk patients with stress-induced myocardial ischemia a 10-fold reduction in the incidence of perioperative cardiac death and myocardial infarction in patients receiving bisoprolol, compared to patients receiving placebo [40]. On the basis of these trials, the guidelines of the American College of Cardiology/American Heart Association have recommended beta-blocker therapy in all vascular surgery patients with a positive stress test [12].

However, controversy still surrounds the clinical benefit of perioperative beta-blocker therapy [41,42,43**]. A very recently published trial randomized patients to receive either placebo or metoprolol, which was started 2 hours before vascular surgery until hospital discharge or a maximum of 5 days postoperatively [43**]. No reduction in 30-day and 6-month cardiac event rate was observed in patients receiving metoprolol compared to placebo [43**]. The DIPOM trial that randomized diabetic patients to receive metoprolol or placebo from the day before surgery to a maximum of eight days after also failed to demonstrate a beneficial effect in favor of beta-blockers [44**].

The mechanism by which β-blockers exert their cardioprotective effect remains not completely understood. Proposed mechanisms include reduction in heart rate, restoration of the myocardial oxygen supply-

demand balance and prolongation of coronary diastolic filling time [45,46]. Inadequate dosage of β-blockers and insufficient reduction of heart rate during the perioperative period may possibly explain the occurrence of adverse cardiac events and may explain why several studies failed to show a beneficial effect. A recently published study demonstrated in 272 vascular surgery patients that higher doses of beta-blockers and tight heart rate control were associated with reduced perioperative myocardial ischemia and troponin T release and improved long-term outcome (Figure 3) [47**]. Another study also demonstrated that a lower heart rate before surgery was associated with a significantly lower risk of perioperative cardiac events [20**]. In addition to adequate beta-blocker dosage and heart rate control, continuation of beta-blocker therapy in the postoperative period may also be recommended. Withdrawal of beta-blocker therapy in the perioperative period has been associated with a 2.6-fold increased risk of 1-year mortality [48**].

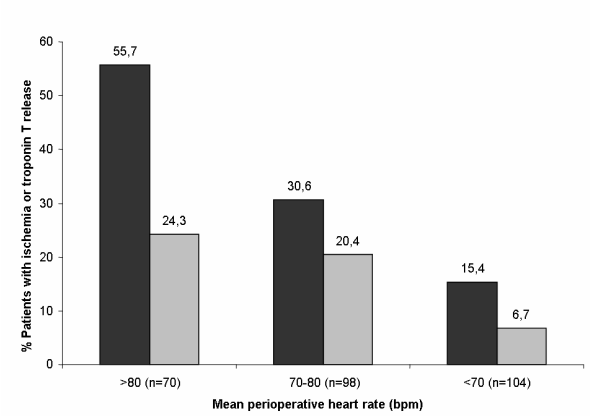

Figure 3. A higher perioperative heart rate is associated with increased perioperative myocardial ischemia during continuous 12-lead electrocardiographic monitoring and troponin T release. Derived from Feringa and colleagues [47**].

Furthermore, the efficacy of beta-blocker therapy in intermediate-risk patients in comparison to high-risk patients has been questioned. The incidence of cardiovascular complications in intermediate risk patients is low, therefore, the number needed to treat to prevent a major cardiovascular complication may be exceedingly high [49*]. In the general population, beta-blockers have been proven to prolong survival in patients with a history of myocardial infarction, with hypertension or with left ventricular dysfunction. In line with this evidence, beta-blockers may especially benefit patients presenting with these cardiovascular conditions. Indeed, a recent study showed that short- and long-term survival was significantly improved in patients with severe left ventricular dysfunction undergoing major vascular surgery who were using chronic beta-blocker therapy, compared to patients not using beta-blockers [50*].

The emerging benefits of statin treatment

Now thought to have properties beyond the lipid-lowering effects, statins have emerged as promising cardioprotective drugs in the perioperative setting. Observational studies and clinical trials have demonstrated marked reductions in cardiovascular events among statin users undergoing major vascular surgery [51]. The beneficial properties of statins beyond the lipid-lowering effect include oxidative stress reduction and decrease in vascular inflammation, suggesting a plaque-stabilizing effect [52]. In human carotid plaques, statins have been demonstrated to decrease lipids, lipid oxidation, inflammation, matrix metalloproteinase-2 and cell death and increase tissue inhibitor of metalloproteinase 1 and collagen [53]. Intensive statin therapy may even result in significant regression of atherosclerosis as demonstrated in the ASTEROID trial [54**]. The many reports published last year in literature reflect the increasing interest in statin therapy as cardioprotective drug. Leurs and colleagues have published the data from the EUROSTAR Data Registry and reported that in patients who underwent endovascular abdominal aortic aneurysm repair, overall mortality rate at 5 years of follow-up was lower in those using statins, compared to those not using statins [55*]. Recent studies not only suggested that statins can lower cardiac events, but that it can also reduce in-hospital length of stay [56*], preserve renal function after suprarenal aortic clamping [57**] and can lower the incidence of stroke after carotid angioplasty and stent placement in patients with symptomatic carotid stenosis [58*]. Finally, several systematic review articles found supportive evidence in favor of statin therapy [59*,60**]. A pooled analysis of 2 randomized studies, 15 cohort studies and 1 case-control study demonstrated that the odds for death or acute coronary syndrome during the perioperative period was significantly lower in statin users, compared to patients not using statins [60**]. However, due to the relative paucity of data, more randomized trials are needed before recommending routine administration of statin therapy in all patients undergoing major surgery.

Other agents with potential cardioprotective effect

Other agents that have been studied for their potential cardioprotective effect in non-cardiac surgery include the α-2-adrenergic agonists (clonidine, dexmedetomidine, mivazerol), calcium-channel

blockers (diltiazem, verapamil) and nitroglycerin. The small-scale studies on calcium-channel blockers and nitroglycerin failed to demonstrate a cardioprotective effect after non-cardiac surgery. In contrast, the α-2-adrenergic agonists have gained much interest, since it has been hypothesized that the α-2-agonist properties, which reduces post-ganglionic noradrenalin output, can moderate the catecholamine response to surgery and anesthesia and therefore the myocardial, hemodynamic and metabolic instability associated with cardiovascular events. The most convincing evidence to date has come from the European Mivazerol Trial, showing no overall effect of mivazerol on the prespecified combined endpoint of cardiac death and myocardial infarction in a study population of 2854 patients [61]. Post hoc analysis in 904 patients who underwent major vascular surgery, however, revealed that mivazerol use was associated with a significantly lower incidence of the combined endpoint. A reduction in perioperative mortality with the use of clonidine, another α-2-adrenergic agonist, has been demonstrated in one prospective, randomized, placebo-controlled clinical trial involving 190 patients with or at risk for coronary artery disease and undergoing non-cardiac surgery [62]. Despite these encouraging findings, evidence in favor of α-2-adrenergic agonists is based on a few studies. In addition, the long-term benefits of short-term perioperative α-2-adrenergic agonist therapy are not yet known. Finally, it remains a question whether α-2-adrenergic agonists are superior to beta-blockers and statins or whether it can complement each other.

Anesthetic management and cardioprotection

It has been speculated that improvements in anesthetic management can reduce the cardiac risk during major non-cardiac surgery. A pulmonary artery catheter and subsequent hemodynamic optimization, for example, has been proposed to improve cardiovascular outcome. A large randomized clinical trial of 1994 high-risk patients, older than 60 years of age, in American Society of Anesthesiologists class III or IV risk and undergoing major non-cardiac surgery, showed no significant benefits of a pulmonary artery catheter over standard care in terms of reduced in-hospital mortality, improved 6- and 12-month survival and reduced length of hospital stay [63]. The application of epidural anesthesia and analgesia is another example which was proposed to improve cardiovascular outcome. Rogers and colleagues demonstrated in a meta-analysis that neuraxial blockade (spinal or epidural) could reduce all-cause mortality by 30% and myocardial infarction by 33%. Recent randomized trials however showed no overall reduction in the incidence of death and major complications between patients with and without neuraxial blockade [64,65]. However, subgroup analysis revealed that patients undergoing abdominal aortic surgery with neuraxial blockade do have a lower incidence of cardiovascular, pulmonary and cerebral complications [64]. Finally, it has been suggested that perioperative hypothermia can result in increased postoperative myocardial ischemia. A recent study demonstrated that maintenance of normothermia could significantly lower the incidence of cardiac events (unstable angina pectoris, cardiac arrest, myocardial infarction) [66]. These studies showed that some improvements in anesthetic management can reduce cardiovascular morbidity, however, it remains unknown to what extent and by which mechanism anesthesiology contributes to perioperative cardiovascular morbidity and mortality.

Conclusion

Despite the impressive progress made in the past to diminish cardiac mortality and morbidity associated with major non-cardiac surgery, the epidemic of cardiovascular disease remains a significant contributor to perioperative morbidity and mortality. New insights in the past year have developed preoperative risk stratification in terms of simplicity, safety, accuracy and cost-effectiveness. The anti-ischemic properties of beta-blockers have been well described. In clinical practice however, adequate beta-blocker dosage, tight perioperative heart rate control and continuation of beta-blockers after surgery may be important factors too. Statins have emerged as promising drugs with perioperative cardioprotective properties. However, before recommending routine administration of statins, more clinical trials are needed to support existing evidence. Perioperative management should not only focus on the short-term outcome, every attempt to improve long-term survival should be welcomed. New perceptions in perioperative medical management and novel developments in surgical and anesthesiologic techniques should continue to benefit the many patients undergoing non-cardiac surgery every year.

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Chapter 21

Protecting the heart with cardiac medication in patients with left ventricular dysfunction undergoing major non-cardiac vascular surgery

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Protecting the Heart with Cardiac Medication in Patients with Left Ventricular Dysfunction Undergoing Major Noncardiac Vascular Surgery

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Patients with left ventricular dysfunction who are undergoing major noncardiac vascular surgery are at increased risk of adverse postoperative events. We sought to evaluate whether perioperative medication use, including angiotensin-converting enzyme (ACE) inhibitors, b-blockers, statins, and aspirin, was associated with a reduced incidence of postoperative in-hospital mortality in these high-risk patients. The study enrolled 511 patients with left ventricular dysfunction (left ventricular ejection fraction <30%) who were undergoing major noncardiac vascular surgery. Cardiac risk factors and medication use were noted before surgery. Preoperative dobutamine stress echocardiography (DSE) was performed to identify patients with stress-induced myocardial ischemia. The end point was postoperative in-hospital mortality. Univariate and multivariate logistic regression analyses were performed to evaluate the relation between perioperative medication use and mortality. The mean age of the study population was 64 ± 11 years, and 75% were men. Perioperative use of ACE inhibitors, b blockers, statins, and aspirin was recorded in 215 (48%), 139 (27%), 107 (21%), and 125 patients (24%), respectively. Stress-induced myocardial ischemia occurred in 82 patients (16%). Sixty-four patients (13%) died. Perioperative use of ACE inhibitors (odds ratio [OR], 0.33; 95% confidence interval [CI], 0.12-0.91), b-blockers (OR, 0.03; 95% CI, 0.01-0.26), statins (OR, 0.06; 95% CI, 0.01-0.53), and aspirin (OR, 0.13; 95% CI, 0.03-0.55), was significantly associated with a reduced incidence of mortality, after adjusting for cardiac risk factors and DSE results. In conclusion, the present study showed that the perioperative use of ACE inhibitors, b-blockers, statins, and aspirin is independently associated with a reduced incidence of in-hospital mortality in patients with left ventricular dysfunction who are undergoing major noncardiac vascular surgery.

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CONGESTIVE HEART FAILURE is a disorder characterized by an abnormal cardiac ventricular performance that develops as a consequence of many forms of heart disease. The prevalence of congestive heart failure ranges from 1.2% in the adult population to 8.0% in the population of individuals older than 75 years of age.[1,2] Angiotensin- converting enzyme (ACE) inhibitors and b- blockers have been shown to improve morbidity and mortality in patients with left ventricular dysfunction.[3,4] Statins and aspirin may also be of benefit in patients with left ventricular dysfunction because these patients frequently have coronary artery disease as a comorbidity.

Patients with left ventricular dysfunction who are undergoing major noncardiac vascular surgery are at increased risk for postoperative mortality.[5-7] Perioperative management of these patients is aimed at maximizing hemodynamic status and providing intensive postoperative surveillance. However, limited information is available about whether concomitant perioperative cardiac medication use reduces the postoperative mortality rate in these high-risk patients. We therefore conducted this study to evaluate whether perioperative use of cardiac medication, including ACE-inhibitors, b-blockers, statins, and aspirin, was associated with a reduced incidence of in-hospital mortality in patients with left ventricular dysfunction undergoing major noncardiac vascular surgery.

METHODS

Study Population

We enrolled patients with left ventricular dysfunction who were undergoing major noncardiac vascular surgery at the Erasmus Medical Center, Rotterdam, during the period 1990 to 2004. Left ventricular dysfunction was defined as an ejection fraction of 30% or less, or by a rest wall motion score of 1.70 or more, as assessed by preoperative two-dimensional (2D) echocardiography. The left ventricular ejection fraction

was calculated by using the Simpson's rule formula, after left ventricular end-diastolic and end-systolic volumes were obtained from the apical four- and two-chamber views. The major noncardiac vascular surgery procedures were abdominal aortic repair, lower-extremity revascularization, and carotid artery surgery. Before surgery, patients were screened for cardiac risk factors (history of coronary artery disease, cerebrovascular disease, diabetes mellitus, renal dysfunction, hypertension, hypercholesterolemia, smoking, and chronic obstructive pulmonary disease) and medication use (ACE inhibitors, b-blockers, statins, aspirin, calcium channel blockers, coumarin, diuretics, digoxin, and nitrates). A baseline 12-lead electrocardiogram was obtained. A preoperative dobutamine stress echocardiography (DSE) was performed to identify patients with stress-induced myocardial ischemia.

Dobutamine Stress Echocardiography
Patients underwent a resting 2D precordial echocardiographic examination. Dobutamine hydrochloride was then administered intravenously by infusion pump, starting at 5 μg/ kg/min for 5 minutes, followed by 10 μg/kg/ min for 5 minutes and increasing by 10 μg/ kg/min every 3 minutes to a maximum of 40 μg/kg/min, and continued for 6 minutes. The dobutamine infusion was stopped if a target heart rate (85% of the age- and gender-corrected maximal heart rate) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulphate (0.25 to 2.0 mg intravenously) was given while the administration of dobutamine was continued. Metoprolol was administered (1.0 to 5.0 mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine-atropine combination if the side effects did not revert spontaneously and quickly. Two experienced investigators, blinded to the clinical data, performed off-line assessment of echocardiographic images. A standard 16-segment model was used to score wall motion on a 5-point scale (a score of 1 indicating normal; 2, mild hypokinesis; 3, severe hypokinesis; 4, akinesis; and 5, dyskinesis), and a wall-motion score index was calculated (total score divided by the number of segments scored).8 The results of DSE were considered positive if new wall-motion abnormalities occurred, that is, if wall motion in any segment worsened by 1 or more grades during the test, with the exception of akinesis becoming dyskinesis.

End Point
The end point was in-hospital mortality, which was defined as death occurring during the postoperative in-hospital stay or occurring after discharge but within the first 30 days after surgery.

Statistical Analysis
Continuous data are expressed as mean ± SD and compared with the Student t test. Categorical data are presented as percent frequencies. Univariate and multivariate logistic regression models were used to analyze the relation between the use of perioperative medication and in-hospital mortality. In multivariate analyses, adjustments were made for baseline clinical variables and stress-induced myocardial ischemia, irrespective of the significance level in univariate analysis. Odds ratios (OR) are given with 95% confidence intervals (CI). For all tests, $P < .05$ (two-sided) was considered significant.

RESULTS

Table 1. Baseline Characteristics of the 511 Patients with Left Ventricular Dysfunction

Characteristic N	
Age (years) (mean ± SD)	64 ± 11
Gender (male) (%)	383 (75)
History of coronary artery disease (%)	308 (60)
History of cerebrovascular disease (%)	80 (16)
Hypertension (%)	203 (40)
Hypercholesterolemia (%)	126 (25)
Diabetes Mellitus (%)	72 (14)
Renal failure (%)	57 (11)
Current smoker (%)	168 (33)
COPD (%)	88 (17)
Electrocardiography	
Left ventricular hypertrophy (%)	37 (7)
Q-waves (%)	183 (36)
ST-segment changes (%)	105 (21)
Left bundle branch block (%)	20 (4)
Right bundle branch block (%)	28 (5)
Atrial fibrillation (%)	37 (7)
Cardiac medication	
Aspirin (%)	125 (24)
ACE inhibitors (%)	215 (48)
b-blockers (%)	139 (27)
Calcium channel blockers (%)	162 (32)
Coumarin (%)	111 (22)
Digoxin (%)	41 (8)
Diuretic (%)	136 (27)
Nitrates (%)	163 (32)
Statins (%)	107 (21)

COPD = chronic obstructive pulmonary disease; ACE = angiotensin-converting enzyme.

The study enrolled 511 patients with left ventricular dysfunction. Their mean age was 64 ± 11 years, and 383 patients (75%) were men. Perioperative use of ACE inhibitors, b-blockers, statins, and aspirin was recorded in 215 (48%), 139 (27%), 107 (21%), and 125 patients (24%), respectively. Baseline characteristics of the study population are presented in Table 1. The mean

rest wall motion score index was 2.11 ± 0.37. Stress-induced myocardial ischemia occurred in 82 patients (16%). No fatal complications occurred during preoperative DSE. Abdominal aortic repair was performed in 237 patients (46%), lower-extremity revascularization in 221 patients (43%), and carotid artery surgery in 53 patients (10%). Sixty-four patients (13%) died. Table 2 presents the univariate association between perioperative medication and in-hospital mortality. Table 3 presents the association between perioperative medication and in-hospital mortality, after adjusting for cardiac risk factors and DSE results. ACE inhibitors (OR, 0.33; 95% CI, 0.12-0.91), b-blockers (OR, 0.03; 95% CI, 0.01-0.26), statins (OR, 0.06; 95% CI, 0.01-0.53), and aspirin (OR, 0.13; 95% CI, 0.03-0.55), were significantly and independently associated with a reduced incidence of inhospital mortality.

DISCUSSION

This study shows that perioperative use of ACE inhibitors, b-blockers, statins, and aspirin was associated with a reduced incidence of in-hospital mortality in patients with left ventricular dysfunction undergoing major noncardiac vascular surgery. These associations were independent of cardiac risk factors and stress-induced myocardial ischemia during preoperative DSE.

ACE Inhibitors

Blockade of the renin-angiotensin system with ACE inhibitors has been shown to improve survival in patients with reduced left ventricular function.9-12 Recently, randomized, placebo controlled studies have suggested that ACE inhibitors reduce cardiovascular events in patients at high risk for coronary events who were not known to have heart failure.13,14 There is evidence that activation of the renin-angiotensin system stimulates atherosclerosis and contributes to ischemic events.15 ACE inhibitors have been shown to exert their vasculoprotective properties through several mechanisms. There is a growing body of evidence that ACE inhibitors improve the endogenous fibrinolytic balance, an important determinant in the defense mechanism against intravascular thrombus formation that is implicated in the pathogenesis of myocardial infarction and other acute vascular syndromes.16 In addition, ACE inhibitors may positively influence vasoactive substances, such as nitric oxide and angiotensin II, which have been shown to be involved in adverse vascular remodeling processes.17 These observations suggest that patients with reduced left ventricular function undergoing major noncardiac vascular surgery, who are at increased risk for postoperative adverse cardiac events, may benefit from perioperative ACE inhibitor therapy. In these patients who frequently present with concomitant coronary artery disease, ACE inhibitors may not only improve the perioperative hemodynamic status but may also prevent acute coronary events through their vasoprotective properties. To our knowledge, no previously published studies have investigated the protective effect of ACE inhibitors in patients with left ventricular dysfunction undergoing major noncardiac vascular surgery. Our results suggest that these patients may benefit from perioperative ACE inhibitor therapy; however, large randomized controlled trials are needed to confirm our conclusion.

Table 2. Univariate Relation Between Medication and In-hospital Mortality

Medication	OR* 95% CI	P
Aspirin	1.36 0.76-2.42	.3
ACE inhibitors	1.44 0.85-2.44	.2
b-Blockers	0.24 0.10-0.58	<.001
Calcium-channel blockers	1.57 0.91-2.68	.1
Coumarin	1.12 0.60-2.08	.7
Digoxin	0.43 0.10-1.86	.3
Diuretic	2.10 1.21-3.61	.008
Nitrates	1.44 0.84-2.47	.2
Statins	0.36 0.15-0.85	.02

OR = odds ratio; CI = confidence interval; ACE = angiotensin-converting enzyme.
*Adjusted for the following baseline characteristics: age, gender, history of coronary artery disease, cerebrovascular disease, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, smoking, chronic obstructive pulmonary disease, electrocardiographic abnormalities and stress induced ischemia during dobutamine stress echocardiography.

Table 3. Multivariate Analysis Between Medication and In-hospital Mortality

Medication	OR* 95% CI	P
Aspirin	0.13 0.03-0.55	.005
ACE inhibitors	0.33 0.12-0.91	.03
b-Blockers	0.03 0.01-0.26	.002
Calcium-channel blockers	0.89 0.35-2.27	.8
Coumarin	1.22 0.42-3.58	.7
Digoxin	0.27 0.05-1.62	.2
Diuretic	0.46 0.16-1.32	.2
Nitrates	0.66 0.26-1.67	.4
Statins	0.06 0.01-0.53	.01

OR = odds ratio; CI = confidence interval; ACE = angiotensin-converting enzyme.
*Adjusted for the following baseline characteristics: age, gender, history of coronary artery disease, cerebrovascular disease, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, smoking, chronic obstructive pulmonary disease, electrocardiographic abnormalities and stress induced ischemia during dobutamine stress echocardiography.

b-Blockers

Large randomized trials have demonstrated the usefulness of b-blockers in nonsurgical patients with reduced left ventricular function. The Metoprolol in Dilated Cardiomyopathy Trial, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart

Failure trial, Cardiac Insufficiency Bisoprolol Study I and II, and Carvedilol Prospective Randomized Cumulative Survival Study Group, have all demonstrated the benefits of metoprolol, bisoprolol, and carvedilol for survival in stable advanced patients with heart failure.18-21 As a result, consensus guidelines strongly recommended the use of b-blockers in these patients, unless there is a strong contraindication.22 Several randomized trials have demonstrated that patients with coronary artery disease undergoing major noncardiac surgery benefit from perioperative b-blocker therapy in terms of reduced postoperative morbidity and mortality.23,24 Our results suggest that the perioperative use of b-blocker therapy may also be beneficial in patients with left ventricular dysfunction undergoing major noncardiac vascular surgery. It has been shown that b-blockers reverse the process of left ventricular remodeling, leading to improved hemodynamics with favorable effects on prognosis.25 In addition, b-blockers may also have beneficial effects through their heart rate-regulating, anti-arrhythmic, and anti-inflammatory effects. 26 It might be suggested that these mechanisms may explain the cardioprotective effect of b-blockers.

Statins

Statins (3-hydroxy 3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors) have been shown to reduce cardiac events and improve survival in patients with hypercholesterolemia coronary artery disease, or both.27-31 Statins also have been associated with a lower perioperative and long-term mortality rate after major noncardiac vascular surgery.32,33 In addition to their lipid-lowering effects, the pleiotropic effects of statins, which include inflammation reduction, reduction in free-radical production in the vascular wall, improvement in endothelial function, and stabilization of atheromatous plaques, may contribute to its beneficial properties.34 An issue of debate is whether statins should be given to patients with congestive heart failure. Higher cholesterol levels in patients with heart failure predict a better outcome.35 Lower cholesterol levels may not be directly responsible for a worse outcome, however, but may reflect developing cachexia. Furthermore, it remains unknown whether patients with nonischemic heart failure will also benefit from statin therapy. Future large-scale mortality trials will tell us whether we should give statins to patients with congestive heart failure. Until the safety and efficacy of statin therapy in heart failure patients who are or are not undergoing major noncardiac vascular surgery is established, we do not recommend statin therapy to be prescribed in a standard fashion in this patient population.

Antiplatelet Drugs

Antiplatelet drugs are now established agents for preventing cardiovascular and cerebrovascular ischemic events. The meta-analysis of the antithrombotic trialists collaboration showed a proportional reduction of 23% in serious vascular events among 9214 patients with peripheral arterial disease using antiplatelet therapy (primarily aspirin) compared with those using no antiplatelet therapy (5.8 vs. 7.1%, P <.04).36 Current evidence indicates that aspirin or clopidogrel seem to be the first-line oral antiplatelet drugs of choice. Antiplatelet drugs may be recommended in patients with heart failure who have concomitant atrial fibrillation for the prevention of possible acute vascular occlusions.

Should patients with left ventricular dysfunction undergoing major noncardiac vascular surgery be treated with perioperative aspirin therapy?

Firstly, no evidence exists to suggest antiplatelet therapy in patients with heart failure who are in sinus rhythm. Secondly, there is no convincing evidence that aspirin reduces perioperative cardiac complications in patients with or without left ventricular dysfunction undergoing noncardiac surgery. Moreover, patients with heart failure might be at increased risk for bleeding complications because of difficult anticoagulant control, which may be explained by variable hepatic congestion and various drug interactions. However, it remains a matter of debate whether aspirin treatment is associated with an increased risk of bleeding complications. Our results support the use of perioperative aspirin therapy in reducing in-hospital mortality in patients with left ventricular dysfunction undergoing major vascular surgery. Unfortunately, bleeding complications were not investigated in this study. Before routine aspirin treatment is recommended in this patient population, more studies are needed to investigate the efficacy and safety of perioperative aspirin treatment.

Limitations and Conclusion

A major limitation in this study is that the medications were not assigned in a randomly, controlled setting. In addition, patients and physicians were not masked to the different medical treatments. We used multivariate regression analysis to adjust for cardiac risk factors and DSE results; however, other factors may have played a role in the cause of death. This study is one of the first in its kind to investigate the effect of different medication on postoperative outcome in patients with left ventricular dysfunction who are undergoing major noncardiac vascular surgery.

Based on our results, we conclude that in these patients, perioperative ACE inhibitor, b- blocker, aspirin, and

statin therapy is significantly and independently associated with a reduced incidence of in-hospital mortality. However, before standard ACE inhibitor, b-blocker, aspirin, and statin treatment are recommended in this patient population, randomized studies are needed to establish its safety and efficacy.

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Chapter 22

High dose beta-blockers and tight heart rate control reduce the incidence of perioperative myocardial ischemia and troponin release

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High dose β-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients

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Background: Adverse perioperative cardiac events occur frequently despite the use of β-blockers. We examined whether higher doses of β-blockers and tight heart rate control was associated with reduced perioperative myocardial ischemia and troponin T release and improved long-term outcome.
Methods and Results: In an observational cohort study, 272 vascular surgery patients were preoperatively screened for cardiac risk factors and β-blocker dose. Beta-blocker dose was converted to a percentage of maximum recommended therapeutic dose. Heart rate and ischemic episodes were recorded by continuous 12-lead electrocardiography, starting one day before to 2 days after surgery. Serial troponin T levels were measured after surgery. All-cause mortality was noted during follow-up.
Myocardial ischemia was detected in 85/272 (31%) patients and troponin T release in 44/272 (16.2%). Long-term mortality occurred in 66/272 (24.2%) patients. In multivariate analysis, higher β-blocker doses (per 10% increase) were significantly associated with a lower incidence of myocardial ischemia (HR: 0.62, 95% CI: 0.51-0.75), troponin T release (HR: 0.63, 95% CI: 0.49-0.80) and long-term mortality (HR: 0.86, 95% CI: 0.76-0.97). Higher heart rates during electrocardiographic monitoring (per 10 bpm increase) were significantly associated with an increased incidence of myocardial ischemia (HR: 2.49, 95% CI: 1.79-3.48), troponin T release (HR: 1.53, 95% CI: 1.16-2.03) and long-term mortality (HR: 1.42, 95% CI: 1.14-1.76).
Conclusion: This study showed that higher doses of β-blockers and tight heart rate control are associated with reduced perioperative myocardial ischemia and troponin T release and improved long-term outcome in vascular surgery patients.

LARGE CLINICAL TRIALS have demonstrated the beneficial effect of β-adrenoreceptor blocking agents in preventing perioperative cardiac morbidity and mortality in patients undergoing major non-cardiac vascular surgery [1-3]. The ACC/AHA has therefore recommended the use of β-blockers in surgical patients who are at increased risk for postoperative adverse events [4]. The mechanism by which β-blockers exert their cardioprotective effect remains not completely understood, but proposed mechanisms include reduction in heart rate, restoration of the myocardial oxygen supply-demand balance, and prolongation of coronary diastolic filling time [5,6]. Despite the presumed benefits of perioperative β-blocker therapy, cardiovascular mortality and non-fatal myocardial infarction may still occur in patients using β-blockers, especially during the stressful perioperative period characterized by rapidly changing physiologic responses [7,8]. Inadequate dosage of β-blockers and insufficient reduction of heart rate during the perioperative period may possibly explain the occurrence of adverse cardiac events in these patients.

Early postoperative episodes of myocardial ischemia, i.e. during the first 48 hours after surgery, are an important correlate of adverse cardiac outcome after surgery [2]. Continuous 12-lead electrocardiographic monitoring and measurement of cardiac troponins are accurate and reliable methods for the detection of perioperative myocardial ischemia. We conducted this study to assess whether higher doses of β-blockers and tight heart rate control during surgery are associated with a reduced incidence of perioperative myocardial ischemia as detected by continuous 12-lead electrocardiographic monitoring, with reduced troponin T release and with a reduced incidence of long-term mortality and cardiac events.

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METHODS

Patients

The study population consisted of 273 patients, undergoing elective major vascular surgery at the Erasmus MC in Rotterdam, the Netherlands, during the period July 2001 to August 2005. The study was performed with informed consent of all patients. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block and atrial fibrillation were excluded. Prior to surgery, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure ≥140/90 mmHg), diabetes mellitus (fasting glucose level ≥7.0 mmol/L, or insulin therapy), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or cholesterol-lowering medication) and renal failure (serum creatinine level ≥ 2.0 mg/dL (177 μmol/L)). The presence of definite coronary artery disease was indicated by a previous myocardial infarction, previous coronary intervention, or present stable angina pectoris. The use of chronic β-blocker therapy was noted and β-blocker dose was converted to a percentage of maximum recommended therapeutic dose (MRTD) according to the FDA's Center for Drug Evaluation and Research database. The MRTD for atenolol was 3.330 mg/kg (body-weight)/day, for bisoprolol 0.330 mg/kg (body-weight)/day, for metoprolol 6.670 mg/kg (body-weight)/day, for carvedilol 0.417 mg/kg (body-weight)/day, for propranolol 10.700 mg/kg (body-weight)/day, and for labetolol 40.700 mg/kg (body-weight)/day.

Dobutamine stress echocardiography

Before surgery, all patients underwent dobutamine stress echocardiography for preoperative risk stratification, which was performed according to established protocols [10]. The left ventricle was divided into 17 segments and wall motion was scored on a 5-point scale (a score of 1 indicating normal, 2 mild hypokinesis, 3 severe hypokinesis, 4 akinesis, and 5 dyskinesis). The results were considered positive if wall motion in any segment decreased by one or more grades during testing. Patients who had a positive result on dobutamine stress echocardiography were considered to be at high risk of developing myocardial ischemia in the perioperative period.

Table 1. Baseline characteristics of the study population.

	No β-blockers (n=97)	Low dose β-blockers (n=97)	High dose β-blockers (n=78)	p-value
Age (years)	68.4 +/-9.9	67.3 +/-10.0	66.3 +/-10.3	0.39
Male gender	74 (76.3)	80 (82.5)	64 (82.1)	0.49
Current stable angina pectoris	13 (13.4)	15 (15.5)	19 (24.4)	0.14
History of myocardial infarction	41 (42.3)	40 (41.2)	40 (51.3)	0.36
Previous coronary artery revascularization	17 (17.5)	14 (14.4)	17 (21.8)	0.45
Coronary artery disease (summary variable)	43 (44.3)	45 (46.4)	45 (57.7)	0.18
History of congestive heart failure	4 (4.1)	2 (2.1)	2 (2.6)	0.68
History of cerebrovascular event	25 (25.8)	29 (29.9)	19 (24.4)	0.68
Renal failure	7 (7.2)	2 (2.1)	1 (1.3)	0.069
Diabetes mellitus	15 (15.5)	15 (15.5)	13 (16.7)	0.97
Hypertension	42 (43.3)	38 (39.2)	38 (48.7)	0.45
Hypercholesterolemia	35 (36.1)	39 (40.2)	34 (43.6)	0.60
Current or past smoking	74 (76.3)	62 (63.9)	56 (71.8)	0.16
Aspirin	46 (47.4)	54 (55.7)	46 (59.0)	0.28
Angiotensin-converting enzyme inhibitors	24 (24.7)	24 (24.7)	25 (32.1)	0.47
Statins	46 (47.4)	59 (60.8)	42 (53.8)	0.17
Calcium channel blockers	31 (32.0)	22 (22.7)	26 (33.3)	0.22
Preoperative heart rate	76.0 +/-12.9	66.2+/-11.9	64.1 +/-11.3	<0.001
Atenolol	-	5 (5.2)	4 (5.1)	0.74
Bisoprolol	-	67 (69.1)	47 (60.3)	0.29
Metoprolol	-	15 (15.5)	19 (24.4)	0.20
Carvedilol	-	9 (9.3)	3 (3.8)	0.27
Propranolol	-	2 (2.1)	1 (1.3)	0.85
Labetolol	-	1 (1.0)	1 (1.3)	0.58

Values are given in number (%), or in mean +/- standard deviation

The baseline ST segment level was defined as the average ST segment during a stable period (duration of 20 minutes) preceding each ischemic episode. ST segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST segment change was measured 40 ms after that point. Heart rate was recorded and means of heart rate before, during and after surgery were calculated. A measure of absolute heart rate change was used and expressed as the sum of the differences between the mean heart rate before,

Holter electrocardiography

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts), starting one day before surgery up to 2 days after. Recordings were performed in the continuous 12-lead mode with a recording length of 10 seconds every minute. The frequency response was 0.05 – 150Hz. Electrocardiographic data were initially processed by a technician and analyzed by two experienced investigators, who were blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the ambulatory ECG recordings were analyzed for ST-segment deviations. A continuous ST segment trend was generated and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST-segment changes, lasting at least one minute and shifting from baseline to more than 0.1 mV (1 mm). during and after surgery. The mean heart rate after surgery was calculated from a standard 24-hour time period. For example, a patient with a mean heart rate of 75, 80 and 85 before, during and after surgery, respectively, had an absolute heart rate change of 5+5=10 bmp.

Perioperative management and follow-up

Prior to surgery, patients with beta-blockers were asked about medication adherence. Beta-blockers were withheld if patients presented with a systolic blood pressure <100 mmHg or with a heart rate <50 bpm. The dosage of beta-blockers on the day of surgery and after surgery was kept similar to the preoperative beta-blocker dose. It was ascertained that beta-blockers were administered on the morning of surgery and on each day after surgery until discharge. Beta-blockers were administered orally or by naso-gastric tube in patients who were not able to take medication orally. All patients received standard perioperative pain management. Surgical procedures were classified as abdominal aortic aneurysm repair (129 patients, 47%), lower extremity revascularization (100 patients, 37%) and carotid artery surgery (43 patients, 16%). In all patients, troponine T levels were measured on postoperative day 1, 3 and 7 and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Troponin T level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany). A value of >0.1 ng/ml was used to define positive troponin T levels. During a median follow-up of 2.6 years, outpatient visits were scheduled every 3 months after discharge. Endpoints were mortality and cardiac events (cardiac death and non-fatal myocardial infarction). Non-fatal myocardial infarction was diagnosed when at least two of the following were present: elevated cardiac enzyme levels (CK level > 190 U/L and CK-MB >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/ml), development of typical electrocardiographic changes (new Q waves >1 mm or > 30 ms), and typical symptoms of angina pectoris. In case of death, the cause of death was identified. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. No patients were lost to follow-up.

Statistical analysis

Continuous data were expressed as mean (+/- SD) and analysis of variance (ANOVA) was used to compare means in different groups of β-blockers. Categorical data are presented as percentages and analyzed using the chi-square test with Yates' correction. The study group was divided in patients receiving no, low dose (1-25% of MRTD) and high dose (>25% of MRTD) β-blockers. Binary logistic regression analysis was used to study the effect of β-blockers and heart rate on the occurrence of myocardial ischemia and troponin T release. The C-index for the different multivariate logistic regression models was calculated to evaluate how well the model performed. Cox proportional hazards models were used to analyze the effect of β-blockers and heart rate control on postoperative survival and cardiac events. In multivariate analysis, adjustments were made for age, gender, cardiac risk factors according to the Revised Cardiac Risk Index (coronary artery disease, history of congestive heart failure, cerebrovascular disease, diabetes mellitus and renal failure), dobutamine stress test results, hypertension, statins and angiotensin converting enzyme inhibitors. Odds and hazard ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics

The baseline characteristics of the 272 patients (mean age 67.4 +/- 10.0, 80% male) are presented in Table 1. No significant differences were observed between

baseline characteristics in the groups of patients with different doses of β-blockers. A total of 175 patients (64%) were using β-blockers; 3 of these patients (1.7%) presented with renal failure. Dobutamine stress echocardiography prior to surgery detected myocardial ischemia in 78 patients (29%). The majority of the 78 patients with a positive preoperative stress test received β-blockers (n=69, 88%). Mean duration of surgery (from intubation to skin closure) was 5.4 +/-2.1 hours. Mean duration of continuous 12-lead ECG registration was 62.9 +/-13.8 hours. The mean heart rate during 12-lead ECG monitoring was 72.7 +/-12.4 bpm. Mean absolute heart rate change was 9.7 +/- 7.1 bmp. Higher doses of β-blockers were significantly associated with lower heart rates during 12-lead ECG monitoring (78.8 +/-11.8, 73.1 +/- 11.1, and 68.0 +/-10.9 bpm in patients with no, low dose and high dose β-blockers, respectively p<0.0001), and non-significantly with lower absolute heart rate change (11.3 +/-8.8, 9.6 +/-7.2, and 8.5 +/-9.7 bpm in patients with no, low dose and high dose β-blockers, respectively, p=0.092).

Predictors for myocardial ischemia and troponin T release

Myocardial ischemia was detected in 85 patients (31%). A total of 141 periods of myocardial ischemia were detected (33, 61 and 47 periods before, during and after surgery, respectively). The number of ischemic events per patient ranged from 1 to 5. The median duration of ischemic events was 64.5 minutes (range 9-1020 minutes) and the median ST-segment deviation was 1.5 mm (range 1.0-5.4 mm). Troponin T levels >0.1 ng/ml were measured in 44 patients (16.2%). Troponin T values ranged from 0.1 to 8.14 ng/ml (median: 1.1 ng/ml).

In univariate analysis, higher β-blockers doses, lower heart rates and lower absolute heart rate change were associated with a lower incidence of myocardial ischemia (for all: p<0.0001), and with a lower incidence of troponin T release (for all: p<0.0001) (Figure 1). In multivariate analysis, these associations remained significant (Table 2). In a final multivariate model including β-blocker dose, heart rate, absolute heart rate change and baseline clinical variables, we found that these variables remained independently associated with myocardial ischemia (β-blocker dose per 10% increase: HR: 0.66, 95% CI: 0.55-0.79, p<0.0001; heart rate per 10 bpm increase: HR: 2.10, 95% CI: 1.52-2.91, p<0.0001; absolute heart rate change per 10 bpm increase: HR: 1.46, 95% CI: 1.03-2.07, p=0.032) (C-index: 0.86).

Predictors for long-term mortality and cardiac events

During long-term follow-up, mortality, cardiac death and non-fatal myocardial infarction occurred in 66 (24.2%), 48 (17.6%), and 6 (2.2%) patients, respectively. Multivariate results are summarized in Table 3. In multivariate analysis, higher doses of β-

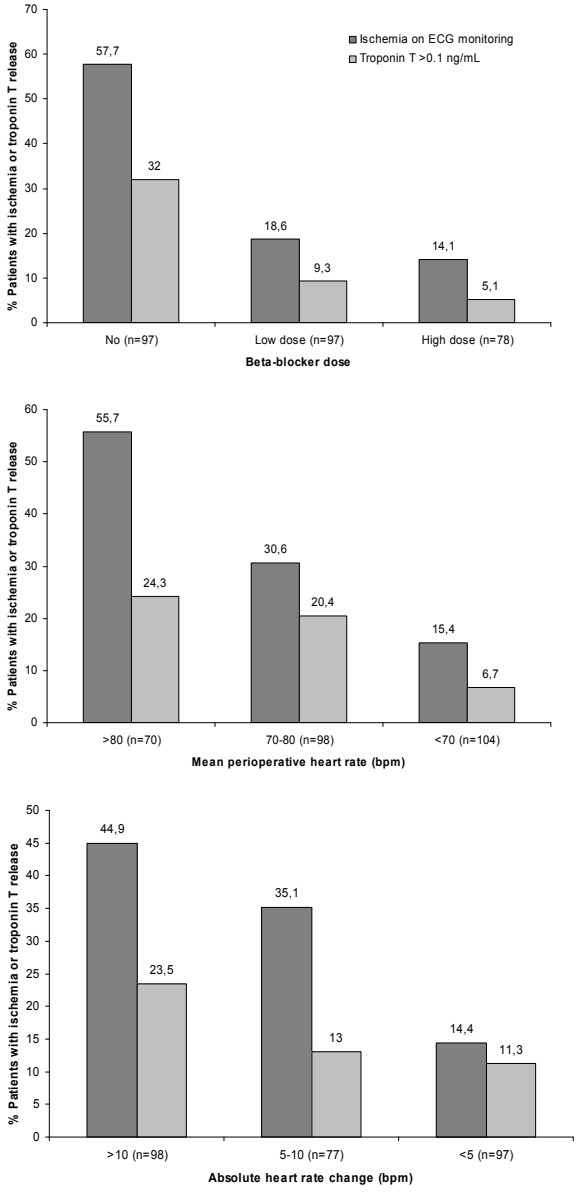

Figure 1. The dose of β-blockers, mean heart rate and absolute heart rate change in relation to myocardial ischemia and troponin T release.

Table 2. Multivariate models to predict myocardial ischemia (detected by continuous 12-lead electrocardiographic monitoring) and myocardial damage (troponin T release).

Characteristic	Myocardial ischemia			Troponin T release		
	Odds ratio (95% CI)	P-value	C-index	Odds ratio (95% CI)	P-value	C-index
Dose of β-blockers per 10% increase*	0.62 (0.51-0.75)	<0.0001	0.80	0.63 (0.49-0.80)	<0.0001	0.77
Heart rate (per 10 bpm increase)*	2.49 (1.79-3.48)	<0.001	0.80	1.53 (1.16-2.03)	0.003	0.76
- Mean HR prior to surgery (per 10 bpm increase)*	1.51 (1.19-1.92)	<0.001	0.73	1.06 (0.82-1.38)	0.64	0.63
- Mean HR during surgery (per 10 bpm increase)*	2.62 (1.88-3.66)	<0.0001	0.82	1.57 (1.21-2.03)	<0.001	0.74
- Mean HR after surgery (per 10 bpm increase)*	2.12 (1.62-2.77)	<0.0001	0.81	1.41 (1.12-1.77)	0.003	0.73
Absolute heart rate change (per 10 bpm increase)*	1.75 (1.25-2.45)	<0.001	0.73	1.37 (1.04-1.89)	0.030	0.69

* Adjusted for age, gender, coronary artery disease, history of congestive heart failure, history of cerebrovascular events, diabetes mellitus, renal failure, hypertension, dobutamine stress echocardiography results, statins and angiotensin converting enzyme inhibitors.

Table 3. Multivariate models to predict postoperative mortality and cardiac events (cardiac death or non-fatal myocardial infarction).

Characteristic	Long-term mortality		Long-term cardiac events	
	Hazards ratio (95% CI)	p-value	Hazards ratio (95% CI)	p-value
Dose of β-blockers per 10% increase*	0.86 (0.76-0.97)	0.0080	0.71 (0.60-0.84)	<0.0001
Heart rate (per 10 bpm increase)*	1.42 (1.14-1.76)	0.002	1.56 (1.22-2.00)	<0.001
- Heart rate prior to surgery (per 10 bpm increase)*	1.21 (0.99-1.45)	0.052	1.28 (1.02-1.59)	0.030
- Heart rate during surgery (per 10 bpm increase)*	1.37 (1.09-1.70)	0.005	1.53 (1.20-1.97)	<0.001
- Heart rate after surgery (per 10 bpm increase)*	1.45 (1.16-1.67)	<0.001	1.62 (1.31-2.02)	<0.001
Absolute heart rate change (per 10 bpm increase)*	1.37 (1.06-1.77)	0.016	1.60 (1.20-2.13)	0.0013
Myocardial ischemia during ECG monitoring*	2.23 (1.25-3.62)	0.0054	4.84 (2.38-9.84)	<0.0001
Troponin T release*	2.60 (1.49-4.55)	<0.001	3.95 (2.11-7.42)	<0.0001

Adjusted for age, gender, coronary artery disease, history of congestive heart failure, history of cerebrovascular events, diabetes mellitus, renal failure, hypertension, dobutamine stress echocardiography results, statins and angiotensin converting enzyme inhibitors.

blockers were significantly associated with a reduced incidence of mortality and cardiac events. Higher heart rates and higher absolute heart rate changes were associated with an increased incidence of long-term mortality and cardiac events. We also demonstrated that myocardial ischemia and troponin T release were significant predictors of adverse long-term outcome. Interestingly, higher levels of troponin T release were associated with a higher incidence of mortality (HR per 1.0 ng/ml increase: 1.30, 95% CI: 1.03-1.68, p=0.037) and cardiac events (HR per 1.0 ng/ml increase: 1.40, 95% CI: 1.05-1.85, p=0.027)

DISCUSSION

The clinical characteristics of our study population demonstrate that coronary artery disease is highly prevalent among patients undergoing major vascular surgery. These patients are therefore at increased risk of adverse postoperative cardiac events and may benefit from perioperative β-blocker therapy [1-3]. Several studies have demonstrated the association between perioperative β-blockers and myocardial ischemia reduction. In the study of Mangano et al., up to 10 mg atenolol or placebo was intravenously administered 30 min before and after surgery and up to 100 mg/day was orally given throughout the hospital stay (up to 7 days) to 200 non-cardiac surgical patients. Continuous 3-lead Holter monitoring showed a 50% reduction of myocardial ischemia in the atenolol treated group during the first 2 postoperative days [2,11]. Another study demonstrated in 26 patients with preoperative myocardial ischemia that strict heart rate control (heart rate of 20% below the ischemic threshold) using continuous esmolol infusion significantly decreased the rate of postoperative myocardial ischemia during Holter monitoring [12]. Two patients experienced a cardiac event; one in the placebo and one in the esmolol group. Both patients had extensive myocardial ischemia and were unable to maintain target heart rate control, suggesting that heart rate control, more than β-blocker therapy, may be the key element in reducing postoperative ischemia and adverse postoperative events.

Myocardial ischemia and troponin T release are markers for coronary artery disease and have been identified as predictors of adverse cardiac events after non-cardiac surgery [2,13]. This finding has been confirmed in our study. Moreover, our study also demonstrates that a higher level of troponin T was associated with worse outcome. During the last decades, much attention has been given to the prevention of postoperative cardiac events. The development of cardiac risk scores has

allowed clinicians to identify patients at increased risk for adverse postoperative events [14]. Coronary artery revascularization before elective major vascular surgery has been proposed as preventive measure, but does not seem to significantly alter the long-term outcome [15]. Cumulating evidence suggests encouraging effects of perioperative β-blocker therapy. However, most studies have not included heart rate, absolute heart rate change and dosage of β-blockers into their analyses, omitting several important potential determinants of postoperative outcome. Our results suggest that higher doses of β-blockers, lower mean heart rates and lower absolute heart rate changes were all important in the reduction of myocardial ischemia, troponin T release and long-term events.

Reductions in heart rate lead to restoration of the myocardial oxygen supply-demand balance and prolongation of coronary diastolic filling time, being of benefit to the surgical patient with a compromised coronary circulation, exposed to the stressful period of surgery [5,6]. In addition, it might be hypothesized that β-blockers improve outcome after major non-cardiac surgery by its anti-inflammatory effect [16]. It also has been demonstrated that elevated heart rates are associated with an increased risk of vulnerable coronary plaque disruption and that β-blockers could reduce the risk of disruption [17]. We defined absolute heart rate change by the cumulative difference between the mean heart rate before, during, and after surgery. It might be suggested that achieving continuous low levels of heart rate during the whole perioperative period may yield the optimal physiological condition to prevent adverse events. However, further studies are needed to confirm and validate the effect of perioperative heart rate change on postoperative outcome.

Although this study demonstrates strong evidence in favor of high doses of β-blockers, low heart rates and low absolute heart rate changes, several limitations should be addressed. The major limitation in this study is that β-blockers were not randomly assigned to the patients. We used multivariate analysis to adjust for known possible confounding factors, such as cardiac risk factors according the Revised Cardiac Risk index, indications for beta-blocker therapy and cardioprotective medication. Although our study focused on beta-blockers, heart rate and heart rate changes, future studies should evaluate the relation between blood pressure, cardiac output and postoperative cardiac events. Our results may explain why several previously published studies failed to show a beneficial effect of β-blockers [7,8]. Administration of β-blockers alone might not be sufficient for postoperative risk reduction. Close perioperative heart rate monitoring and heart rate control together with adequate doses of oral or intravenous β-blockers may improve prognosis and may therefore be recommended in all patients undergoing major vascular surgery.

"All authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written"

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Chapter 23

β-Blockers improve in-hospital and long-term survival in patients with severe left ventricular dysfunction undergoing major vascular surgery

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β-Blockers Improve In-hospital and Long-term Survival in Patients with Severe Left Ventricular Dysfunction Undergoing Major Vascular Surgery

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Objectives: To study whether β-blockers reduce in-hospital and long-term mortality in patients with severe left ventricular dysfunction (LVD) undergoing major vascular surgery.
Design: Observational cohort study.
Materials: Five hundred and eleven patients with severe LVD (ejection fraction<30%) undergoing major non-cardiac vascular surgery.
Methods: In all patients, cardiac risk factors, medication (including β-blockers), and dobutamine stress echocardiography (DSE) results were noted prior to surgery. DSE was evaluated for rest and stress-induced new wall motion abnormalities. Endpoint was in-hospital and long-term mortality. Propensity scores for β-blockers were calculated and regression models were used to analyse the relation between β-blockers and mortality.
Results: Mean age was 64±11 years and 383 patients (75%) were male. 139 patients (27%) used β-blockers. Stress-induced ischemia occurred in 82 patients (16%). Median follow-up was 7 years (interquartile range: 3–10). In-hospital and long-term mortality was observed in 64 (13%) and 171 (33%) patients, respectively. After adjusting for clinical variables, DSE results and propensity scores, β-blockers were significantly associated with reduced in-hospital and long-term mortality (OR: 0.18, 95% CI: 0.04–0.74 and HR: 0.38, 95% CI: 0.22–0.65, respectively).
Conclusion: In patients with severe LVD undergoing major vascular surgery, the use of β-blockers is associated with a reduced incidence of in-hospital and long-term postoperative mortality.

THE PREVALENCE OF congestive heart failure in the adult population in the United States and United Kingdom has been estimated to be 1.2 and 1.8%, respectively, and has been demonstrated to be higher among the older population with prevalence values of 5.5 and 8.0%, respectively, in patients aged 75 years or older.[1 and 2] Both congestive heart failure and coronary artery disease have been identified as significant predictors of postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.[3, 4 and 5] Because patients who are at increased risk of postoperative events may benefit from medical treatment or other preoperative interventions, the identification of these patients has been an important goal in preoperative screening strategies. Tools for preoperative screening include cardiac risk scores, such as the revised cardiac risk index, resting echocardiography, and dobutamine stress echocardiography, which may detect both left ventricular dysfunction and stress induced myocardial ischemia.[4, 6 and 7]

β-Blockers are established therapeutic agents for patients with hypertension and coronary artery disease. In addition, β-blockers have been shown to reduce morbidity and mortality in patients with mild, moderate and severe chronic heart failure.[8, 9 and 10] As a result, consensus guidelines strongly recommended the use of β-blockers in heart failure patients, unless there is a strong contraindication.[11 and 12] Several randomized trials have demonstrated that patients with coronary artery disease benefit from perioperative β-blocker therapy in terms of reduced postoperative morbidity and mortality.[13 and 14]

We conducted this study to assess whether chronic β-blocker therapy reduces the incidence of in-hospital and long-term mortality in patients with severe left ventricular dysfunction undergoing major non-cardiac vascular surgery. In this cohort study, we used propensity analysis to adjust for selection bias in the comparison of treatments.

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1. MATERIALS AND METHODS

1.1. Study cohort

Patients who were referred to the Erasmus Medical Centre between January 1990 and January 2004 for elective major vascular surgery were routinely screened for cardiac risk factors and underwent resting echocardiography and dobutamine stress echocardiography (DSE) for pre-operative risk stratification. A total of 511 consecutive patients with markedly decreased left ventricular function were retrospectively identified and were included in this study. Left ventricular systolic dysfunction was defined as an ejection fraction of 30% or less by preoperative two-dimensional echocardiography, or as a resting wall motion-score index of 1.70 or more. Left ventricular end-diastolic and end-systolic volumes were obtained from the apical four- and two-chamber views by using the Simpson's rule formula, from which the ejection fraction was calculated. Wall motion score index was calculated according to the guidelines of the American Society of Echocardiography (ASE), using a 16-segment model.[15]

β-Blocker therapy was recorded when β-blockers were started at least 1 month prior and continued to at least 2 months after surgery. Diabetes mellitus was recorded if patients presented with a fasting glucose level of ≥7.0 mmol/L, or in those who required treatment. Hypertension was recorded if patients presented with a blood pressure ≥140/90 mmHg or if patients were medically treated for hypertension. Hypercholesterolemia was recorded if patients presented with a plasma cholesterol level ≥5.5 mmol/L, or if patients were taking lipid-lowering agents. Renal dysfunction was recorded if patients presented with a serum creatinine level ≥2.0 mg/dL (177 μmol/L) or in those who required dialysis. A baseline 12-lead electrocardiography was obtained and was considered abnormal in the presence of one or more of the following; Q-waves, ST-segment depression or elevation, left ventricular hypertrophy, right or left bundle branch block and atrial fibrillation. Surgical procedures included elective aortic abdominal repair, lower extremity revascularization and carotid artery surgery.

1.2. Dobutamine stress echocardiography

All patients underwent a resting two-dimensional precordial echocardiographic examination and a 12-lead electrocardiogram was recorded. Dobutamine hydrochloride was then administered intravenously by infusion pump, starting at 5 μg/kg/min for 5 min, followed by 10 μg/kg/min for 5 min and increasing by 10 μg/kg/min every 3 min to a maximum of 40 μg/kg/min, and continued for 6 min. The dobutamine infusion was stopped if a target heart rate (85% of the age and gender corrected maximal heart rate) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulphate (0.25–2.0 mg intravenously) was given while the administration of dobutamine was continued. Metoprolol was administered (1.0–5.0 mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine–atropine combination if the side effects did not revert spontaneously and quickly. Two experienced investigators performed off-line assessment of echocardiographic images, and were blinded to the clinical data in order to give an objective interpretation. Using a standard 16-segment model, wall motion was scored on a 5-point scale (a score of 1 indicating normal, 2 mild hypokinesis, 3 severe hypokinesis, 4 akinesis, and 5 dyskinesis) and a wall motion score index was calculated (total score divided by the number of segments scored). The results of DSE were considered positive if new wall-motion abnormalities occurred (i.e. if wall motion in any segment worsened by ≥1 grades during the test, with the exception of akinesis becoming dyskinesis). This criterion was used consistently during the whole study period.

1.3. Postoperative outcome

End-point was mortality. In-hospital mortality was defined as death occurring during postoperative in-hospital stay or as death occurring after hospital discharge but within the first 30 days after surgery. Long-term mortality was defined as death occurring at any time from day 1 after surgery. Information about the patient's vital status was obtained by reviewing the hospital's medical records, by approaching the patient's general physician and by approaching the Office of Civil Registry. The date of the last review or the date that an endpoint was reached was used to calculate follow-up time. Median follow-up time was 7 years (interquartile range: 3–10 years). Follow-up was completed in all patients.

1.4. Statistical analysis

Continuous data are expressed as mean (±SD) or median (±interquartile range) and compared using the Student t-test or Mann–Whitney U-test when appropriate. Categorical data are presented as percent frequencies and differences between proportions were

Table 1. Baseline characteristics of the 511 patients

	β-Blockers (n=139)	No β-blockers (n=372)	p-Value
Age (years)	64±11	65±12	0.35
Male gender	97 (70%)	286 (77%)	0.19
Angina pectoris	53 (38%)	107 (29%)	0.05
Previous myocardial infarction	85 (61%)	182 (49%)	0.02
Previous coronary revascularization	51 (37%)	62 (17%)	<0.001
Previous stroke or transient ischemic attack	26 (19%)	54 (15%)	0.31
Hypertension	88 (63%)	115 (31%)	<0.001
Current smoker	42 (30%)	126 (34%)	0.50
Chronic obstructive pulmonary disease	28 (20%)	60 (16%)	0.35
Hypercholesterolemia	57 (41%)	69 (19%)	<0.001
Diabetes mellitus	29 (21%)	43 (12%)	0.01
Renal failure	21 (15%)	36 (10%)	0.11
Electrocardiography			
Left ventricular hypertrophy	8 (6%)	29 (8%)	0.55
Q-waves	58 (42%)	125 (34%)	0.11
ST-segment changes	39 (28%)	66 (18%)	0.01
Left bundle branch block	8 (6%)	12 (3%)	0.29
Right bundle branch block	6 (4%)	22 (6%)	0.63
Atrial fibrillation	16 (12%)	21 (6%)	0.04
Type of surgery			
Abdominal aortic repair	71 (51%)	166 (45%)	0.23
Lower extremity revascularization	55 (40%)	166 (45%)	0.35
Carotid artery surgery	13 (9%)	40 (11%)	0.76
Cardiac medication			
Aspirin	51 (37%)	74 (20%)	<0.001
Angiotensin-converting enzyme inhibitors	74 (53%)	141 (38%)	0.002
Calcium channel blockers	65 (47%)	97 (26%)	<0.001
Coumarin	38 (27%)	73 (20%)	0.08
Digoxin	15 (11%)	26 (7%)	0.22
Diuretic	44 (32%)	92 (25%)	0.14
Nitrates	66 (48%)	97 (26%)	<0.001
Statins	61 (44%)	46 (12%)	<0.001

compared using the chi-square test with Yates' correction. The Kaplan–Meier method with log-rank test was used to compare survival curves in two or more groups. Because β-blockers were not assigned in a random fashion and selection bias may distort the results of our study, a propensity score for β-blockers was constructed using multiple logistic regression analyses. Propensity analyses are reliable tools to correct for selection bias and the rationale for using propensity scores has been described previously.[16 and 17] A propensity score is generally defined as the conditional probability of assignment to a particular treatment given a vector of observed covariates. To assess the effect of a treatment in a situation in which randomization is difficult or impossible, propensity scores are a useful method for matching members of different groups. Comparisons of different groups reveal reliable information on the impact of the treatment of interest with a small residual bias.[17] Clinical variables and medication that were independently associated with the decision to prescribe β-blockers (p-value<0.25) were included in the multivariate propensity score. Important determinants to prescribe β-blockers were angina pectoris, previous myocardial infarction, hypertension, and hypercholesterolemia ($p<0.05$). Propensity scores ranged from 0.007 to 0.97.

Logistic regression models were used to analyse the relation between β-blocker therapy and in-hospital mortality. Cox hazards regression models were used to analyse the relation between β-blocker therapy and long-term mortality. In multivariate analyses, adjustments were made for baseline clinical variables, DSE results, and propensity scores, irrespective of the significance level in univariate analysis. In order to reveal possible heterogeneity between intermediate risk procedures (carotid artery surgery) and high-risk procedures (abdominal aortic aneurysm repair and lower extremity revascularization procedures), an interaction term was evaluated. Interaction was considered

Table 2. Univariate predictors of 30-day and long-term mortality

	30-Day mortality (n=64)		Long-term mortality (n=171)	
	Odds ratio (95% CI)	**p-Value**	**Hazard ratio (95% CI)**	**p-Value**
Age>70 years	2.11 (1.24–3.57)	0.006	1.64 (1.21–2.23)	0.002
Male gender	1.52 (0.78–2.95)	0.22	1.28 (0.88–1.87)	0.19
Angina pectoris	1.27 (0.73–2.20)	0.39	1.32 (0.96–1.82)	0.09
Previous MI	4.19 (2.22–7.92)	<0.001	3.07 (2.19–4.34)	<0.001
Previous stroke or TIA	5.43 (2.06–9.62)	<0.001	2.06 (1.42–2.99)	<0.001
Hypertension	1.61 (0.95–2.73)	0.07	1.05 (0.79–1.44)	0.84
Current smoker	0.74 (0.32–1.70)	0.47	1.15 (0.81–1.65)	0.38
Hypercholesterolemia	0.53 (0.23–1.21)	0.22	1.21 (0.85–1.72)	0.31
Diabetes mellitus	1.00 (0.47–2.12)	0.99	1.61 (1.08–2.40)	0.02
Renal failure	4.54 (2.42–8.54)	<0.001	2.72 (1.84–4.03)	<0.001
COPD	1.56 (0.83–2.93)	0.17	1.27 (0.87–1.87)	0.16
Abnormal ECG	0.83 (0.49–1.40)	0.49	1.74 (1.25–2.43)	<0.001
NWMA	3.23 (1.84–5.66)	<0.001	4.11 (2.99–5.67)	<0.001
β-Blockers	0.24 (0.10–0.58)	0.001	0.49 (0.32–0.75)	<0.001

MI, myocardial infarction; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; NWMA, new wall motion abnormalities

statistically significant at the 0.05 probability level. Odds ratios (OR) and hazard ratios (HR) are given with 95% confidence intervals. For all tests, a p-value<0.05 (two-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

2. RESULTS

Mean age was 64±11 years and 383 patients (75%) were male. A total of 139 patients (27%) were using chronic β-blockers; 99 patients (71%) used a selective β-blocker and 40 patients (29%) a non-selective β-blocker. Selective β-blockers included atenolol (n=8), bisoprolol (n=41) and metoprolol (n=50). Non-selective β-blockers included carvedilol (n=26) and sotalol (n=14). Baseline characteristics of the patients subdivided according to the use of β-blockers are summarized in Table 1. During preoperative DSE, heart rate increased from 72±15 beats/min at rest to 132±18 beats/min at peak stress. The maximum dose of dobutamine infusion was 37.6±8 μg/kg/min. Atropine was administered in 312 patients (61%) to achieve target heart rate. The mean wall motion score index at rest was 2.11±0.37. The mean wall motion score index at rest was 2.07±0.28 in patients using beta-blockers and of 2.11±0.36 in patients who did not (p=0.52). The mean wall motion score index at peak stress was 1.80±0.47. Stress induced myocardial ischemia occurred in 82 patients (16%). No fatal complications occurred during or immediately after the stress test. Abdominal aortic repair was performed in 237 patients (46%), lower extremity revascularization in 221 patients (43%), and carotid artery surgery in 53 patients (10%).

In-hospital mortality occurred in 64 patients (13%) and long-term mortality in 171 patients (33%). Univariate associations between clinical variables and mortality are summarized in Table 2. Age above 70 years, previous myocardial infarction, history of stroke or transient ischemic attack, renal failure and stress induced myocardial ischemia were significant unadjusted determinants for in-hospital and long-term mortality. The use of β-blockers was associated with a significant reduction of in-hospital and long-term mortality (OR: 0.24, 95% CI: 0.10–0.58 and HR: 0.49, 95% CI: 0.32–0.75, respectively). Kaplan–Meier estimates for long-term mortality, stratified according to the use of β-blockers, showed a better survival for those patients using β-blocker therapy (p<0.001) (Fig. 1). In multivariate analysis, the relation between β-blocker therapy and post-operative mortality was adjusted for clinical variables, DSE results and propensity scores for β-blockers. The use of β-blockers remained significantly associated with a reduced incidence of in-hospital and long-term mortality (OR: 0.18, 95% CI: 0.04–0.74 and HR: 0.38, 95% CI: 0.22–0.65, respectively) (Fig. 2).

In patients using β-blockers (n=139), we observed no significant effect of selective β-blockers as compared to non-selective β-blockers on postoperative mortality (in-hospital mortality: OR: 0.4, 95% CI: 0.1–2.0; long-term mortality: HR: 0.7, 95% CI: 0.3–1.4); in multivariate analyses, this association was also non-significant (in-hospital mortality: OR: 0.6, 95% CI: 0.1–3.5; long-term mortality: HR: 0.6, 95% CI: 0.3–1.3). Tests for heterogeneity revealed no evidence for a differential effect of β-blockers in patients undergoing intermediate risk procedures (carotid artery surgery) and high-risk procedures (abdominal aortic aneurysm repair and lower extremity revascularization) (p-value for interaction =0.96).

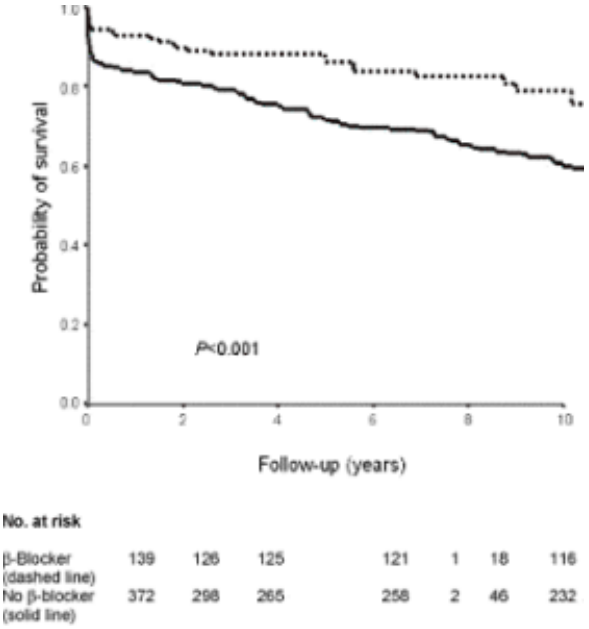

Fig. 1. Kaplan–Meier estimates of all-cause mortality, stratified according to the use of β-blockers. Dashed line denotes β-blocker use; solid line denotes no β-blocker use.

3. DISCUSSION

This study shows that β-blockers improve in-hospital and long-term survival in patients with severe left ventricular dysfunction undergoing major non-cardiac vascular surgery. This association was independent of clinical risk factors, stress induced myocardial ischemia during DSE, and propensity scores for β-blockers.

Congestive heart failure has been identified as an important risk factor for adverse events after major non-cardiac surgery. In 1977, Goldman developed the multifactorial cardiac risk index, which allows preoperative estimation of cardiac risk in non-cardiac surgical procedures.[3] They demonstrated that clinical signs of congestive heart failure such as a preoperative third heart sound and jugular venous distension were strongly associated with the development of postoperative life threatening or fatal cardiac complications. Twelve years later, Lee et al. developed and validated the revised cardiac risk index, which included congestive heart failure as an important predictor for postoperative cardiac events, among other

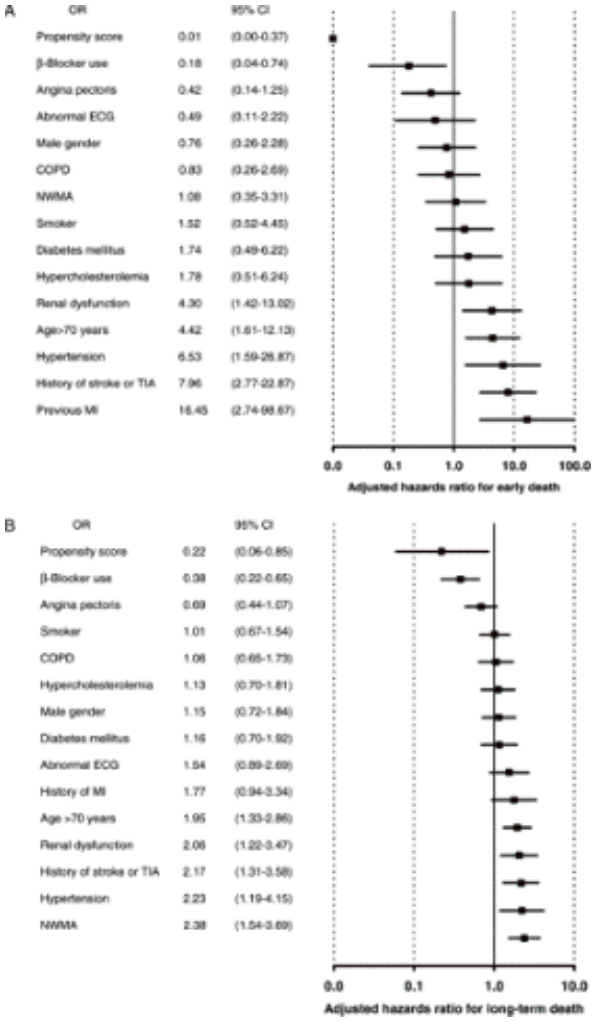

Fig. 2. Multivariate models to predict 30-day (A) and long-term (B) mortality after major vascular surgery. ECG, electrocardiogram; COPD, chronic obstructive pulmonary disease; NWMA, new wall motion abnormalities; TIA, transient ischemic attack; MI, myocardial infarction.

predictors, such as ischemic artery disease, high-risk type of surgery, a history of cerebrovascular disease, insulin therapy for diabetes mellitus, and preoperative serum creatinine levels of more than 2.0 mg/dL.[4] Although decompensated and compensated heart failure have been identified as, respectively, a major and intermediate determinant of increased perioperative cardiovascular risk, resting left ventricular dysfunction as measured by invasive and non-invasive tests has not been demonstrated to be a consistent predictor of perioperative cardiac events.[18, 19, 20 and 21] Therefore, the ACC/AHA guidelines for perioperative cardiovascular evaluation for non-cardiac surgery do not recommend routine testing of left ventricular function in patients

without a history of congestive heart failure.[6] However, the identification of patients with an ejection fraction of 30% or less might be important, especially because these patients may benefit from β-blocker therapy.

Large randomized trials have demonstrated the usefulness of β-blockers in non-surgical patients with reduced left ventricular function. The MDC-trial (Metoprolol in Dilated Cardiomyopathy Trial), MERIT-HF trial (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure), CIBIS-I and II trial (Cardiac Insufficiency Bisoprolol Study I and II), and COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study Group), all have demonstrated the benefits of metoprolol, bisoprolol and carvedilol for survival in stable advanced heart-failure patients.[22, 23, 24 and 25] The CAPRICORN study demonstrated that patients with left ventricular dysfunction following a recent acute myocardial infarction also benefit from β-blockers (carvedilol) in addition to angiotensin-converting enzyme inhibitors.[26] Meta-analyses have confirmed the usefulness of β-blockers in patients with reduced left ventricular function, demonstrating that β-blockers reduced all-cause mortality by around 30%.[27, 28 and 29] As a result, consensus guidelines strongly support and recommended the use of β-blockers in a-symptomatic to severe symptomatic heart failure patients, unless there is an absolute contraindication to the use of these drugs.[11 and 12]

Perioperative management of patients with dilated or hypertrophic cardiomyopathy undergoing major surgery is aimed at maximizing preoperative hemodynamic status and providing intensive postoperative medical therapy and surveillance.[6] Although randomized trials have demonstrated that patients who are at risk for coronary artery disease and who undergo major vascular surgery benefit from perioperative β-blocker therapy in terms of reduced postoperative morbidity and mortality, limited is known about the role of β-blocker therapy in patients with left ventricular dysfunction to improve early and long-term outcome after major vascular surgery.[13 and 14] In the present study, we demonstrated the beneficial effect of β-blockers on in-hospital and long-term survival in patients with left ventricular dysfunction, independent of the presence or absence of coronary artery disease or other possible confounding factors. These results suggest that the effect of beta-blockers is not only due to its long-term protective effect, but also due to its myocardial protective effect during the perioperative period of surgery. Preoperative screening of patients with left ventricular dysfunction might, therefore, be recommended. However, randomized controlled trials should be conducted before recommending this approach.

It is known that an increase in cardiac adrenergic drive is an early compensatory mechanism for the failing heart and that chronic activation of the adrenergic nervous system results in increased cardiac output and heart rate with increased myocardial oxygen demand, ischemia and oxidative stress. This may result in histopathologic changes with subsequent ventricular remodeling. β-Blockers reverse the process of left ventricular remodeling, leading to improved hemodynamics with favorable effects on prognosis.[30] In addition, β-blockers may also have beneficial effects through their heart rate regulating, anti-arrhythmic and anti-inflammatory effects.[31, 32 and 33] We speculate that the same mechanisms may be responsible for the reduction in postoperative mortality in patients with left ventricular dysfunction undergoing major non-cardiac vascular surgery using concomitant β-blocker therapy. It may take a prolonged period for β-blockers to exert its cardioprotective effect and, therefore, β-blockers should be started at least several weeks before elective major non-cardiac surgery, when possible.

The major limitation in this study is that β-blockers were not administered in a randomized controlled fashion. Selection bias is a major determinant for distorted results. However, we applied propensity analysis, which has been shown to be a reliable method to adjust for selection bias.[16 and 17] Another limitation which should be considered when interpreting the results is that some patients with severe left ventricular dysfunction and especially those with extensive co-morbidity, such as renal dysfunction and chronic obstructive pulmonary disease, were not referred to our clinic for major surgery, and, therefore, were not included in our study.

Based on our results we conclude that β-blockers are independently associated with a reduced incidence of in-hospital and long-term mortality in patients with severe left ventricular dysfunction.

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Chapter 24

Hemodynamic responses and long-term follow-up results in patients using chronic β_1-selective and non-selective β-blockers during dobutamine stress echocardiography

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Hemodynamic responses and long-term follow-up results in patients using chronic β_1-selective and non-selective β-blockers during dobutamine stress echocardiography

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Objective: This study was undertaken to determine to what extent hemodynamic responses to dobutamine infusion between patients using concomitant β1-selective or non-selective β-blockers differ and whether this difference affects the long-term prognostic value of dobutamine stress echocardiography (DSE) with respect to cardiac events.

Design: Single centre, observational study.

Methods: A total of 1234 patients using chronic β-blockers underwent DSE and were prospectively included in the study. Heart rate and blood pressure responses were measured during the DSE protocol. During a median follow-up time of 4 years (range: 0.5-14 years), overall and cardiac mortality and non-fatal myocardial infarction were noted.

Results; A total of 954 and 280 patients were using β1-selective and non-selective β-blockers, respectively. During DSE, the heart rate response was significantly higher, systolic and diastolic blood pressure responses were significantly lower and the double product of heart rate and systolic blood pressure was similar in patients using β1-selective, compared to patients using non-selective β-blockers. In patients with and without new wall motion abnormalities during DSE, a similar cardiac event-free survival was observed irrespective of the selectivity of β-blockers (p=0.9 and p=0.3, respectively)

Conclusion: During DSE, heart rate and blood pressure response was different, but the double product was similar in patients using β1-selective or non-selective β-blockers, which may explain why the long-term prognostic value of DSE is similar in these two groups.

STRESS ECHOCARDIOGRAPHY is a widely used non-invasive technique for the long-term risk assessment in patients with known or suspected coronary artery disease [1,2]. Dobutamine, a synthetic catecholamine with predominant β1-adrenergic receptor activity and with mild agonistic effects on β2- and α1-adrenergic receptors, is commonly used as a pharmacologic stressor in stress echocardiography [1,3]. Escalating doses of dobutamine are administered in conjunction with echocardiography to increase myocardial oxygen demand through positive inotropic and chronotropic effects and to detect new wall motion abnormalities in regions with a mismatch between myocardial oxygen supply and demand.

In patients referred for dobutamine stress echocardiography (DSE), β-blockers are commonly prescribed and are frequently continued during the stress test. Beta-blockers can be classified into β1-selective, predominantly blocking β1-adrenergic receptors, and non-selective β-blockers, blocking both β1- and β2-adrenergic receptors [4-6]. β1-selective β-blockers are established therapeutic agents for patients with hypertension, angina pectoris and heart failure [7]. The beneficial effect of non-selective β-blockers in patients with congestive heart failure has been established more recently [8,9]. During exercise and stress, both β1-selective and non-selective β-blockers attenuate the expected increase in heart rate and cardiac output [4-6]. It has been observed that during exercise and dobutamine induced stress the increase in heart rate was more attenuated in patients using non-selective, than in patients using β1-selective β-blockers [10-12].

During DSE, the hemodynamic responses may be different in patients using either β1-selective or non-selective β-blockers, and this may influence the prognostic value of DSE. The purpose of this study was to compare the hemodynamic effects of incremental dobutamine infusion rates during stress echocardiography in patients using β1-selective or non-selective β-blockers, and to evaluate whether the use of each of these two agents during DSE has any influence on the long-term prognostic value of DSE with respect to cardiac mortality or cardiac events.

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METHODS

Study population

During the period January 1990 through December 2003, 3875 patients underwent DSE at the Erasmus Medical Center in Rotterdam, the Netherlands. A total of 1234 patients were receiving either chronic β1-selective or non-selective β-blocker therapy and were prospectively included in the study after giving informed consent. Clinical risk factors (hypertension, smoking, hypercholesterolemia, diabetes mellitus, angina pectoris, a history of myocardial infarction, a history of congestive heart failure) and the use of cardiac medication were recorded at the time of DSE. Hypertension was recorded if patients presented with a blood pressure ≥140/90 mmHg or if patients were medically treated for hypertension. Hypercholesterolemia was recorded if patients presented with a plasma cholesterol level ≥5.5 mmol/L, or if patients were taking lipid-lowering agents. Diabetes mellitus was recorded if patients presented with a fasting glucose level of ≥7.8 mmol/L, or in those who required treatment. Follow-up data were obtained from all patients.

Dobutamine stress echocardiography and assessment of hemodynamic response

The DSE protocol was approved by the Hospital Ethical Committee and was performed in accordance with well-established protocols [13,14]. Patients underwent a resting two-dimensional precordial echocardiographic examination and standard apical and parasternal views were recorded on videotape and a 12-lead ECG was recorded. Dobutamine hydrochloride was then administered intravenously by infusion pump with incremental doses of 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min (stage 4), and continued for 6 minutes. The dobutamine infusion was stopped if a target heart rate (85% of a theoretic maximal heart rate (men: (220 – age) x 85%; women: (200 – age) x 85%) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulphate (starting with 0.25 mg, increased to a cumulative maximum of 2.0 mg) was given intravenously at the end of stage 4 while the dobutamine administration was continued. Beta-blocker therapy was continued during the study. During the test, a 12-lead ECG was recorded every minute. Blood pressure was measured by sphygmomanometry every 3 minutes (Accutorr A1; Datascope Corp., Paramus, NY, U.S.A.). Metoprolol was administered (1,0 to 5,0 mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine-atropine combination if the side effects did not revert spontaneously and quickly. Atropine was administered as an antidote if bradycardia and hypotension occurred. The criteria for stopping the test were: (1) severe new echocardiographic wall motion abnormalities in multiple locations, (2) horizontal or downsloping electrocardiographic ST depression of ≥0.2 mV measured 80 ms after the J point, or ST-segment elevation of ≥0.2 mV in the absence of Q waves, (3) symptomatic decline in systolic blood pressure of more than 40 mmHg from the resting value, or a systolic blood pressure of less than 100 mmHg, (4) hypertension (blood pressure >240/140 mmHg), (5) the occurrence of cardiac arrhythmias, (6) severe angina pectoris, and (7) intolerable adverse effects considered to be the result of dobutamine or atropine.

Off-line assessment of echocardiographic images was performed by two experienced investigators without knowledge of the patient's clinical data, but with knowledge of the doses of dobutamine and atropine used. From 1990 to 1993, the left ventricle was divided into 14 segments and wall motion was scored on a 4-point ordinal scale [15]. After 1993 a 16-segment 5-point score was used [16]. The results of DSE were considered positive if new wall motion abnormalities occurred (i.e., if wall motion in any segment worsened by ≥1 grade(s) during the test, with the exception of akinesis becoming dyskinesis). The extent and location of ischemia were evaluated and a wall-motion score index (total score divided by the number of segments scored) was calculated, both at rest and during peak stress. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessments, and a majority decision was reached.

Clinical follow-up

Follow-up data were obtained in January 2004. The patient's status was determined by contacting the patient's general physician and/or by reviewing hospital records. The date of the last interview or review was used to calculate follow-up time. Endpoints were as follows: death from all causes, cardiac death, non-fatal myocardial infarction and coronary revascularization (performed >2 months after DSE). After reaching an endpoint, follow-up was discontinued. Cardiac death was defined as death caused by acute myocardial

infarction, cardiac arrhythmias, or congestive heart failure. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: elevated levels of CK, CK-MB and cardiac troponin T (CK level >190 U/L and CK-MB >14 U/L, or CK-MB fraction >6% of total CK, or cardiac troponin T >0.1 ng/mL), development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms), and typical symptoms of angina pectoris. Coronary revascularization included coronary angioplasty or coronary artery bypass surgery.

Statistical analysis

The study population was divided in two subgroups according to the type of β-blocker therapy. Continuous data are expressed as means (+/- SD) and compared using the Independent-samples t test or Paired-samples t test when appropriate. Categorical data are presented as percent frequencies and differences between proportions were compared using the chi-square test with Yates' correction. ANOVA for repeated measurements was used to compare the hemodynamic responses between the two subgroups during the DSE protocol. Univariate Cox regression analysis was performed to study the prognostic value of the selected clinical characteristics and DSE results with respect to the endpoints. To investigate the prognostic value of β1-selective β-blockers with respect to cardiac death or non-fatal myocardial infarction, multivariate Cox regression analysis was used to adjust for baseline characteristics and DSE results. Hazard ratios (HR) are given with 95% confidence intervals (95% CI). The cardiac event-free survival was compared using Kaplan-Meier curves. Differences between cardiac event-free survival curves were tested with the log-rank chi-square statistic. For all tests, a p-value <0.05 (two-sided) was considered significant.

RESULTS

Patient characteristics

The study population consisted of 1234 consecutive patients undergoing dobutamine stress echocardiography (mean age: 61 +/-12 years, 68% male); 954 patients (77%) used a β1-selective β-blocker and 280 patients (23%) used a non-selective β-blocker. Beta1-selective β-blockers included atenolol, bisoprolol, celiprolol, metoprolol and nebivolol. Non-selective β-blockers included carvedilol, pindolol, propranolol, sotalol and labetalol.

Table 1. Baseline characteristics of patients using β1-selective β-blockers and non-selective β-blockers.

Characteristics	Patients with β1-selective β-blockers (n=954)	Patients with non-selective β-blockers (n=280)	p-value
Demographics			
Age (years) (mean +/- SD)	60 +/-12	62 +/-11	0.053
Gender (male) (%)	68	66	0.5
Weight (kg) (mean +/- SD)	77 +/-13	76 +/-14	0.3
Length (m) (mean +/- SD)	1.71 +/-0.09	1.73 +/-0.1	0.07
Hemodynamics			
Heart rate (bpm) (mean +/- SD)	70 +/- 13	71 +/-13	0.3
Systolic blood pressure (mmHg) (mean +/- SD)	132 +/-24	130 +/-24	0.3
Diastolic blood pressure (mmHg) (mean +/- SD)	74 +/-13	75+/-13	0.6
Double product (bpm x mmHg) (mean +/- SD)	9213 +/- 2447	9233 +/- 2390	0.9
Clinical characteristics			
History of myocardial infarction (%)	49	44	0.3
History of congestive heart failure (%)	14	23	<0.001
Previous CABG (%)	19	22	0.2
Previous PTCA (%)	25	17	0.4
Stable angina pectoris (%)	41	36	0.4
Hypertension (%)	38	30	0.02
Smoking (%)	28	26	0.5
Hypercholesterolemia (%)	35	31	0.2
Diabetes Mellitus (%)	16	11	0.06
Medication			
Calcium antagonist (%)	33	34	0.9
Digitalis (%)	4	14	<0.001
Diuretic (%)	17	32	<0.001
ACE inhibitor (%)	31	36	0.1

CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; ACE inhibitor, angiotensin converting enzyme inhibitor

Table 2. Dobutamine stress echocardiography results in patients using β1-selective β-blockers and non-selective β-blockers

	Patients with β1-selective β-blockers (n=954)	Patients with non-selective β-blockers (n=280)	p-value
Maximal dose of dobutamine (μg/kg/min) (mean +/- SD)	37 +/- 7	36 +/- 8	0.4
Use of atropine (%)	64	64	1.0
New arrhythmias during DSE (%)			
SVT (%)	3	5	0.1
VT (<10 consecutive complexes) (%)	2	4	0.06
VT (>10 consecutive complexes) (%)	1	2	0.2
Atrial fibrillation (%)	1	1	1.0
ST-segment changes during DSE (%)	39	39	1.0
Heart rate at rest (bpm[§]) (mean +/- SD)	70 +/-13	70 +/-13	0.7
Heart rate at peak stress (bpm[§]) (mean +/- SD)	129 +/-17	127 +/-18	0.1
Test endpoints			
Target heart rate achieved (%)	80	78	0.5
Angina pectoris (%)	3	3	1.0
ST changes (%)	5	5	1.0
Arrhythmias (%)	2	3	0.5
Abnormal blood pressure response (%)	1	0	0.7
Adverse effects of drugs (%)	39	39	1.0
Rest wall motion abnormalities (%)	62	68	0.07
New wall motion abnormalities (%)	54	53	0.7
Rest wall motion score index (mean +/- SD)	1.31 +/-0.37	1.36 +/-0.44	0.5
Peak wall motion score index (mean +/- SD)	1.51 +/-0.57	1.62 +/-0.65	0.006

DSE, dobutamine stress echocardiography; SVT, supraventricular tachycardia; VT, ventricular tachycardia

The maximum difference of mean systolic blood pressure (+/-SEM) between patients with selective and non-selective beta-blockers was observed during atropine administration (-0.6 +/-1.1 vs. 13.6 +/-2.4 mmHg, respectively). The maximum difference of mean diastolic blood pressure (+/-SEM) between patients with selective and non-selective beta-blockers was also observed during atropine administration (-2.1 +/-0.6 vs. 4.5 +/- 1.3 mmHg, respectively). In our study, the presence of congestive heart failure was significantly higher in patients using non-selective β-blockers, compared to selective beta-blockers. Congestive heart failure may blunt the hemodynamic response to dobutamine through β1-adrenergic receptor down-regulation. We have repeated our analysis after the exclusion of patients with chronic congestive heart failure and we observed that the hemodynamic responses to dobutamine infusion was comparable with the hemodynamic responses in the total study population. We have therefore presented only the results for the total study population.

Dobutamine stress echocardiography and follow-up results

Dobutamine stress data are presented in Table 2. No fatal complications occurred during DSE. The maximal dose of dobutamine administration, the additional administration of atropine and the percentage of patients who achieved target heart rate were comparable between patients using β1-selective β-blockers and non-selective β-blockers. No significant differences were observed between the two groups with regard to the development of cardiac arrhythmias, the achievement of test endpoints and the development of electrocardiographic ST segment changes. Finally, the incidence of rest wall motion abnormalities and the incidence of new wall motion abnormalities during DSE were similar in both groups.

During a mean follow-up of 4 years (range: 0.5-14 years), death from all causes occurred in 280 (23%) patients. Cardiac death occurred in 169 (14%) and non-cardiac death in 111 (9%) patients. Non-fatal myocardial infarction occurred in 85 (7%) patients and coronary revascularization was performed in 441 (36%) patients. Adverse cardiac outcomes occurred with similar incidence in patients using β1-selective and non-selective β-blockers (overall death: 23% vs. 22% respectively (p=0.7); cardiac death: 14% vs. 12% respectively (p=0.3), cardiac death or non-fatal myocardial infarction: 21% vs. 19% respectively (p=0.4); coronary revascularization: 36% vs. 36% respectively (p=0.9). Univariate and multivariate predictors of the composite endpoint of cardiac death or non-fatal myocardial infarction are presented in Table 3. After adjustment for clinical risk factors and rest wall motion abnormalities, new wall motion abnormalities during DSE remained a strong significant predictor of long-term cardiac death or non-fatal myocardial infarction (HR: 2.1, 95% CI: 1.5-3.0). In univariate and multivariate analyses, there was no significant relation

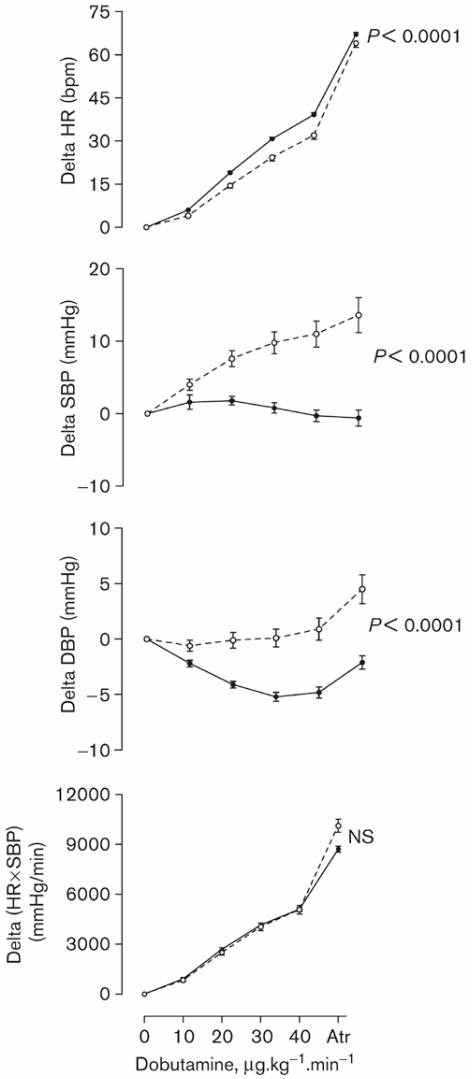
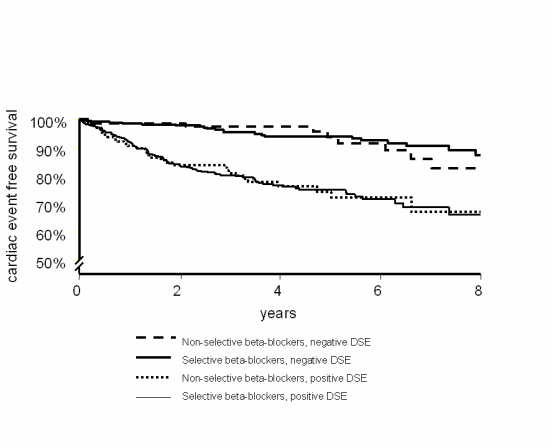


Figure 1. Line plots showing responses of heart rate, systolic blood pressure, diastolic blood pressure and heart rate-systolic blood pressure double product in patients using β1-selective (solid line) or non-selective β-blockers (dashed line) during dobutamine stress echocardiography (DSE). HR denotes heart rate, SBP and DBP denote systolic and diastolic blood pressure, Atr denotes atropine, ns denotes non significant. Values are means +/-SEM.

between the selectivity of β-blockers with regard to long-term cardiac death or myocardial infarction.

Kaplan-Meier curves for the prediction of the composite endpoint cardiac death or non-fatal myocardial infarction are presented in Figure 2. In summary, a similar cardiac event-free survival was observed between patients using β1-selective and non-selective β-blockers in patients with (p=0.9) and in patients without new wall motion abnormalities (p=0.3) during DSE. A lower cardiac event-free survival was

Figure 2. Kaplan-Meier curves for the prediction of the composite endpoint of cardiac death or non-fatal myocardial infarction (MI) in patients with or without new wall motion abnormalities during dobutamine stress echocardiography (DSE), stratified according to the use of β1-selective or non-selective β-blockers.



observed in patients with, than in patients without new wall motion abnormalities in the group of patients using β1-selective (p<0.001) or non-selective β-blockers (p=0.02).

DISCUSSION

The results of this study demonstrate that the hemodynamic response to dobutamine during DSE is different for patients using β1-selective versus non-selective β-blockers. The heart rate response was significantly higher and the responses of systolic and diastolic blood pressure were significantly lower in patients using β1-selective β-blockers, compared to those using non-selective β-blockers. The additional use of atropine, a competitive antagonist of muscarinic cholinergic receptors, at peak dobutamine infusion rate abolished the difference in heart rate response. Due to the reciprocal differences in heart rate and blood pressure in patients using β1-selective and non-selective β-blockers, the double product of heart rate and systolic blood pressure in response to dobutamine infusion was similar. The percentage of patients who achieved target heart rate was similar for the two groups. Importantly, the long-term predictive value of DSE for adverse cardiac events was also similar in patients using β1-selective or non-selective β-blockers, although a non-significant higher risk was observed in patients using selective beta-blockers. These findings indicate that the selectivity of concomitant β-blocker therapy during DSE does not influence the ability of DSE to predict the composite endpoint of cardiac death or non-fatal myocardial infarction.

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

	Univariate HR (95% CI)	Multivariate HR (95% CI)
Age <70 years	1.03 (1.02-1.05)	1.04 (1.03-1.05)
Gender (male)	1.8 (1.3-2.5)	1.4 (1.0-1.9)
History of myocardial infarction	1.1 (0.8-1.4)	1.1 (0.8-1.4)
History of congestive heart failure	2.1 (1.4-2.9)	1.9 (1.4-2.6)
Angina pectoris	0.6 (0.4-0.9)	0.7 (0.5-0.9)
Hypertension	0.9 (0.7-1.2)	1.1 (0.8-1.4)
Smoking	1.3 (0.9-1.7)	1.0 (0.8-1.4)
Hypercholesterolemia	0.4 (0.3-0.6)	1.1 (0.8-1.4)
Diabetes Mellitus	1.6 (1.1-2.2)	1.9 (1.4-2.5)
Rest wall motion abnormalities	1.0 (0.7-1.3)	1.1 (0.8-1.4)
New wall motion abnormalities	1.4 (1.1-1.9)	2.1 (1.5-3.0)
β1-selective β-blockers	1.1 (0.8-1.5)	1.3 (0.9-1.7)

Hemodynamic response

Beta-blockers can be classified into β1-selective and non-selective β-blockers. β1-selective β-blockers have predominant affinity for the β1-adrenergic receptors. Non-selective β-blockers produce a competitive blockade of both β1- and β2-adrenergic receptors [4-6]. Both β1-selective and non-selective β-blockers have negative chronotropic and negative inotropic effects, resulting in a decrease in cardiac output [4-6]. β-blockers cause peripheral vasoconstriction in response to this decrease [17]. In addition, non-selective β-blockers also block β2-adrenergic receptors, mediating peripheral vasodilatation [17]. Dobutamine, a synthetic catecholamine, has been approved for short-term positive inotropic support in circulatory decompensation secondary to depressed myocardial contractility and is used as a pharmacologic stressor in stress echocardiography [1,3]. The positive inotropic and chronotropic effects of dobutamine are predominantly mediated by β1-receptor stimulation [3]. At therapeutic doses, dobutamine also has mild β2 and α1 agonist effects [3].

The lower systolic and diastolic blood pressure response to dobutamine infusion in patients using β1-selective β-blockers may be explained by unopposed β2-adrenergic receptor stimulation and subsequent peripheral vasodilatation. This fall in blood pressure may cause a baroreflex-mediated withdrawal of vagal tone that may explain the greater increase in heart rate in patients using β1-selective β-blockers. The hypothesis that a different heart rate response in patients using β1-selective or non-selective β-blockers is mediated by a difference in cardiac vagal tone, is supported by the current observation that this difference was abolished during infusion of an anticholinergic agent (atropine) at peak dose of dobutamine infusion. Other causes of difference in hemodynamic response should be considered. Beta-2 adrenergic receptors have a positive chronotropic effect and at therapeutic doses, dobutamine has mild beta-2 adrenergic effects. Therefore, during dobutamine infusion, a lower heart rate response may be observed in patients using non-selective β-blockers compared to selective β-blockers [18]. Furthermore, it might be hypothesized that carvedilol has a tighter binding to beta-1 adrenergic receptors, compared to metoprolol and that a more effective degree of blockade of the beta-1 adrenergic receptor may explain the lower chronotropic response to dobutamine with non-selective, compared to selective agents [19,20].

Although different in design, our hemodynamic results are supported by previously published studies evaluating the effect of β1-selective and non-selective β-blockers during dobutamine infusion. In the prospective crossover study reported by Maack et al. [11], comparing carvedilol (non-selective β-blocker) and metoprolol (β1-selective β-blocker) treatment in 44 patients with heart failure, the increase in heart rate during DSE (with incremental dobutamine infusion rates up to 40 μg/kg/min) was more pronounced in patients receiving metoprolol treatment. Systolic and mean blood pressure increased in patients receiving carvedilol, while it remained unchanged in patients receiving metoprolol. In another published study comparing hemodynamic responses between carvedilol and metoprolol treatment in 10 patients with congestive heart failure, a higher heart rate, a higher cardiac output and a lower mean arterial pressure were observed in referred for DSE, β-blockers are commonly prescribed. Several studies have demonstrated that concomitant β-blocker therapy lowers the sensitivity of pharmacologic stress echocardiography, but institutional policies for withholding β-blockade for patients undergoing DSE vary [21,22]. Beta-blockers are frequently continued during the stress test, because β-blocker withdrawal prior to the test can evoke adverse cardiac events in patients with metoprolol, compared to patients with carvedilol treatment during low infusion rates of dobutamine (5 and 15 μg/kg/min) [12].

Clinical implications

DSE is an established non-invasive technique for the long-term risk assessment in patients with known or suspected coronary artery disease [1,2]. In patients

patients with coronary artery disease and left ventricular dysfunction [23,24]. Atropine has been demonstrated to increase the diagnostic sensitivity for ischemia and for coronary artery disease, especially in patients receiving β-blockers [25]. Therefore, our protocol did not included withdrawal of ongoing beta-blocker therapy. Unfortunately, our study did not allow us to compare the prognostic value of DSE in patients with and without β-blockers. To our knowledge, the impact of the selectivity of β-blockers on the prognostic value of DSE has not been reported before. This study provides evidence that the selectivity of β-blockers does not influence the long-term prognostic value of DSE and we propose that the hospital policy for patients undergoing DSE should not be different for patients receiving a β1-selective or a non-selective β-blocker.

Conclusion

In this study, heart rate and blood pressure response to higher doses of dobutamine infusion differed significantly in patients using β1-selective β-blockers, compared to patients using non-selective β-blockers. The difference in heart rate was abolished after the addition of atropine. Importantly, the long-term prognostic value of DSE with regard to adverse cardiac events appeared to be similar for patients using either β1-selective or non-selective β-blockers, although a non-significant higher risk was observed in patients using selective beta-blockers.

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Chapter 25

Intensity of statin therapy in relation to myocardial ischemia, troponin T release and clinical cardiac outcome in patients undergoing major vascular surgery

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Intensity of statin therapy in relation to myocardial ischemia, troponin T release and clinical cardiac outcome in patients undergoing major vascular surgery

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Objectives: To examine whether higher statin doses and lower low-density lipoprotein (LDL)-cholesterol are associated with improved cardiac outcome in vascular surgery patients.

Background: Statins may have cardioprotective effects during major vascular surgery.

Methods: In a prospective study of 359 vascular surgery patients, statin dose and cholesterol levels were recorded preoperatively. Myocardial ischemia and heart rate variability were assessed by 72-hour 12-lead electrocardiography starting 1 day before to 2 days after surgery. Troponin T was measured on postoperative day 1, 3, 7 and before discharge. Cardiac events included cardiac death or non-fatal Q-wave myocardial infarction at 30 days and follow-up (mean: 2.3 years).

Results: Perioperative myocardial ischemia, troponin T release, 30-day and late cardiac events occurred in 29%, 23%, 4% and 18%, respectively. In multivariate analysis, lower LDL-cholesterol (per 10 mg/dL) correlated with lower myocardial ischemia (OR: 0.87, 95% CI: 0.80-0.95), troponin T release (OR: 0.89, 95% CI: 0.82-0.96), 30-day (OR: 0.89, 95% CI: 0.78-1.00) and late cardiac events (HR: 0.91, 95% CI: 0.84-0.96). Higher statin doses (per 10% of maximum recommended dose) correlated with lower myocardial ischemia (OR: 0.85, 95% CI: 0.76-0.93), troponin T release (OR: 0.84, 95% CI: 0.76-0.93), 30-day (OR: 0.62, 95% CI: 0.40-0.96) and late cardiac events (HR: 0.76, 95% CI: 0.65-0.89), even after adjusting for LDL-cholesterol. Significantly higher perioperative heart rate variability was observed in patients with higher statin doses.

Conclusions: Higher statin doses and lower LDL-cholesterol correlate with lower perioperative myocardial ischemia, perioperative troponin T release, 30-day and late cardiac events in major vascular surgery.

IN THE THIRTY MILLION individuals undergoing non-cardiac vascular surgery in the United States annually, cardiac complications remain the leading cause of perioperative morbidity and mortality. A pooled analysis found an incidence of 6.2% (range: 2.2% to 19.0%) for the composite endpoint of perioperative myocardial infarction or cardiac death in unselected patients >40 years of age [1]. Ischemic myocardial injury also remains a common complication, which is observed in up to 41% of patients as detected by continuous 12-lead electrocardiographic monitoring and in up to 25% of patients as detected by elevated troponin T levels [2]. During recent years, HMG-CoA reductase inhibitors (statins) have emerged as promising cardioprotective drugs in the primary prevention of cardiac events and mortality in patients undergoing major vascular surgery [3,4,5].

Although studies showed that lower cholesterol levels are associated with improved outcome, optimal cholesterol levels in patients scheduled for major vascular surgery are not well known [6]. The main effect of statins is believed to be a reduction in cholesterol levels which attenuates the atherosclerotic process, however, statins may also have effects beyond its lipid-lowering properties [7]. Controversy exists whether statins have a positive effect on the cardiac autonomous nervous system [8]. Since decreased heart rate variability may trigger ischemic events, an improvement of heart rate variability by statins may be a potential mechanism of cardioprotection [9].

The current prospective study was conducted to clarify the following: 1) are higher statin doses and

lower cholesterol levels associated with reduced myocardial compromise on subclinical level, i.e. myocardial ischemia assessed with continuous 12-lead electrocardiographic monitoring and troponin T release, 2) are higher statin doses and lower cholesterol levels associated with improved clinical cardiac outcome, 3) are statins cardioprotective independent of cholesterol levels, 4) are statins associated with perioperative heart rate variability.

METHODS

Patients

The study population consisted of 359 patients undergoing elective abdominal aortic aneurysm repair (n=175), peripheral artery bypass surgery (n=127) and carotid artery surgery (n=57) at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period 2002 to 2006. The study was approved by the hospital's ethical committee and performed with informed consent of all patients. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block and atrial fibrillation were excluded. No patient presented with a myocardial infarction within 6 months prior to surgery Patients who participated in clinical intervention trials at or outside the Erasmus MC (i.e. the DECREASE-II, III and V trial) were also excluded. Patients were enrolled up to 3 months prior to surgery at the outpatient clinic. At study enrolment, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure ≥140/90 mmHg), diabetes (fasting glucose ≥7.0 mmol/L, or insulin therapy), renal failure (serum creatinine ≥ 2.0 mg/dL (177 μmol/L)), smoking and a history of cerebrovascular events. In all patients, beta-blockers were considered prior to surgery to obtain perioperative heart rates of 60-65 beats per minute.

Dobutamine stress echocardiography

Before surgery, all patients underwent dobutamine stress echocardiography for the assessment of coronary artery disease. Dobutamine stress echocardiography was performed according to established protocols. The left ventricle was divided into 17 segments and wall motion was scored on a 5-point scale (a score of 1 indicating normal, 2 mild hypokinesis, 3 severe hypokinesis, 4 akinesis, and 5 dyskinesis). The results were considered positive if wall motion in any segment decreased by ≥1 grades during testing. Patients with positive dobutamine stress echocardiography results were referred for further cardiac management. It was not standard policy to perform prophylactic preoperative coronary artery revascularization in patients with stress-induced ischemia, with the exception of patients in whom results were suggestive for left main stenosis.

Statin dose and cholesterol measurements

Type, dose and duration of statins were noted at enrolment in all statin users. The dose of statin therapy was converted to the percentage of maximum recommended therapeutic dose (MRTD) according to the FDA's Center for Drug Evaluation and Research database [10]. The MRTD for simvastatin, pravastatin and fluvastatin was 0.667 mg/kg/day. A MRTD of 0.333 mg/kg/day was used for atorvastatin and rosuvastatin. The duration of statin therapy was calculated from time of prescription to time of surgery. Long-term statin therapy was defined as statin treatment ≥3 months prior to surgery. All patients who presented with hypercholesterolemia at enrolment (plasma LDL-cholesterol >200 mg/dL) received statins. After 2003, LDL-cholesterol levels were targeted to levels less than 100 mg/dL. During the study period, high-risk surgery has not been a standard indication for statin treatment. Patients continued statin treatment after hospital discharge. Cholesterol levels were measured at enrolment and 1 day prior to surgery. For the current analysis, measurements obtained at the day before surgery were used. Measurements were obtained with an automated enzymatic method and included low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides and total cholesterol.

Assessment of perioperative myocardial ischemia

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts), starting 1 day before surgery up to 2 days after. Recordings were performed in the continuous 12-lead mode with a recording length of 10 seconds every minute. The frequency response was 0.05 – 150Hz. Electrocardiographic data were initially processed by a technician and analyzed by 2 experienced cardiologists who were blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the ambulatory electrocardiography recordings were analyzed for ST-segment deviations. A continuous ST segment trend was generated and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST-segment changes, lasting at least one minute and shifting from baseline to more than 0.1 mV (1 mm). The baseline ST segment level was defined as the average ST segment during a stable period (duration of 20 minutes) preceding each ischemic episode. ST segment change was measured 60 ms after the J point. If the J point fell

Table 1. Baseline characteristics of the study population according to statin therapy (n=359).

Characteristic	Statins (n=187)	No statins (n=172)	p-value
Age (years)	66 ± 10	67 ± 10	0.8
Male gender	141 (75.4)	143 (83.1)	0.07
Angina pectoris	35 (18.7)	27 (15.7)	0.5
History of myocardial infarction	68 (36.4)	68 (39.5)	0.5
Previous coronary revascularization	33 (17.6)	21 (12.2)	0.2
History of congestive heart failure	9 (4.8)	5 (2.9)	0.4
History of cerebrovascular event	64 (34.2)	33 (19.2)	0.001
Renal failure	11 (5.9)	6 (3.5)	0.3
Diabetes	30 (16.0)	25 (14.5)	0.7
Hypertension	87 (46.5)	59 (34.4)	0.02
Hypercholesterolemia	107 (57.2)	22 (12.8)	<0.001
Current or past smoking	113 (60.4)	105 (61.0)	1.0
Aspirin	102 (54.5)	93 (54.1)	1.0
Angiotensin-converting enzyme inhibitors	52 (27.8)	40 (23.3)	0.4
β-Blockers	139 (74.3)	124 (72.7)	0.8
Calcium channel blockers	45 (24.1)	49 (28.5)	0.3
Stress-induced myocardial ischemia	36 (19.3)	42 (24.4)	0.2
Low-density lipoprotein cholesterol	106 ± 38	136 ± 43	<0.001
High-density lipoprotein cholesterol	50 ± 16	45 ± 17	0.02
Triglycerides	152 ± 71	190 ± 101	<0.001
Total cholesterol	175 ± 42	212 ± 51	<0.001

Values are expressed as mean (± SD) or number (%).

within the T-wave, the ST segment change was measured 40 ms after that point.

Assessment of perioperative troponin T release

Troponin T levels were measured on postoperative day 1, 3, 7, before discharge and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The recommended lower limit of 0.03 ng/ml was used to define positive troponin T levels since lower levels do not meet the imprecision criteria of <10%.

Clinical cardiac outcome

Study endpoints were major cardiac events (cardiac death and non-fatal Q-wave myocardial infarction) during the perioperative period (30-day period after surgery) and during follow-up (mean: 2.3 years). During follow-up, outpatient visits were scheduled every 3 months after discharge. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. Non-fatal myocardial infarction was diagnosed when at least the following were present: elevated cardiac enzyme levels, development of new Q waves (>1 mm or > 30 ms), and typical symptoms of angina pectoris. No patients were lost to follow-up.

Assessment of perioperative heart rate variability

Heart rate variability was computed for each subject using time-domain analysis of short-term 5-minute preoperative, intraoperative and postoperative recordings. Consecutive 5-minute recordings of 2-hour periods were obtained in a standard fashion at the evening before surgery, during the first 2-hours of surgery and at the second evening after surgery. The average heart rate variability of the 5-minute recordings during the 2-hour period was calculated. We used standard time domain measures including the standard deviation of the normal-to-normal (NN) intervals (SDNN) and the square root of the mean squared differences of successive NN intervals (rMSSD). The standard deviation of the average NN intervals (SDANN) and the mean of the 5-minute standard deviations (SDNN index) were also calculated for the first 24-hour recording. This 24-hour recording started at the evening prior to surgery and included night time and surgical period.

Statistical analysis

Continuous data were compared using the Student t test and categorical data were analyzed using the chi-square test with Yates' correction. Binary logistic regression analysis was used to evaluate the association of statin dose and cholesterol levels on perioperative myocardial ischemia, troponin T release and 30-day clinical cardiac outcome. Cox proportional hazard analysis was used to assess the association of statin dose and cholesterol levels with late cardiac events. Propensity analysis is a reliable tool to correct for selection bias [11]. A propensity score for statin therapy was calculated, which was constructed using multiple logistic regression analysis. In multivariate analysis, adjustments were made for age, gender, coronary artery disease

(according to medical history or stress test results), history of congestive heart failure, cerebrovascular disease, diabetes, renal failure, hypertension, type of surgery, cardiovascular medication (beta-blockers, aspirin, angiotensin-converting enzyme inhibitors and calcium-channel blockers) and propensity scores. Analysis of variance (ANOVA) techniques were used to compare heart rate variability between groups of patients with different statin doses. Tests for heterogeneity were used to reveal a differential effect of statins between patients with or without perioperative myocardial ischemia and/or troponin T release. Odds and hazard ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (two-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics

The mean age of the study population was 67 ± 10 years and 79% were male. A total of 187 (52%) patients received statin therapy. The following statins were used: simvastatin in 54, pravastatin in 42, fluvastatin in 35, atorvastatin in 49 and rosuvastatin in 7 patients. Long-term statin therapy was recorded in 150 patients (42%). Statins were newly prescribed in 37 patients (10%). The mean dose of statins was 41 ± 32% of MRTD. Patients with statins more frequently had a history of cerebrovascular events, hypertension and hypercholesterolemia, as compared to patients without statins (Table 1). Propensity analysis demonstrated that patients were more likely to have statins if they had a history of cerebrovascular events (p<0.001) and hypercholesterolemia (p<0.001). Propensity score ranged from 0.11 to 0.94. No differences in coronary artery disease, renal failure, diabetes, smoking and dobutamine stress test results were observed between the two groups.

Statin dose and cholesterol levels in relation to myocardial ischemia

A total of 187 ischemic episodes in 103 patients (29%) were detected during continuous 72-hour 12-lead electrocardiography. The median duration of an ischemic episode was 72 minutes (interquartile range: 49-235 minutes). The median ST-segment deviation was 1.4 mm (interquartile range: 1.0-2.4 mm). The highest incidence of myocardial ischemia was detected in patients undergoing abdominal aortic repair (34%), followed by patients with lower extremity bypass surgery (25%) and carotid surgery (19%) (p=0.003). Univariate (Figure 1 and 2, Table 2) and multivariate

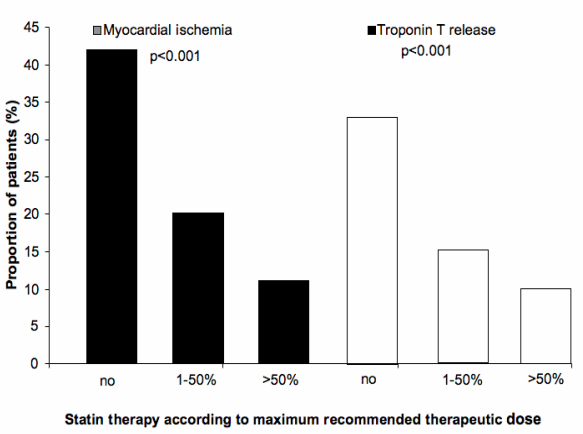

Figure 1. Incidence of myocardial ischemia and troponin T release. The lowest incidence of myocardial ischemia and troponin T release in the perioperative period was observed in patients with statin doses of more than 50% of the maximum recommended therapeutic dose.

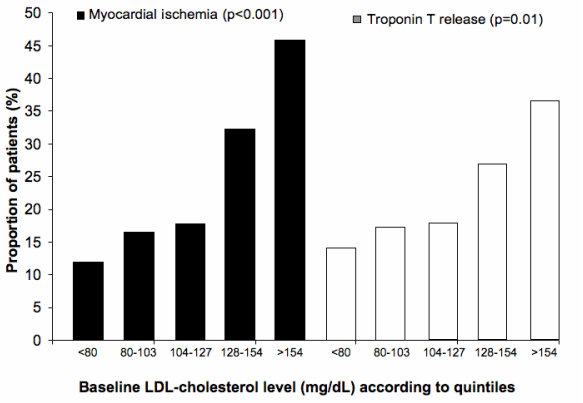

Figure 2. Incidence of myocardial ischemia and troponin T release. The incidence of myocardial ischemia and troponine T release in the perioperative period was lowest in patients with baseline low-density lipoprotein (LDL)-cholesterol levels below 80 mg/dL.

analysis (Table 2) revealed that higher statin doses and lower LDL-cholesterol levels were both significantly associated with a lower incidence of myocardial ischemia. Higher statin doses remained significantly associated with a lower incidence of perioperative myocardial ischemia, after adjusting for baseline cholesterol levels (Table 2).

Statin dose and cholesterol levels in relation to troponin T release

Troponin T release was detected in 83 patients (23%). The median troponin T value was 0.5 ng/ml (interquartile range 0.1-0.8 ng/ml). The highest incidence of troponin T release was observed in patients undergoing abdominal aortic repair (29%), followed by

Table 2. Statin therapy in relation to perioperative ischemia and troponin T release in patients undergoing major vascular surgery.

Characteristic	Perioperative myocardial ischemia (n=103) OR (95% CI)		Perioperative troponin T release (n=83) OR (95% CI)	
	Univariate	Multivariate*	Univariate	Multivariate*
Statins				
Statin therapy (n=187)	0.29 (0.17-0.47)	0.33 (0.18-0.60)	0.33 (0.19-0.55)	0.24 (0.12-0.47)
Statin treatment <3 months† (n=37)	0.22 (0.08-0.58)	0.52 (0.13-2.03)	0.25 (0.08-0.72)	0.75 (0.19-2.96)
Statin treatment ≥3 months† (n=150)	0.31 (0.18-0.51)	0.30 (0.17-0.53)	0.35 (0.18-0.62)	0.32 (0.17-0.59)
Statin dose per 10% increase of MRTD	0.82 (0.75-0.89)	0.85 (0.76-0.93)	0.85 (0.77-0.94)	0.84 (0.76-0.93)
Statin dose per 10% increase of MRTD (with adjustment for baseline LDL-cholesterol)	0.87 (0.80-0.95)	0.88 (0.80-0.96)	0.90 (0.81-0.98)	0.87 (0.79-0.95)
Level of baseline cholesterol*				
LDL-cholesterol (per 10 mg/dL decrease)	0.89 (0.83-0.96)	0.87 (0.80-0.95)	0.93 (0.87-1.00)	0.89 (0.82-0.96)
HDL-cholesterol (per 10 mg/dL decrease)	1.07 (0.91-1.25)	1.06 (0.88-1.28)	1.14 (0.95-1.37)	1.19 (0.96-1.47)
Triglycerides (per 10 mg/dL decrease)	0.96 (0.93-0.99)	0.96 (0.93-0.98)	0.96 (0.93-0.98)	0.95 (0.93-0.98)
Total cholesterol (per 10 mg/dL decrease)	0.87 (0.83-0.93)	0.86 (0.81-0.91)	0.93 (0.87-0.98)	0.91 (0.85-0.96)

* Adjusted for age, gender, coronary artery disease (according to medical history or stress test results), history of congestive heart failure, cerebrovascular disease, diabetes, renal failure, hypertension, type of surgery and cardiovascular medication (beta-blockers, aspirin, angiotensin-converting enzyme inhibitors and calcium-channel blockers) and propensity scores.
† In comparison to patients with no statin treatment
‡ No perioperative major cardiac events occurred in patients with statin treatment <3 months.
MRTD = maximum recommended therapeutic dose.

Table 3. Statin therapy in relation to perioperative and late cardiac outcome in patients undergoing major vascular surgery..

Characteristic	Perioperative cardiac death or non-fatal Q-wave myocardial infarction (n=15) OR (95% CI)		Late cardiac death or non-fatal Q-wave myocardial infarction (n=64) HR (95% CI)	
	Univariate	Multivariate*	Univariate	Multivariate*
Statins				
Statin therapy (n=187)	0.31 (0.10-0.96)	0.32 (0.10-0.96)	0.42 (0.23-0.77)	0.41 (0.21-0.75)
Statin treatment <3 months† (n=37)	‡	‡	0.75 (0.02-3.22)	0.81 (0.05-4.15)
Statin treatment ≥3 months† (n=150)	0.24 (0.05-0.98)	0.25 (0.06-0.97)	0.50 (0.28-0.90)	0.52 (0.29-0.93)
Statin dose per 10% increase of MRTD	0.60 (0.39-0.95)	0.62 (0.40-0.96)	0.75 (0.64-0.89)	0.76 (0.65-0.89)
Statin dose per 10% increase of MRTD (with adjustment for baseline LDL-cholesterol)	0.60 (0.37-0.95)	0.66 (0.42-0.98)	0.78 (0.65-0.96)	0.80 (0.67-0.94)
Level of baseline cholesterol*				
LDL-cholesterol (per 10 mg/dL decrease)	0.86 (0.76-0.98)	0.89 (0.78-1.00)	0.93 (0.86-0.99)	0.91 (0.84-0.96)
HDL-cholesterol (per 10 mg/dL decrease)	1.05 (0.69-1.55)	1.10 (0.72-1.70)	0.92 (0.78-1.09)	1.05 (0.87-1.24)
Triglycerides (per 10 mg/dL decrease)	1.01 (0.93-1.08)	1.01 (0.93-1.08)	0.99 (0.97-1.02)	1.01 (0.97-1.03)
Total cholesterol (per 10 mg/dL decrease)	0.98 (0.87-1.12)	0.95 (0.85-1.07)	0.94 (0.90-1.01)	0.94 (0.88-1.00)

* Adjusted for age, gender, coronary artery disease (according to medical history or stress test results), history of congestive heart failure, cerebrovascular disease, diabetes, renal failure, hypertension, type of surgery and cardiovascular medication (beta-blockers, aspirin, angiotensin-converting enzyme inhibitors and calcium-channel blockers) and propensity scores.
† In comparison to patients with no statin treatment
‡ No perioperative major cardiac events occurred in patients with statin treatment <3 months.
MRTD = maximum recommended therapeutic dose.

patients with lower extremity bypass surgery (22%) and carotid surgery (9%) ($p<0.001$). Univariate (Figure 1, Table 2) and multivariate analysis (Table 2) revealed that higher statin doses and lower LDL-cholesterol levels were both significantly associated with a lower incidence of troponin T release. Higher statin doses remained significantly associated with a lower incidence of troponin T release, irrespective of baseline cholesterol levels (Table 2).

Statin dose and cholesterol levels in relation to clinical cardiac outcome

Perioperative cardiac death and non-fatal Q-wave myocardial infarction occurred in 3% and 1% of patients, respectively. Late cardiac death and non-fatal Q-wave myocardial infarction occurred in 13% and 5% of patients, respectively. During follow-up, statins were discontinued in 2 patients (1%) due to side effects (myopathy in one patient and nausea and/or diarrhea in another). In multivariate analysis, higher statin doses and lower LDL-cholesterol levels were both significantly associated with a lower incidence of 30-day and late cardiac events (Table 3). Higher statin doses remained significantly associated with lower 30-day and late cardiac events, after adjusting for absolute baseline cholesterol levels. In subgroup analysis, the long-term benefit of statin therapy was also comparable between patients with and myocardial ischemia and/or troponin T release (p for interaction: 0.92)

Table 4. The association between heart rate variability and statin therapy.

Characteristic	Statins >50% of MRTD (n=53)	Statins 1-50% of MRTD (n=134)	No statins (n=172)	p-value
Prior to surgery				
SDNN (ms)	52 ± 29	48 ± 28	37 ± 19	<0.001
rMSSD (ms)	40 ± 35	36 ± 31	28 ± 22	0.01
Heart rate (bpm)	68 ± 11	67 ± 12	68 ± 12	0.7
During surgery				
SDNN (ms)	39 ± 27	32 ± 21	29 ± 19	0.002
rMSSD (ms)	32 ± 31	26 ± 19	25 ± 23	0.06
Heart rate (bpm)	73 ± 13	71 ± 14	72 ± 13	0.4
After surgery				
SDNN (ms)	48 ± 45	39 ± 24	36 ± 31	0.04
rMSSD (ms)	34 ± 32	33 ± 30	29 ± 28	0.1
Heart rate (bpm)	76 ± 13	77 ± 14	77 ± 14	0.8
First 24-hour recording				
SDNN (ms)	139 ± 44	131 ± 45	119 ± 42	<0.001
SDANN (ms)	116 ± 39	114 ± 39	88 ± 30	<0.001
SDNN index (ms)	47 ± 28	40 ± 18	38± 17	0.002
rMSSD (ms)	53 ± 47	49 ± 29	50 ± 37	0.3
Heart rate (bpm)	72 ± 12	72 ± 13	72 ± 13	0.9

MRTD = maximum recommended therapeutic dose. SDANN = standard deviation of the average normal-to-normal intervals. SDNN = standard deviation of the normal-to-normal intervals. rMSSD = square root of the mean squared differences of successive normal-to-normal intervals.

Statins and heart rate variability

Heart rate variability was highest before and lowest during surgery (SNDD: 47±28, 34 ±23 and 39±29 ms before, during and after surgery, respectively (p=0.007)). We found that lower heart rate variability prior to surgery (SDNN per 10 ms decrease) significantly predicted myocardial ischemia during or after surgery (OR: 1.59, 95% CI: 1.19-2.13) and troponin T release after surgery (OR: 1.54, 95% CI: 1.17-2.01). Lower heart rate variability during surgery (SDNN per 10 ms decrease) also significantly predicted myocardial ischemia after surgery (OR: 1.71, 95% CI: 1.14-2.57) and troponin T release after surgery (OR: 1.55, 95% CI: 1.13-2.11). Higher statin doses correlated significantly with higher SDNN prior to, during and after surgery (Table 4).

DISCUSSION

This study found that higher statin doses and lower LDL-cholesterol levels were both significantly associated with a lower incidence of perioperative myocardial ischemia, perioperative troponin T release and 30-day and late cardiac events in patients undergoing major vascular surgery. Higher statin doses remained significantly associated with improved cardiac outcome, irrespective of baseline cholesterol levels. Higher statin doses also correlated significantly with higher perioperative heart rate variability. These results suggest that statins are cardioprotective on clinical and subclinical level and that they should be considered in all patients undergoing major vascular surgery.

Statins and myocardial ischemia

The association between statin treatment and temporarily or prolonged myocardial ischemia is not well known. Myocardial ischemia in the perioperative setting may arise either from increased myocardial oxygen demand or reduced supply. Factors that increase myocardial oxygen demand are mainly tachycardia and hypertension resulting from surgical stress, postoperative pain, interruption of β-blocker use, or the use of sympathomimetic drugs. In contrast, decreased supply may be the result of hypotension, vasospasm, anemia, hypoxia, or coronary artery plaque rupture. Experimental animal studies have demonstrated that administration of statins before induction of myocardial ischemia improved myocardial viability, reduced the extent of inflammatory cell accumulation in the ischemic myocardium and preserved coronary blood flow which was attributed to a reduction in adhesion molecule expression of the endothelial monolayer and to an increase in the bioavailability of nitric oxide [12]. The results of the current study support the view that myocardial ischemia is not only limited by cholesterol-lowering properties of statin therapy, but also by potential mechanisms such as endothelial function improvement and increase in nitric oxide with preservation of coronary blood flow [13].

Statins and clinical cardiac outcome

Large trials have consistently demonstrated that statins reduce cardiovascular morbidity and mortality in high-risk patients [14,15,16,17]. Marked reductions in perioperative cardiovascular events have also been demonstrated in patients undergoing major vascular surgery [3,4,5]. The reduction of acute thrombotic events may be explained by atherosclerotic plaque attenuation and stabilization. Intensive statin therapy can result in significant regression of atherosclerosis as demonstrated in the ASTEROID trial [18]. In human carotid plaques, statins have been demonstrated to decrease lipids, lipid oxidation, inflammation, matrix metalloproteinase-2 and cell death and increase tissue inhibitor of metalloproteinase 1 and collagen [7]. According to the current results, every 10 mg/dL reduction in baseline LDL-cholesterol was significantly associated with a 13% lower risk of perioperative cardiac events. Moreover, a sustained beneficial effect

of high-dose statins and low LDL-cholesterol levels was observed for late cardiac events.

Statins and heart rate variability

Reduced heart rate variability during surgery is most probably the result of anesthetic agents and can be a sign of increased sympathetic or reduced vagal activity. Reduced heart rate variability has been associated with sudden, arrhythmic, cardiovascular and non-cardiovascular mortality in many studies. A recent study demonstrated that a temporal decrease in heart rate variability, i.e. vagal withdrawal, can act as a precipitating factor for myocardial ischemia [9]. High frequency components of heart rate variability showed a consistent decrease prior to an ischemic event and prior to the electrocardiographic appearance suggestive of coronary spasm [9]. We also observed that lower heart rate variability in the period preceding myocardial ischemia and troponin T release significantly predicted its occurrence in the period after this measurement. The beneficial effect of statins on autonomic function has been suggested in previously published studies [8,19,20]. Our results demonstrated that higher statin doses were significantly associated with higher SDNN. Heart rate, a determinant of heart rate variability, was similar between patients with different statin doses. These observations generate the hypothesis that in situations of decreased heart rate variability and increased myocardial oxygen demand, statins may exert an anti-ischemic effect by modulating the autonomic nervous system.

Clinical implications

An important observation in this study was that statins were only prescribed in 52% of patients. This reflects the need for evidence supporting the benefit of statin treatment in patients undergoing major vascular surgery and the need for awareness among physicians. Statins have not yet been recommended as perioperative medical treatment by the American College of Cardiology/American Heart Association [21]. Coronary atherosclerosis is highly prevalent among patients undergoing major vascular surgery, with angiographic coronary abnormalities observed in up to 92% of patients [22]. Surgery poses the patient at additional increased risk of perioperative events [23]. Therefore, the recommendations to achieve LDL cholesterol levels<100 mg/dL in people with (risk equivalents of) coronary artery disease according to the guidelines of the National Cholesterol Education Program Adult Treatment Panel III and the European guidelines on cardiovascular disease prevention in clinical practice should be extrapolated to patients undergoing major vascular surgery [24,25]. The current study further provides evidence that additional risk reduction can be achieved by achieving LDL cholesterol levels <80 mg/dL.

Limitations

Several limitations should be addressed. In this observational study, statins were not assigned randomly, however, the two groups were comparable in demographics and cardioprotective drugs. In addition, multivariate analysis and propensity scores were used to adjust for possible confounding factors. Second, the results apply to patients undergoing major non-cardiac vascular surgery, and our findings may not be generalized to patients undergoing general or low-risk surgery. Third, a lower cut-off level of 0.03 ng/ml was used to define positive troponin T levels. Lower troponin T levels were not used, since they do not meet the imprecision criteria (coefficient of variation) of <10%. Finally, carotid artery surgery has been associated with heart rate changed secondary to baroreceptor reflexes. The inclusion of these patients may potentially have confounded the heart rate variability results.

In conclusion, higher statin doses are lower LDL-cholesterol levels were both significantly associated with lower a lower incidence of perioperative myocardial ischemia during continuous 12-lead electrocardiographic monitoring, perioperative troponin T release, and 30-day and late cardiac events. Analysis of the 72-hour 12-lead electrocardiographic recordings further showed that perioperative heart rate variability was significantly higher in patients with higher statin doses. These results suggest that statins are cardioprotective on clinical and subclinical level.

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Chapter 26

Perioperative management and risk factor control in elderly patients undergoing major non-cardiac surgery

European Vascular Course. 2006;33-44

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Perioperative management and risk factor control in elderly patients undergoing major non-cardiac surgery

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Introduction

Cardiovascular diseases, including coronary artery disease, cerebrovascular disease, and peripheral arterial disease are the leading cause of morbidity and mortality in all age groups. However, its toll is heaviest among the elderly. Age is an important risk factor for cardiovascular disease, especially because pathophysiological mechanisms, such as atherosclerosis, are superimposed on the age-related degeneration of cardiovascular structures. Although age is considered to be a minor predictor of adverse postoperative outcome in patients undergoing major vascular surgery [1], elderly patients often presents with extensive co-morbidity and the surgeon is faced with the challenge to choose the optimal treatment strategy for the older individual. In this article, we will first discuss the growing problem of cardiovascular disease in the elderly and the association between age and atherosclerosis. Thereafter, the pre-operative screening possibilities to identify elderly patients who are at increased risk for adverse postoperative events and the different options of perioperative management, which may be used in the elderly to improve their perioperative and long-term prognosis will be discussed. Finally, we discuss some important issues in risk factor control and life-style modification in elderly (non-)surgical patients for long-term mortality reduction.

Cardiovascular disease in the elderly: A growing problem

Cardiovascular disease is the leading cause of mortality for both men and women among all racial and ethnic groups in industrialised countries, accounting for over 40% of deaths in those aged 35 years and older [2]. More than 80% of deaths attributed to cardiovascular disease occur in people over the age of 65 years. The elderly is a rapidly growing population in industrialized and less industrialized countries. It is estimated that in the second half of the 21st century, more than one in four individuals will be 65 years of age or older. In parallel, cardiovascular disease may reach epidemic proportions. It is expected that morbidity and mortality from cardiovascular disease, together with degenerative cognitive dysfunction and physical disability, which are more prevalent among the elderly, will account for a substantially increased burden for community healthcare and social services.
During the last decades, however, the mortality rate for cardiovascular disease has progressively decreased in industrialised countries. Preventive strategies, risk factor modifications, and improvement in the diagnosis and treatment of atherosclerosis may have contributed to this trend.
In the past, major non-cardiac surgery was rarely performed on patients in their eighties or nineties. Nowadays, many major surgical interventions are performed in this very elderly population. Pre-operative risk assessment is therefore warranted in elderly patients to facilitate decision-making about major surgery, and to identify those at increased risk for postoperative adverse events, who might benefit from preventive treatment strategies.

Should we concern about elderly patients undergoing major vascular surgery?

Many studies have demonstrated that the frequency of perioperative complications increases with age [3,4]. This finding may be attributed to the prevalence of co-morbidities, such as atherosclerosis, that increases with increasing chronological age. However, even in the absence of confounding influences of disease, advanced age itself may be an independent risk factor. An age-dependent increase in central arterial stiffness, independent of blood pressure and other risk factors, has

been confirmed in several studies [5]. A pathophysiological explanation for this may be mechanical fracture and fragmentation of elastin fibers after repetitive stress cycles, resulting in progressive fibrosis of the arterial wall and arterial stiffening. In addition, intimal and medial thickening, the occurrence of elastic lamina discontinuities due to elastin degradation, and deviations in the morphologic orientation of smooth muscular cells, have been demonstrated to be typical age-associated changes in large arteries [6]. These age-related changes are similar to underlying mechanisms that lead to atherosclerosis. Atherosclerosis is characterized by stiffening of the intimal and medial layers of arteries and plaque formation within the inner wall of the artery. Rupture of the plaque, with subsequent thrombosis and vessel occlusion causes significant cardiovascular morbidity and mortality. In addition to vascular changes, advanced age is associated with a general decline in cardiac function and with diminished cardiac reserve in times of increased cardiovascular stress [6]. Thus, age-related cardiovascular changes, in combination with the increased prevalence and severity of risk factors in the elderly population, probably explain the increased incidence of (perioperative) mortality in this segment of the population. The primary and secondary prevention of cardiovascular disease is the cornerstone of reducing mortality in the elderly population and in elderly patients undergoing major non-cardiac surgery.

Preoperative risk stratification in elderly patients scheduled for major noncardiac surgery

Cardiac complications, such as myocardial infarction and congestive heart failure are the major cause of perioperative mortality in elderly patients undergoing major non-cardiac surgery. Pre-operative risk stratification should be based on the identification of risk factors for perioperative morbidity and mortality. High-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine >2.0 mg/dL have been identified as independent predictors of adverse perioperative events in the surgical population [7,8]. Advanced age has not been identified as an independent predictor. Moreover, current practice guidelines for perioperative cardiovascular evaluation by the American College of Cardiology and the American Heart Association (ACC/AHA) have listed age as a minor clinical predictor of perioperative cardiovascular risk [1]. In addition, several studies have demonstrated relative low perioperative complication rates in the elderly, although the overall frequency of perioperative complications is increased [9-11]. Thus, the preoperative evaluation and perioperative management of the elderly patient should be directed by the presence and extent of possible co-morbidity, such as coronary artery disease, renal dysfunction, diabetes mellitus, and aortic valve stenosis. Aortic valve stenosis has been recognized as a major independent risk factor for perioperative cardiac events in patients undergoing non-cardiac surgery [7,12]. In a study by Kertai et al., patients with aortic valve stenosis had a 5-fold increased risk of perioperative complications, in comparison to patients without aortic stenosis [12]. Although several studies have reported promising results and low postoperative event rates in selected patients with aortic valve stenosis undergoing noncardiac surgery [13,14], aortic valve replacement prior to non-cardiac surgery is recommended with indications similar to those in the non-preoperative setting [1]. Aortic valve sclerosis is common in the elderly and it has the potential to progress to clinically significant aortic valve stenosis. Recently, it has been demonstrated that aortic valve sclerosis, even in the absence of hemodynamically significant obstruction of left ventricular outflow, is associated with an increased risk of cardiovascular death in patients 65 years of age or older [15]. Preoperative assessment of the aortic valve may especially be beneficial in the elderly, and future studies are needed to identify aortic valve sclerosis as possible independent risk factor for adverse postoperative cardiac events.
The stepwise approach to preoperative cardiac assessment, as suggested by the ACC/AHA practice guidelines, include history, physical examination and electrocardiographic assessment to assess age, functional capacity, and type of surgery and to identify potentially serious cardiac disorders and co-morbid conditions [1]. Recommendations for supplemental preoperative evaluations have to be individualized to the specific patient and may include one or more of the following: echocardiography (assessment of resting left ventricular function and aortic valve), exercise or pharmacologic stress testing, ambulatory electrocardiographic monitoring, and coronary angiography [1].

Perioperative medical treatment possibilities

Perioperative medical treatment in the elderly is aimed at reducing the incidence of postoperative cardiac complications. Medical treatment possibilities include the use of β-blockers, α-2-adrenergic agonists, statins, calcium channel blockers and myocardial revascularization.

Beta-blockers

Beta-blockers are established therapeutic agents for hypertension, coronary artery disease, and heart failure, since they improve the prognosis in these patients. The mechanism by which β-blockers exert their cardioprotective effect remains not completely understood, but proposed mechanisms include the following: reduction in heart rate and contractility and restoration of the myocardial oxygen supply-demand balance, prolongation of coronary diastolic filling time, anti-arrhythmic properties, anti-renin/angiotensin properties, and inhibition of catecholamine induced cardiac necrosis (apoptosis) [16,17]. Randomized, placebo-controlled trials have demonstrated that patients who are at risk for coronary artery disease and who undergo major vascular surgery benefit from perioperative β-blocker therapy in terms of reduced postoperative morbidity and mortality [18,19]. Observational studies in elderly patients undergoing non-cardiac surgery show consistent findings and show that β-blockers reduce the incidence of perioperative myocardial infarction [20]. Therefore, β-blockers are now recommended by the ACC/AHA in patients undergoing major vascular surgery, who are at increased risk for postoperative adverse events, based on the finding of ischemia on preoperative testing.

Serious side effects of β-blockers are bradycardia, hypotension, dyspnoea and (worsening of) intermittent claudication. Physicians have been reluctant in prescribing β-blockers to patients with presumed contraindications to their use, especially to elderly patients and patients with impaired left ventricular function, transient heart failure, and chronic obstructive pulmonary disease [21]. However, these patients may derive the greatest benefit from β-blocker therapy, as has been demonstrated in a recent study in which β-blockers had significant benefit in patients who had a myocardial infarction and who presented with presumed contraindications to β-blocker use (elderly, heart failure, pulmonary disease) [22].

Alpha-2-adrenergic agonists

Alpha-2-adrenergic agonists are used for the treatment of hypertension, migraine, for the suppression of autonomically mediated signs and symptoms in opioid withdrawal, and as anesthetic premedication, providing sedative, anxiolytic, and analgesic effects. These drugs prevent tachycardia and hypertension and have both sympatholytic and anti-ischemic properties. It was therefore proposed that these drugs might be beneficial in perioperative cardiac protection. In a randomized, placebo-controlled, double blind study, the Multicenter Study of Perioperative Ischemia European Study Group evaluated the safety and efficacy of mivazerol hydrochloride in patients with coronary artery disease undergoing non-cardiac surgery [23]. Mivazerol has been shown to be relatively safe, and to be associated with a decreased incidence of perioperative tachycardia, hypertension, and myocardial ischemia. However, no differences in perioperative death or myocardial infarction were observed [23]. More recently, the European Mivazerol Trial demonstrated no differences in perioperative cardiac death or myocardial infarction in patients with coronary artery disease undergoing non-cardiac surgery [24]. However, in a subgroup of patients with coronary artery disease undergoing major vascular surgery, mivazerol was associated with a significant reduced incidence in perioperative cardiac death and myocardial infarction [24].

Side effects of α-2-adrenergic agonists are bradycardia and hypotension and may limit its use. Although the evidence is conflicting, α-2-adrenergic agonists may be recommended as perioperative medical therapy for perioperative control of hypertension or known coronary artery disease, and may be considered as an alternative therapy in patients with contraindications for perioperative β-blockers [1]. The response of α-2-adrenergic agonists may be different in elderly patients. However, no studies have yet evaluated the safety and efficacy of α-2-adrenergic agonists in elderly patients undergoing major non-cardiac surgery.

Statins

Statins (HMG-CoA reductase inhibitors) are effective drugs for reducing LDL-cholesterol levels and have been shown to reduce cardiac events and improve survival in patients with hypercholesterolemia and/or coronary artery disease [25-29]. In addition to the lipid-lowering effect of statins, the pleiotropic effects of statins, which includes inflammation reduction, reduction in free-radical production in the vascular wall, improvement in endothelial function, and stabilization of atheromatous plaques, may contribute to its beneficial properties [30]. Statins have been associated with a lower perioperative and long-term mortality rate after major non-cardiac vascular surgery [31-34]. In a case-controlled study among patients who underwent major vascular surgery, nonusers were at 4.5-fold increased risk of perioperative mortality, as compared to statin users [31]. A prospective randomized, placebo-controlled trial confirmed that statin use was significantly associated with a reduced incidence of major adverse cardiovascular events up to 6 months after non-cardiac vascular surgery [32]. The long-term beneficial effect of statin use after abdominal aortic surgery was confirmed in a retrospective study, which demonstrated reduced all-cause and cardiovascular mortality during a median follow-up of 4.7 years [33]. The protective effect of statin use has been

demonstrated to be independent of clinical risk factors, β-blocker use, and hypercholesterolemia [33,34].
Side effects of peri-operative statin therapy are elevated serum transaminases, myopathy, rhabdomyolysis, and proteinuria. Analgesia and postoperative pain may mask signs of myopathy, with failure to recognize it, leading to the development of rhabdomyolysis and acute renal failure. Most trials on statin therapy have been published after 2003, and perioperative statin therapy has not (yet) been implemented in clinical guidelines. However, the results from one randomized clinical trial and several retrospective trials provide a condition for general agreement for perioperative statin use. Limited is known about perioperative statin therapy in the elderly population. In a post hoc analysis, tests for heterogeneity showed that perioperative mortality reduction by statins was stronger in patients below the age of 70 years, as compared to patients above 70 years of age [31]. However, statin use in patients above 70 years of age was still associated with a reduced incidence of perioperative mortality (Odds ratio: 0.27, 95% confidence interval: 0.09-0.76). It appears that statin therapy is well tolerated and safe in elderly patients [35,36]. In addition, statins have been shown to reduce the risk of adverse cardiovascular events in elderly high-risk patients [37,38]. Elderly patients, who have a high absolute risk of events, may show the greatest benefit of perioperative statin use.

Calcium-channel blockers
Calcium-channel blockers are used in the treatment of hypertension, and prophylaxis of angina pectoris or coronary artery spasm. Verapamil and diltiazem are also used as antiarrhythmics. Calcium channel blockers block calcium entry into cells of vascular smooth muscle and myocardium. By reducing heart rate, myocardial contractility and blood pressure, calcium channel blockers can reverse the myocardial oxygen supply-demand mismatch. In addition, they dilate coronary arteries in both normal and ischemic myocardium and inhibit coronary artery spasm. A recent meta-analysis reviewed the efficacy of calcium channel blockers during non-cardiac surgery [39]. Eleven studies (1007 patients) were included and it was demonstrated that calcium channel blockers significantly reduced perioperative ischemia and supraventricular tachyarrhythmias in patients undergoing non-cardiac surgery. In a post hoc analysis, diltiazem significantly reduced perioperative ischemia, supraventricular tachyarrhythmias, death and myocardial infarction.
Side effects of calcium channel blockers are ankle edema, flushing, headache, and postural hypotension, and may be more frequently observed in the elderly. Greater reductions in blood pressure usually occur in the elderly, compared with younger patients receiving the same dosages of calcium antagonists. Compared with younger patients, greater heart rate suppression may be seen in older patients treated with verapamil and diltiazem [40]. Future studies are needed to prove the safety and efficacy of calcium channel blockers in elderly patients undergoing major non-cardiac surgery.

Myocardial revascularization
Myocardial revascularization prior to surgery may prevent myocardial ischemia and adverse outcome in patients with significant coronary artery disease, and therefore may be considered in high-risk patients undergoing major non-cardiac surgery. The Coronary Artery Revascularization Prophylaxis trial showed that long-term outcome after elective major vascular surgery was not significantly altered by coronary artery revascularization before surgery in 510 patients with stable coronary artery disease randomly assigned to either revascularization or no revascularization [41]. Although the primary end-point was late mortality, 30-days findings did also not show any differences in mortality or non-fatal myocardial infarction. Therefore, the criteria for coronary revascularization in major vascular surgery patients should be similar to the non-surgical population.

Risk factor control in elderly (non-)surgical patients

It is unclear to what extent the increased frequency of perioperative complications in the elderly is attributed to co-morbidities, or to advanced age itself. Patients with co-morbidities may not only benefit from adequate specific perioperative management, as have been discussed previously, but may also benefit from more general measures, such as adequate control of risk factors and life-style modifications. Lifestyle changes include reduction of overweight, physical activity, dietary modifications (a low-fat, low-cholesterol, and high-fiber diet), cessation of smoking, and blood pressure control. Medical treatment is also efficient for control of risk factors including hypertension, hypercholesterolemia, and diabetes mellitus. Although these measures have not yet been studied specifically for perioperative outcome, it has been demonstrated that functional status (behaviors necessary to maintain daily life and encompassing areas of physical, cognitive, and social functioning) is a strong predictor of 90-day and 2-year mortality after hospitalization [42]. Risk factor control and life-style modification should be considered in (non-)surgical elderly patients for improving long-term survival

Should obesity be treated in the elderly?
The relationship between overweight and mortality in the elderly remains controversial. Higher values of the body mass index have been associated with both increased and decreased mortality rates [43-45]. In a review of 13 studies evaluating the relation between overweight and mortality in the elderly, Heiat et al showed that most studies failed to show a significant association between high body mass index and increased mortality in elderly patients, despite the large number of participants [46]. They demonstrated that current data did not support mild to moderate overweight (body mass index between 25 and 27) to be associated with higher mortality in the elderly. Although some studies demonstrated that body mass index values above 27 were associated with increased mortality, the relative risks were not large. In addition, they demonstrated that higher body mass index values were consistent with a smaller relative mortality risk in elderly persons compared with young and middle-aged populations. The loss of muscle mass and the gain of fat that occurs with aging is called sarcopenia, and has been associated with an increase in mortality. The above mentioned conflicting results may be due to the use of the body mass index as surrogate of body fat, since the body mass index does not account for changes in the body composition. The body mass index also does not account for weight fluctuations over time, for stable weight has been associated with lower mortality rate [47,48]. It has been demonstrated that weight loss is associated with better glucose tolerance and increased insulin sensitivity, and with improvement in blood pressure [49-52]. Therefore, elderly (non-) surgical patients with impaired glucose tolerance or elderly hypertensive patients may indeed benefit from intentional weight loss.

How important is physical activity in the elderly?
Frequent and occasional physical activity decreases the risk of mortality among elderly people [53,54]. Physicians should especially recommend physical activity to sedentary older individuals. Moderate exercise programs suitable for the elderly involve walking, climbing stairs, bicycling or swimming. Cardio-respiratory fitness seems to be more important than the amount of body fat in predicting the risk of mortality. Lee et al have evaluated the separate and joint effects of obesity and cardio-respiratory fitness in a study population of middle-aged men [55]. They demonstrated a higher all-cause and cardiovascular mortality rate in unfit obese individuals, compared to fit lean individuals and a higher all-cause and cardiovascular mortality rate in fit obese individuals, compared to unfit lean individuals. These results still have to be confirmed in elderly (non-)surgical patients. Physical activity is not only important for the reduction of cardiovascular related morbidity and mortality in the elderly, it also has been demonstrated to reduce the risk of morbidity and mortality due to diabetes mellitus, cancer and osteoporosis [56].

Smoking cessation should be encouraged in the elderly
Both nicotine and carbon monoxide harm the cardiovascular system. Autopsy studies have shown an association between cigarette smoking and the presence of coronary atherosclerosis. In addition, cigarette smoking is associated with a decreased serum HDL-C level and acts synergically with other risk factors to increase the risk of cardiovascular disease. Large studies have shown that smoking is a significant risk factory for cardiac and overall death in elderly men and women [57]. In addition, ex-smokers have risks similar to individuals who never smoked, which are significantly lower than risks in individuals who continue smoking [58]. Therefore, elderly (non-)surgical patients should be strongly encouraged to quit smoking.

Dietary modifications – the mediterranean diet
Potential cardiovascular benefits of dietary fibers include effects on serum lipid levels, triglyceride levels and blood pressure. Cereal fiber consumption in the elderly has been associated with a lower incidence of cardiovascular disease. In addition, several studies have demonstrated the beneficial effect of healthy dietary patterns on overall survival [59,60]. The Mediterranean diet may meet the characteristics necessary for beneficial effects on health and survival. Components of the traditional mediterranean diet include high monounsaturated: saturated fat ratio, moderate ethanol consumption, high consumption of legumes, high consumption of cereals, high consumption of fruits, high consumption of vegetables, low consumption of meat and meat products, low consumption of milk and dairy products. Elderly (non-)surgical patients, combining adherence to a Mediterranean diet with life-style modifications (not smoking, physical activity, moderate alcohol consumption), may expect to have more than 50% reduction in all-cause and cause-specific mortality in comparison to those who did not [61].

Diabetes mellitus in the elderly
It is estimated that almost 1 out of 5 elderly individuals have diabetes. Among those with diabetes, approximately 90% have type II diabetes mellitus. It is widely known that diabetes is a powerful predictor of cardiovascular disease. The risk of cardiovascular disease is 2-fold in men, whereas the risk is 5 to 10 fold in women. Obesity and physical inactivity can accelerate the progression of impaired glucose tolerance to disease. A major obstacle in treating patients with

diabetes mellitus and coronary artery disease is that diabetes is undiagnosed in many patients. Cardiovascular progression may accelerate before the onset of diabetes mellitus. In addition, it remains difficult to modify life-style factors involved in the aetiology of diabetes and coronary artery disease. The Diabetes Prevention Program examined the effects of lifestyle interventions and metformin in persons with impaired glucose tolerance in preventing or delaying the onset of diabetes [62]. It was demonstrated that among patients over 60 years of age, the development of diabetes was prevented or delayed by 71% in the intensive lifestyle intervention group and by 11% in the metformin group as compared to the placebo group. Strict glycemic control has been associated with improved outcomes among critically ill patients (primarily cardiac surgery patients) in the surgical intensive care unit [63], among diabetic patients with acute myocardial infarction [64], and among diabetic patients undergoing coronary artery bypass surgery [65]. These findings suggest that in elderly patients, attention should not only be focused on the detection of diabetes mellitus and on lifestyle modifications, but also on strict (perioperative) glycemic control.

Antihypertensive treatment in the elderly

The prevalence of systolic hypertension rises with increasing age. Several large trials have suggested that treating elderly patients for diastolic and systolic hypertension, and isolated systolic hypertension was beneficial in terms of a decrease in overall mortality rate [66-68]. Drug treatment is recommended if life style modifications have been proved to be unsuccessful during a 3-6 month period. Drugs, which have been proven to reduce morbidity and mortality in the elderly, are diuretics and β-blockers and are therefore the first choice drugs recommended by national guidelines [69].

Lipid-lowering drugs in the elderly

Dyslipidemia is a very powerful predictor of cardiovascular disease. Alone, it predicts all major clinical manifestations of atherosclerorosis, with the possible exception of cerebrovascular disease. The landmark publication of Kannel et al from the Framingham study, publicated in 1961, identified serum cholesterol and blood pressure as the most important risk factors for cardiovascular disease except for age and sex [70]. The ratio of total cholesterol and high-density lipoprotein-C has been demonstrated as probably the best risk estimate. Serum triglycerides are far less consistent to have predictive value. Lipid lowering diets, comprising high polyunsaturated fat-and low saturated fats, are probably beneficial in elderly patients to reduce mortality from cardiovascular diseases, Drug therapy should be considered for elderly (non-)surgical patients, since several studies have clearly established its beneficial effects. Bile acid sequestrates appear to be effective in the elderly persons; however, gastrointestinal side effects may be a major reason for poor acceptance in older patients. Nicotinic acid is associated with multiple side effects and may not be the first drug of choice. HMG-CoA reductase inhibitors are well tolerated by older patients and are effective for lowering LDL-C and even produce modest increased in HDL-C. Reductions in LDL cholesterol of 35 to 40% seem to be sufficient for achieving lipid-lowering goals [fair]. Additional use of cereals, vegetables and fruits may result in an additional 6 to 10% lowering in LDL cholesterol levels, an equivalent to doubling or quadrupling the dose of a statin drug [71].

Summary

Cardiovascular disease is the leading cause of mortality in industrialised countries. The prevalence of cardiovascular disease and its risk factors increases with age. Age itself is associated with age-related degeneration of cardiovascular structures. The preoperative evaluation and perioperative management of the elderly patient should be directed by the presence and extent of possible co-morbidity. The recommendation of perioperative treatment with β-blockers to prevent postoperative adverse cardiac events in high-risk patients is based on a firm scientific basis. Statins, α-2-adrenergic receptor agonists, and calcium channel blockers may also have potential benefit in high-risk elderly patients. In addition to specific perioperative medical treatment, general measures for risk factor reduction and life-style modifications have been proven to favor long-term survival in the general population, and should also be considered in the elderly surgical patient.

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Chapter 27

Elderly patients undergoing major vascular surgery: risk factors and medication associated with risk reduction

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Elderly patients undergoing major vascular surgery: risk factors and medication associated with risk reduction

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This study assesses risk factors in elderly vascular surgery patients and evaluates whether perioperative cardiac medication can reduce postoperative mortality rate. In a cohort study, 1693 consecutive patients ≥65 years undergoing major non-cardiac vascular surgery were preoperatively screened for cardiac risk factors and medication. During follow-up (median: 8.2 years), mortality was noted. Hospital mortality occurred in 8.1% and long-term mortality in 28.5%. In multivariate analysis, age, coronary artery disease, heart failure, cerebrovascular disease, renal failure and diabetes were significantly associated with increased hospital and long-term mortality. Perioperative aspirin (OR [95% CI]: 0.53 [0.34-0.83]), β-blockers (OR 0.32,[0.19-0.54]) and statins (OR 0.35, [0.18-0.68]) were significantly associated with reduced hospital mortality. In addition, aspirin (HR 0.65, [0.53-0.81]), angiotensin-converting enzyme (ACE)-inhibitors (HR 0.74, [0.59-0.92]), β-blockers (HR 0.61, [0.48-0.76]) and statins (HR 0.65, [0.49-0.87]) were significantly associated with reduced long-term mortality. Heterogeneity tests revealed a gradient decrease of mortality risk in patients from low to high age using statins (P = .03). In conclusion, age is an independent predictor of hospital and long-term mortality in elderly patients undergoing major vascular surgery. Aspirin, ACE-inhibitors, β-blockers and statins reduce long-term mortality risk. Especially the very elderly may benefit from statin therapy.

THE ELDERLY IS A rapidly growing population, often undergoing surgery. Many studies have demonstrated that the frequency of perioperative complications increases with age, which may possibly be related to co-morbidity, such as atherosclerosis, that increases with advanced age (Mangano, 1990; Tiret et al., 1986). However, even in the absence of confounding influences of disease, advanced age itself may be an independent risk factor. Cardiac complications are the major cause of perioperative mortality in elderly patients undergoing major surgery. High-risk surgery, ischemic heart disease, heart failure, cerebrovascular disease, diabetes mellitus, and renal dysfunction, as summarized in the Revised Cardiac Risk Index, have been identified as independent predictors of adverse perioperative events in the surgical population (Goldman et al., 1977; Lee et al., 1999). Limited information is available whether advanced age itself independently predicts hospital and long-term mortality in elderly surgical patients (Eagle et al., 2002).

Several medications may potentially be beneficial in elderly patients undergoing major vascular surgery. β-blockers, statins and calcium channel blockers have been demonstrated to reduce adverse cardiac events in patients undergoing non-cardiac surgery (Poldermans et al., 1999; Mangano et al., 1990; Poldermans et al., 2003; Durazzo et al., 2004; Kertai et al., 2004; Wijeysundera and Beattie, 2003). Angiotensin-converting enzyme (ACE) inhibitors and antiplatelet drugs have been demonstrated to prevent cardiovascular events in high-risk non-surgical patients (Hirsch and Duprez, 2003; Yusuf et al., 2000; Antithrombotic Trialists'Collaboration, 2002). Data whether these medications may reduce postoperative and long-term mortality in elderly surgical patients are limited.

The goal of this study was to evaluate whether age and cardiac risk factors according to the Revised Cardiac Risk Index are significant independent predictors of hospital and long-term mortality in elderly patients undergoing major non-cardiac vascular surgery and whether perioperative medication use, including ACE-inhibitors, aspirin, β-blockers, calcium channel blockers and statins may reduce hospital and long-term mortality risk.

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2. METHODS

2.1 *Patient population*

A total of 1 693 consecutive patients aged 65 years and older who underwent major non-emergent non-cardiac vascular surgical procedures at the Erasmus Medical Centre in Rotterdam, the Netherlands, from January 1990 to January 2004 were enrolled in this cohort study. Major non-cardiac vascular surgical procedures included the following: abdominal aortic aneurysm repair, lower extremity revascularization and carotid artery surgery. The hospital's Medical Ethical Committee was informed about the study protocol, and for this observational cohort study no official approval was required.

Prior to surgery, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure ≥140/90 mmHg or antihypertensive treatment), diabetes mellitus (fasting glucose level ≥7.0 mmol/L, or treatment for diabetes mellitus), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or cholesterol-lowering treatment), and renal failure (serum creatinine level ≥ 2.0 mg/dl (177 μmol/L) or renal dialysis). The presence of definite coronary artery disease was indicated by a previous myocardial infarction, by a previous coronary intervention, or by the presence of stable angina pectoris. Data were stored in the computerized hospital database and in medical records, Cardiac risk factors according to the Revised Cardiac Risk Index by Lee (high-risk type of surgery, coronary artery disease, history of congestive heart failure, history of cerebrovascular disease, diabetes mellitus, and renal failure) were identified in all patients (Lee et al., 1999). Perioperative use of medication was recorded and included the following: ACE inhibitors, aspirin, β-blockers, calcium channel blockers and statins. Cardiac medication was continued during the perioperative period; however, aspirin was discontinued 5-7 days prior to surgery in patients undergoing aortic aneurysm repair and lower extremity revascularization procedures, and restarted 1-5 days after surgery. Chronic medication use was ascertained if medication was documented at least one to three months prior to hospital admission for surgery and at discharge after hospital stay.

2.2 *Follow-up and outcome*

The median follow-up period was 8.2 years (interquartile range: 5.1-10.9). Endpoint was mortality. Hospital mortality was defined as death occurring during postoperative in-hospital stay or as death occurring after hospital discharge but within the first 30 days after surgery. Long-term mortality was defined as death occurring in the period after surgery. Mortality data were collected by reviewing the medical records and by approaching the Office of Civil Registry. The cause of death was ascertained by reviewing medical records, the computerized hospital database, autopsy reports, or by contacting the referring physician or general practitioner.

2.3 *Analysis of data*

Continuous data were expressed as mean (+/-SD) and categorical data were presented as percent frequencies. Analysis of variance (ANOVA) techniques were used to evaluate the association between the mean number of cardiac risk factors and age. Univariate and multivariate logistic regression was used to analyse the relation between baseline characteristics and in-hospital mortality, and Cox proportional-hazards regression to analyse the relation between baseline characteristics and long-term mortality. In multivariate analysis, pre-selected variables were age, gender, cardiac risk factors according to the Revised Cardiac Risk Index, irrespective of the significance level in univariate analysis, hypertension, hypercholesterolemia, smoking, chronic obstructive pulmonary disease and propensity scores for medication use. Propensity scores were calculated for statins, beta-blockers, aspirin, ACE-inhibitors and calcium channel blockers, which were constructed using multiple logistic regression analysis. Variables that were independently associated with the decision to prescribe the medications were included in the multivariate propensity score. The Kaplan-Meier method with the log-rank test was used to assess differences in survival. The effect of perioperative medication use may be different across the range of age. Therefore, tests for heterogeneity were used to evaluate interaction between perioperative medication and age. Odds ratios and hazards ratios are reported with corresponding 95% confidence intervals. For all tests, a *P*-value <.050 (two-sided) was considered significant.

3. RESULTS

3.1 *Cardiac risk factors and age*

The baseline characteristics, including the prevalence of cardiac risk factors according to the Revised Cardiac Risk Index, are presented in Table 1. Mean age was 73 (+/-5) years and 76.0% were male. Perioperative aspirin, ACE inhibitors, β-blockers, calcium channel blockers and statins were used in 548 (32.4%), 404 (23.8%), 447 (26.4%), 456 (26.9%), and 274 (16.2%) patients, respectively. Propensity analysis demonstrated that patients were more likely ($p<0.001$) to be prescribed statins if they had hypercholesterolemia and coronary artery disease, β –blockers if they had hypertension or coronary artery disease, aspirin if they had coronary artery disease or cerebrovascular disease, ACE inhibitors if they had a history of heart failure and calcium channel blockers if they had hypertension.

Table1. Baseline Characteristics of the Study Population.

Characteristic	N=1 693
Age (years)	73.0 +/-5.4
Male gender	1 287 (76.0)
Coronary artery disease*	613 (36.2)
History of congestive heart failure*	104 (6.1)
History of cerebrovascular accident*	254 (15.0)
Renal failure*	97 (5.7)
Diabetes mellitus*	161 (9.5)
Hypertension	668 (39.5)
Hypercholesterolemia	270 (15.9)
Smoking	457 (27.0)
Chronic obstructive pulmonary disease	290 (17.1)
Abnormal electrocardiography	668 (49.5)
Aspirin use	548 (32.4)
Angiotensin-converting enzyme inhibitors use	404 (23.8)
Beta-blocker use	447 (26.4)
Calcium channel blocker use	456 (26.9)
Statin use	274 (16.2)

Values are expressed as mean (+/-SD) or as number (%).

Aortic abdominal aneurysm repair was performed in 42.4%, lower extremity revascularization in 37.0%, and carotid artery surgery in 20.6%. The mean number of cardiac risk factors according to the Revised Cardiac Risk Index was 1.7 +/-0.8. The number of cardiac risk factors increased with increasing age (mean number of cardiac risk factors: 1.6, 1.8, 1.8, and 1.9 in patients aged 65 to 70, 70 to 75, 75 to 80 and ≥80 years, respectively, *P* for trend .005) (Figure 1).

3.2 *Predictors of mortality*

Hospital mortality occurred in 137 patients (8.1%), and long-term mortality occurred in 482 (28.5%). The most common cause of death was cardiac disease, which accounted for 48.0% of all deaths (Figure 2). Survival analysis, stratified according to the number of cardiac risk factors according to the Revised Cardiac Risk Index, showed a significant worse survival for patients with an increased number of cardiac risk factors (log rank: $P < .001$). In multivariate analysis, age and cardiac risk factors according to the Revised cardiac risk index were significantly and independently associated with increased hospital and long-term mortality (Table 2).

In multivariate analysis, perioperative use of aspirin, β-blockers and statins was significantly associated with a 47%, 68%, and 65% lower risk of hospital mortality, respectively (Table 2). In addition, perioperative use of aspirin, ACE inhibitors, β-blockers and statins was significantly associated with a 35%, 26%, 39%, and 35% lower risk of long-term mortality, respectively (Table 2). Tests for heterogeneity revealed no significant interaction between age and medication use. However, in patients using statins, it was observed that the risk for overall mortality was decreasing in a gradient manner from patients with the lowest age to patients with the highest age ($P = .03$) (Figure 3). Tests for heterogeneity were repeated for the endpoint cardiovascular mortality and a significant interaction remained between age and statin use ($P = .02$). For the endpoint non-cardiovascular mortality, no significant interaction was observed between age and statin use ($P = .36$)

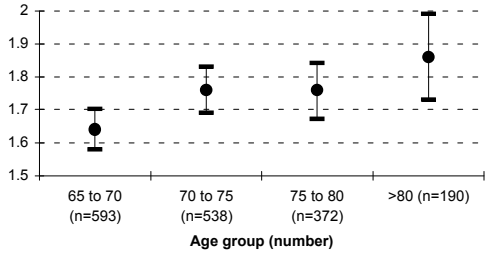

Figure 1. The association between the number of cardiac risk factors according to the Revised Cardiac Risk Index by Lee (high-risk type of surgery, coronary artery disease, history of congestive heart failure, history of cerebrovascular disease, diabetes mellitus, and renal failure) and age (*P* for trend: .005).

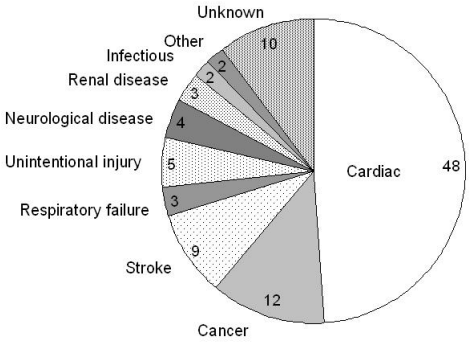

Figure 2. The different causes of long-term mortality. Values are presented as percentages.

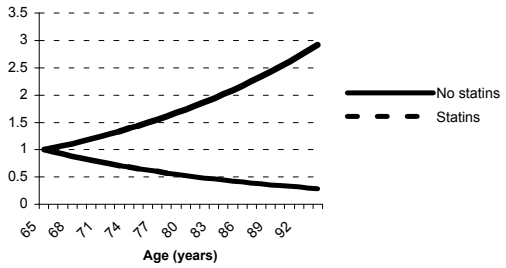

Figure 3. Graph illustrating heterogeneity between age and statin use.

Table 2. Multivariate Model to Predict Long-term Mortality, Including Age, Gender and Cardiac Risk Factors According to the Revised Cardiac Risk Index by Lee.

Characteristic	In-hospital mortality (n=137)		Long-term mortality (n=482)	
	OR (95%CI)	*P* -value	HR (95%CI)	*P* -value
Age (per year increase)	1.05 (1.02-1.09)	<.001	1.04 (1.01-1.05)	<.001
Male gender	1.15 (0.72-1.84)	.64	1.24 (0.99-1.54)	.06
Coronary artery disease	1.93 (1.31-2.85)	<.001	1.37 (1.14-1.66)	<.001
History of congestive heart failure	3.64 (2.15-6.16)	<.001	2.22 (1.68-2.95)	<.001
History of cerebrovascular accident	2.81 (1.85-4.26)	<.001	1.32 (1.04-1.67)	.02
Renal failure	5.54 (3.33-9.21)	<.001	2.63 (2.00-3.48)	<.001
Diabetes mellitus	1.87 (1.12-3.13)	.001	1.46 (1.11-1.90)	.006
β-Blocker use	0.32 (0.19-0.54)	<.001	0.61 (0.48-0.76)	<.001
Statin use	0.35 (0.18-0.68)	<.001	0.65 (0.49-0.87)	.004
Aspirin use	0.53 (0.34-0.83)	.006	0.65 (0.53-0.81)	<.001
ACE inhibitors use	0.69 (0.44-1.09)	.09	0.74 (0.59-0.92)	.008
Ca-channel blocker	0.92 (0.60-1.40)	.76	0.80 (0.61-1.05)	.12

4. DISCUSSION

In this cohort study of 1 693 elderly patients undergoing major vascular surgery, the number of cardiac risk factors increased with increasing age. This study further showed that cardiac risk factors according to the Revised Cardiac Risk Index were significant predictors of hospital and long-term mortality in elderly surgical patients.

Age itself was also identified as an independent predictor of hospital and long-term mortality. Importantly, this study demonstrated that perioperative use of aspirin, β-blockers and statins was significantly associated with a 47%, 68%, and 65% lower risk of hospital mortality, respectively. The use of aspirin, ACE inhibitors, β-blockers and statins was associated with a 35%, 26%, 39%, and 35% lower risk of long-term mortality, respectively. Especially in the very elderly, perioperative use of statins may be beneficial in reducing long-term mortality.

Beta-blockers are established therapeutic agents for hypertension, coronary artery disease, and heart failure, since they improve the prognosis in these patients (Lopez-Sendon et al., 2004). Proposed mechanisms by which β-blockers exert their cardioprotective effect include reduction in heart rate and contractility and restoration of the myocardial oxygen supply-demand balance (Cruickshank, 2000). Randomized, placebo-controlled trials have demonstrated that high-risk patients undergoing major vascular surgery benefit from perioperative β-blocker therapy in terms of reduced postoperative morbidity and mortality (Poldermans et al., 1999; Mangano et al., 1990). Physicians have been reluctant in prescribing β-blockers to patients with presumed contraindications to their use, especially to elderly patients and patients with impaired left ventricular function, transient heart failure, and chronic obstructive pulmonary disease (Viskin et al., 1995). However, it has been suggested that these patients may derive the greatest benefit from β-blocker therapy (Gottlieb et al., 1998).

Statins (HMG-CoA reductase inhibitors) are effective drugs for reducing LDL-cholesterol levels and have been shown to reduce the risk of adverse cardiovascular events in elderly high-risk patients (Miettinen et al., 1997; Shepherd et al., 2002). Statins have also been associated with a lower perioperative and long-term mortality rate after major vascular surgery (Poldermans et al., 1999; Durazzo et al., 2004; Kertai et al., 2004). In addition to the lipid-lowering effect of statins, the pleiotropic effects of statins, which includes inflammation reduction and stabilization of atheromatous plaques may contribute to its beneficial properties (Moreno and Fuster, 2004). Not much is known about perioperative statin therapy in the elderly population. It appears that statin therapy may be well tolerated and safe (Santinga et al., 1994). The present study demonstrated the beneficial effect of statins in the elderly. Moreover, especially the very elderly seemed to benefit from statins in terms of reduced cardiac death. No interaction was observed between age and statin use in terms of reduced mortality from other causes, such as cancer.

The meta-analysis of the anti-thrombotic trialists collaboration showed a proportional reduction of 23% in serious vascular events among 9 214 patients with peripheral arterial disease using antiplatelet therapy (primarily aspirin), compared with those using no antiplatelet therapy (5.8 vs. 7.1%, $P = .004$) (Antithrombotic Trialists' Collaboration, 2002). To our knowledge, no randomised studies have been published evaluating perioperative aspirin therapy in elderly surgical patients. The results in this study support the use of aspirin therapy in reducing hospital and long-term mortality in elderly undergoing major vascular

surgery. It remains a matter of debate whether perioperative aspirin treatment is associated with an increased risk of bleeding complications. Unfortunately, bleeding complications were not investigated in this study. Prior to recommending routine aspirin treatment in this patient population, more studies are needed to investigate the efficacy and safety of this drug.

Growing evidence suggest that ACE-inhibitors directly inhibit the atherosclerotic process and improve vascular endothelial function (Lonn et al., 1994). The HOPE study investigators showed that ramipril significantly reduced the rate of mortality, myocardial infarction and stroke in 9,297 high-risk patients without a low ejection fraction or heart failure (Yusuf et al., 2000). Activation of the renin-angiotensin system seems to be associated with an increased risk of cardiovascular events. It may be hypothesized that the beneficial effects of ACE inhibitors on vascular endothelial function and its beneficial effects on hemodynamic status are responsible for postoperative long-term mortality reduction, as demonstrated in the present study.

Calcium-channel blockers are used in the treatment of hypertension, and prophylaxis of angina pectoris or coronary artery spasm. By reducing heart rate, myocardial contractility and blood pressure, calcium channel blockers can reverse the myocardial oxygen supply-demand mismatch. In addition, they dilate coronary arteries in both normal and ischemic myocardium and inhibit coronary artery spasm. These properties might render them potentially cardioprotective during major surgery. A recent meta-analysis reviewed the efficacy of calcium channel blockers during non-cardiac surgery, and demonstrated that calcium channel blockers significantly reduced perioperative ischemia and supraventricular tachyarrhythmia but not mortality (Wijeysundera and Beattie, 2003). This is in line with our study, which failed to show a beneficial effect of calcium-channel blockers on hospital and long-term mortality in elderly patients.

A major limitation in this study is that medication was not assigned in a randomly, controlled setting. In addition, patients and physicians were not masked to the different medical treatments. However, properly conducted observational studies might not produce misleading or biased results (Concato et al., 2000). Although multivariate regression analysis was used to adjust for cardiac risk factors, other factors may have played a role in the cause of death. However, we used propensity scores to adjust for selection bias. To assess the effect of a treatment in a situation in which randomization is difficult or impossible, propensity scores are a useful method for matching members of different groups.

This large cohort study demonstrated in patients aged 65 years and older undergoing major non-cardiac vascular surgery that age itself is an independent and significant risk factor of hospital and long-term mortality, along with the cardiac risk factors according to the Revised Cardiac Risk Index. Furthermore, this study demonstrates that β -blockers, statins, aspirin and ACE inhibitors are associated with lower postoperative mortality rates in this particular patient population. Especially the very elderly may benefit from statin therapy. Further trials and safety studies are needed to explore and confirm the beneficial effects of β -blockers, statins, aspirin and ACE inhibitors in this patient population.

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Chapter 28

Reply: Revascularization before non-cardiac surgery: is there an impact of drug-eluting stent

Journal of the American College of Cardiology. 2007;50:1399

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Letter to the Editor: Revascularization before non cardiac surgery: is there an impact of drug-eluting stent thrombosis

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WE WOULD LIKE TO thank Dr. Steg for his interest regarding our recent study [1]. The more widespread use of drug-eluting stents will have its implications in perioperative management of patients undergoing non cardiac surgery. Especially in the early phase after stent implantation patients are at increased risk, either due to bleeding complications in those who continued dual antiplatelet therapy or because of in-stent thrombosis after antiplatelet discontinuation. These patients might be identified by troponin elevation and abrupt ST-segment elevation in the territory of a recently implanted stent. Although it is recommended to continue antiplatelet therapy in this period during surgery, no convincing safety data exists.

Our report demonstrates that preoperative coronary revascularization in 49 high-risk patients was not associated with an improved outcome, compared to medical therapy. Of this group, a percutaneous coronary intervention was performed in 32 patients, a drug-eluting stent was used in 30 patients. Of these patients, a Q-wave myocardial infarction occurred in 11. Continuous 12-lead electrocardiographic monitoring was performed in a sub-study for the detection of non Q-wave ST-segment changes, which may be present in up to 41% of patients and have prognostic implications [2,3]. Of the 11 patients with Q-wave myocardial infarction, ST-elevation occurred in 7/11 patients. The location of ST-elevation corresponded to the recently stented coronary artery territory in 5/7 patients. Importantly, all stented patients underwent surgery using dual antiplatelet therapy.

One might speculate that the increased thrombotic risk during surgery as a result of cytokine response, catecholamine surge, platelet activation and reduced fibrinolytic activity can not be prevented by dual platelet therapy. As cardiac outcome is not improved after revascularization in this small study, a switch to postoperative coronary revascularization could be considered in this high-risk population.

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Chapter 29

Carotid artery stenting versus endarterectomy in relation to perioperative myocardial ischemia, troponin T release and major cardiac events

Coronary Artery Disease. 2007;18:483-487

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Carotid artery stenting versus endarterectomy in relation to perioperative myocardial ischemia, troponin T release and major cardiac events

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Background. Carotid artery stenting (CAS) is less invasive than endarterectomy. This study examined differences in perioperative myocardial ischemia, troponin T release and clinical cardiac events in patients undergoing CAS compared to endarterectomy.
Methods. In an observational study, CAS was performed in 24 and carotid endarterectomy in 44 patients. Prior to surgery, clinical risk factors were noted and dobutamine stress echocardiography was performed for cardiac risk assessment. Perioperative continuous 72-hour 12-lead electrocardiographic monitoring was used for myocardial ischemia detection. Troponin T (>0.03 ng/ml) was measured on postoperative day 1, 3, 7 or before discharge. Cardiac events (cardiac death or Q-wave myocardial infarction) were noted during hospital stay and during follow-up (mean: 1.2 years).
Results. No significant differences were observed between patients with CAS and endarterectomy in terms of baseline clinical characteristics, dobutamine stress echocardiography results and cardiovascular medication. Perioperative myocardial ischemia was detected in 9 patients (13%), perioperative troponin T release in 7 patients (10%), early cardiac events in 1 patient (1%) and late cardiac events in 3 patients (4%). Significantly less perioperative myocardial ischemia was observed in patients with CAS compared to endarterectomy (0% versus 21%, p=0.02). Troponin T release was also significantly lower in CAS, compared to endarterectomy (0% versus 16%, p=0.04). Early (0% versus 2%, p=0.5) and late (0% versus 7%, p=0.2) cardiac events were lower after CAS, compared to endarterectomy, although these differences were not significant.
Conclusions: CAS is associated with a lower incidence of perioperative myocardial ischemia and troponin T release, compared to endarterectomy.

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STROKE IS THE THIRD leading cause of death in the United States, behind heart disease and cancer [1]. In the year 2003, about 273 000 Americans died due to stroke as underlying or contributing cause [1]. Randomized clinical trials have established the efficacy of carotid endarterectomy in preventing stroke in patients with atherosclerotic carotid stenosis [2-8]. However, carotid endarterectomy has been contraindicated in patients at increased predicted perioperative risk of stroke or death [9]. In these patients, stenting of the carotid artery is a reasonable alternative.

The advantages of carotid artery stenting (CAS) compared to endarterectomy include the use of locoregional anesthesia, reduced tissue injury, reduced wound complications and shorter hospital stay [10]. In addition, the incidence of procedure-related stroke during CAS has reduced considerably with advances in embolic protection devices, [11-15]. Limited information is available about cardiovascular outcome in patients undergoing either CAS or endarterectomy. More invasive surgery and surgical stress may be associated with increased perioperative myocardial ischemia due to a mismatch in myocardial oxygen supply and demand. Prolonged myocardial ischemia may lead to myocardial injury that poses the patient at subsequent increased risk of cardiovascular events [16]. Therefore, CAS may be superior to carotid artery endarterectomy in the prevention of cardiovascular events.

This study reports the differences in perioperative myocardial ischemia, perioperative troponin T release and early and late cardiovascular events in patients with CAS as compared to carotid artery endarterectomy.

METHODS

A total of 68 intermediate to high risk cardiovascular patients underwent elective CAS or endarterectomy at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period 2005 to 2006. The study was performed with informed consent of all patients and approved by the hospital's ethics committee. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block and atrial fibrillation were excluded. Patients who participated in clinical intervention trials in or outside the Erasmus Medical Center were also excluded. At study enrolment, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure ≥140/90 mmHg), diabetes (fasting glucose ≥7.0 mmol/L, or insulin therapy), renal failure (serum creatinine ≥ 2.0 mg/dL (177 µmol/L)), smoking and a history of cerebrovascular events. β-Blockers were considered to achieve resting heart rates of 60-65 beats per minute. Before surgery, patients underwent dobutamine stress echocardiography for the assessment of coronary artery disease.

Surgery

Surgery was performed by experienced surgeons and interventional physicians. Patients with transient ischemic attack or non-disabling stroke within 3 months before enrolment and/or with carotid artery stenosis ≥70% as confirmed by catheter angiography or magnetic resonance angiography were considered for CAS or carotid endarterectomy. CAS was carried out through the femoral route with generally available stents and protection devices. Locoregional and a combination of locoregional and general anesthesia were used for CAS and carotid endarterectomy, respectively. Inotropic agents were used in patients presenting with perioperative bradycardia. All patients received standard perioperative pain management. β-Blockers were continued postoperatively.

Assessment of perioperative myocardial ischemia and troponin T release

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts), starting 1 day before up to 2 days after surgery. Recording lengths were 10 seconds every minute. The frequency response was 0.05 – 150Hz. Electrocardiographic data were processed by a technician and analyzed by 2 experienced cardiologists blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the recordings were analyzed for ST-segment deviations. A continuous ST segment trend was generated and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST-segment changes, lasting >1 minute and shifting from baseline to >0.1 mV (1 mm).

Table 1. Baseline characteristics of the study population (n=68).

Characteristic	Carotid artery stenosis (n=68)		
	Stenting (n=24)	Open (n=44)	P value
Age (years)	66 ± 11	64 ± 11	0.5
Male gender	14 (58.3%)	34 (77.3%)	0.1
Angina pectoris	2 (8.3%)	6 (13.6%)	0.5
History of myocardial infarction	6 (25.0%)	10 (22.7%)	0.9
Previous coronary revascularization	1 (4.2%)	2 (4.5%)	0.9
History of congestive heart failure	0 (0%)	0 (0%)	-
History of cerebrovascular accident	12 (50.0%)	23 (52.3%)	0.9
History of transient ischemic attack	12 (50.0%)	21 (47.7%)	0.9
Renal failure	0 (0%)	1 (2.3%)	0.5
Diabetes	3 (12.5%)	6 (13.6%)	0.9
Hypertension	9 (37.5%)	18 (40.9%)	0.8
Hypercholesterolemia	10 (41.7%)	21 (47.7%)	0.6
Current or past smoking	15 (62.5%)	29 (65.9%)	0.8
Aspirin	22 (91.6%)	41 (93.2%)	0.8
Angiotensin-converting enzyme inhibitors	6 (25.0%)	7 (15.9%)	0.4
Beta-blockers	12 (50.0%)	31 (70.5%)	0.1
Calcium channel blockers	5 (20.8%)	10 (22.7%)	0.9
Statins	13 (54.2%)	29 (65.9%)	0.3
Stress-induced myocardial ischemia	2 (8.3%)	2 (4.5%)	0.5
Duration of surgery (hours)	1.9 ± 0.6	3.0 ± 0.9	<0.001
Fluid infusion during surgery (liters)	0.06 ± 0.1	0.2 ± 0.4	<0.001
Heart rate (beats/minute)	70 ± 14	69 ± 13	0.9

Values are expressed as mean (± SD) or number (%).

The baseline ST segment level was defined as the average ST segment during a stable period (duration of 20 minutes) preceding each ischemic episode. ST segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST segment change was measured 40 ms after that point.
Troponin T levels were measured on postoperative day 1, 3, 7 or before discharge and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The recommended lower limit of 0.03 ng/ml was used to define positive troponin T levels since lower levels do not meet the imprecision criteria of <10%.

Heart rate and heart rate variability
Mean heart rate was calculated before, during and after surgery. Heart rate variability was computed using time-domain analysis of short-term 5-minute recordings. Consecutive 5-minute recordings of 2-hour periods were obtained in a standard fashion at the evening before surgery, during the first 2-hours of surgery and at the second evening after surgery. The standard deviation of the NN intervals (SDNN (ms)) was calculated.

Clinical outcome
During a mean follow-up of 1.2 years, outpatient visits were scheduled every 3 months after discharge. Study end points were all-cause mortality and major cardiac events (cardiac death and non-fatal Q-wave myocardial infarction) during hospital stay and follow-up.

Non-fatal Q-wave myocardial infarction was diagnosed when at least the following were present: elevated cardiac enzyme levels, development of new Q waves (>1 mm or >30 ms), and typical symptoms of angina pectoris. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. No patients were lost to follow-up.

Statistical analysis
The study group was divided according to CAS and open repair. Baseline characteristics and outcome between the two types of procedure were compared using the Student t test or chi-square test. For all tests, a p value <0.05 (two-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Out of 68 patients, 44 patients (65%) received carotid artery endarterectomy and 24 patients (35%) underwent CAS. No significant differences were observed between CAS and carotid endarterectomy in terms of baseline clinical characteristics, dobutamine stress echocardiography results and cardiovascular medication therapy (Table 1). Mean preoperative heart rate and heart rate variability was similar between CAS and carotid endarterectomy (Table 2). Duration of surgery and total fluid infusion, however, were significantly lower in patients with CAS (Table 1).

Myocardial ischemia and troponin T release
Myocardial ischemia during continuous 12-lead electrocardiography was detected in 9 patients (13%). A total of 11 episodes of myocardial ischemia were detected. The median duration of ischemic events was 61 minutes (interquartile range: 52-145 minutes) and the median ST-segment deviation was 1.9 mm (interquartile range: 1.0-3.5 mm). Troponin T release was detected in 7 patients (10%). The median troponin T value was 0.09 ng/ml (interquartile range 0.04-1.2 ng/ml). Perioperative myocardial ischemia was significantly lower in patients with CAS, compared to carotid artery endarterectomy (Table 3). Troponin T release was also significantly lower in patients with CAS, compared to carotid artery endarterectomy (Table 3).

Table 2. Perioperative heart rate and heart rate variability.

	Carotid artery stenosis (n=68)		
	Stenting (n=24)	Open (n=44)	P value
Heart rate	70 ± 13	72 ± 13	0.7
- Before surgery (bpm)	69 ± 14	70 ± 12	0.9
- During surgery (bpm)	71 ± 15	75 ± 14	0.4
- After surgery (bpm)	70 ± 15	72 ± 13	0.8
Heart rate variability (SDNN*)			
- Before surgery (ms)	49 ± 32	51 ± 29	0.9
- During surgery (ms)	56 ± 40	50 ± 27	0.7
- After surgery (ms)	59 ± 29	49 ± 56	0.5

*SDNN = standard deviation of the normal-to-normal RR intervals.
Values are expressed as mean (± SD)

Clinical cardiac outcome
Perioperative mortality did not occur in the study population. A perioperative non-fatal myocardial infarction was observed in one patient who received endarterectomy. A major perioperative stroke with right hemiplegia occurred in one patient who received CAS. During follow-up, mortality, cardiac death, non-fatal myocardial infarction and stroke occurred in 3 (4.4%), 1 (1.5%), 2 (2.9%) and 3 (4.4%) patients, respectively. Major cardiac events during follow-up were observed in 3 patients with carotid endarterectomy, while no major

cardiac events during follow-up were observed in patients with CAS (Table 3). Two out of 3 patients with late cardiac events (67%) had perioperative myocardial ischemia as detected by continuous 12-lead electrocardiography.

Table 3. Myocardial ischemia, troponin T release and clinical outcome after carotid artery stenting or carotid artery endarterectomy.

	Carotid artery stenosis (n=68)		
	Stenting (n=24)	Open (n=44)	P value
ST-segment changes*	0 (0%)	9 (20.5%)	0.02
- Before surgery	0 (0%)	1 (2.3%)	0.5
- During surgery	0 (0%)	5 (11.4%)	0.09
- After surgery	0 (0%)	5 (11.4%)	0.09
Troponin T release	0 (0%)	7 (15.9%)	0.04
Myocardial injury†	0 (0%)	9 (20.5%)	0.02
Perioperative mortality	0 (0%)	0 (0%)	-
Late mortality	1 (4.2%)	2 (4.5%)	0.9
Perioperative cardiac events	0 (0%)	1 (2.3%)	0.5
Late cardiac events	0 (0%)	3 (6.8%)	0.2
Perioperative stroke	1 (4.2%)	0 (0%)	0.2
Late stroke	2 (8.3%)	1 (2.3%)	0.2

*During continuous 72-hour 12-lead electrocardiography. †Composite of myocardial ischemia and troponin T release.

DISCUSSION

In this study, a lower incidence of perioperative myocardial ischemia and troponin T release was observed in patients with CAS compared to endarterectomy, despite comparable baseline characteristics. Perioperative and late cardiac events were not observed in patients with CAS, but did occur in patients with carotid endarterectomy.

The dominance held by carotid artery endarterectomy is currently challenged by CAS. Numerous studies have expressed concerns about the safety of CAS. Although perioperative stroke in CAS is a leading complication, substantial progress in safety has been made due to embolic protection devices. At our institution, patients scheduled for CAS more often presented with a history of myocardial infarction and stress induced ischemia, while patients scheduled for endarterectomy more commonly presented with angina pectoris. These differences, however, were not significant. Most of the intermediate to high-risk cardiovascular patients at our institution received endarterectomy, which is still considered as gold-standard.

An important finding of this study was that the incidence of subclinical myocardial ischemia and injury was lower in patients undergoing CAS, compared to endarterectomy. Favorable results have been reported of CAS among patients with severe cardiac disease. In a study of 170 patients, in whom 92% had angiographically proven coronary artery disease, no deaths or myocardial infarctions were observed at 30 days [17]. In a retrospective study of 167 patients with cardiac disease, CAS followed by open heart surgery was associated with a lower incidence of myocardial infarction, compared to combined endarterectomy and open heart surgery (3% versus 13%, p=0.06) [18] . Finally, a lower incidence of troponin I release has also been shown in patients undergoing CAS, as compared to endarterectomy [19].

These results are in contrast to a study that included 21 high cardiac risk patients, in whom the incidence of perioperative myocardial infarction and congestive heart failure was non-significantly higher in CAS, compared to endarterectomy [20]. The authors discussed that additional strain on the heart due to bradycardia and lower coronary perfusion pressure may have resulted in adverse cardiac events in the CAS treatment group. We observed similar perioperative heart rates between the two treatment groups. Inotropic agents were used in patients presenting with perioperative bradycardia. However, surgery duration and total fluid infusion were significantly increased in patients undergoing endarterectomy. Invasive surgical procedures have been associated with significant changes in mean arterial pressure, cardiac output, systemic vascular resistance and significant increases in blood lactate, catecholamine and arterial pH [21,22]. Increased sympathetic activity associated with invasive procedures may lead to a mismatch in oxygen supply and demand. Prolonged myocardial ischemia can lead to myocardial injury and subsequent cardiac events [16]. Indeed, 2 out of 3 patients with late cardiac events had perioperative myocardial ischemia during continuous 12-lead electrocardiographic monitoring.

Several limitations should be noted. First, owing to the small number of patients in each treatment group, the results should be interpreted cautiously. Second, treatment was not randomly assigned to patients. However, the two treatment groups were comparable in baseline characteristics and may not explain the large differences in perioperative myocardial ischemia and troponin T release. Third, because no cardiovascular events occurred in patients with CAS, adjusted relative risk ratios could not be calculated. Fourth, follow-up was relatively short. Future studies should assess cardiovascular outcome beyond 1.2 years of follow-up.

In conclusion, the results of this contemporary study showed that patients with CAS have a lower incidence of perioperative myocardial ischemia and troponin T release, compared to carotid endarterectomy.

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Chapter 30

Endovascular versus open surgical repair of abdominal aortic aneurysms and the incidence of cardiac arrhythmias, myocardial ischemia and clinical cardiac events

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Comparison of the Incidences of Cardiac Arrhythmias, Myocardial Ischemia and Cardiac Events in Patients Having Endovascular versus Open Surgical Repair of Abdominal Aortic Aneurysms

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This study examines differences in cardiac arrhythmias, perioperative myocardial ischemia, troponin T release and cardiovascular events between endovascular and open repair of abdominal aortic aneurysms. In 175 patients, 126 underwent open and 49 underwent endovascular repair of abdominal aortic aneurysms. Continuous 12-lead electrocardiographic monitoring, starting 1 day before to 2 days after surgery, was used for cardiac arrhythmia and myocardial ischemia detection. Troponin T was measured on postoperative day 1, 3, 7 and before discharge. Cardiac events (cardiac death or Q-wave myocardial infarction) were noted at 30-days and follow-up (mean: 2.3 years). Newly onset atrial fibrillation, non-sustained ventricular tachycardia, sustained ventricular tachycardia and ventricular fibrillation occurred in 5%, 17%, 2% and 1% of patients, respectively. Myocardial ischemia, troponin T release, 30-day and long-term cardiac events occurred in 34%, 29% , 6% and 10% of patients, respectively. Significantly higher heart rates and lower heart rate variability were observed in the open repair group. Cardiac arrhythmias were lower in endovascular repair group (14% vs. 29%, p=0.04). Endovascular repair was also significantly associated with lower myocardial ischemia (OR: 0.14, 95% CI: 0.05-0.40, p<0.001), troponin T release (OR: 0.10, 95% CI: 0.02-0.32, p<0.001), 30-day mortality (0% versus 8.7%, p=0.03) and 30-day cardiac events (0% versus 7.9%, p=0.04). Long-term mortality and cardiac events were not significantly lower in the endovascular group. In conclusion, endovascular repair is associated with a lower incidence of perioperative cardiac arrhythmias, myocardial ischemia, troponin T release, cardiac events and all-cause mortality, compared to open repair of abdominal aortic aneurysms.

THIS PROSPECTIVE OBSERVATIONAL study was conducted to assess whether endovascular repair of abdominal aortic aneurysms (AAA) is associated with a lower incidence of perioperative myocardial ischemia, perioperative troponin T release and 30-day and long-term cardiac events as compared to open repair. In addition, perioperative heart rate, heart rate variability and the incidence of cardiac arrhythmias were compared between the 2 types of procedures.

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METHODS

A total of 175 patients underwent elective open or endovascular repair for infrarenal AAA at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period 2002 to 2006. The study was performed with informed consent of all patients and approved by the hospital's medical ethics committee. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block or atrial fibrillation were excluded. Patients who participated in clinical intervention trials in or outside the Erasmus Medical Center were also excluded. At study enrollment, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure ≥140/90 mmHg), diabetes (fasting glucose ≥7.0 mmol/L, or insulin therapy), renal failure (serum creatinine ≥ 2.0 mg/dL (177 μmol/L)), smoking and a history of cerebrovascular events. β-Blockers were considered to achieve resting heart rates of 60-65 beats per minute.

Before surgery, high-risk patients underwent dobutamine stress echocardiography for the assessment of coronary artery disease. Dobutamine stress echocardiography was performed according to established protocols. The left ventricle was divided into 17 segments and wall motion was scored on a 5-point scale (a score of 1 indicating normal, 2 mild

hypokinesis, 3 severe hypokinesis, 4 akinesis, and 5 dyskinesis). The results were considered positive if wall motion in any segment decreased by ≥ 1 grades during testing.

Surgery was performed by experienced surgeons and interventional physicians. Patients with an infrarenal abdominal aortic aneurysm ≥5.5 cm in diameter as indicated by computed tomography were considered for endovascular or open aneurysm repair. Hospital guidelines recommended endovascular repair in patients at increased cardiac risk. However, the choice of procedure was left to the discretion of the vascular surgeon and was mainly based on patient preference. Endovascular repair was carried out through the femoral route with generally available stents and protection devices. Locoregional anesthesia was used for endovascular repair and a combination of locoregional and general anesthesia was used for open repair. All patients received standard perioperative pain management. β-Blockers were continued postoperatively. In patients who were unable to take β-blockers orally or by nasogastric tube, intravenous metoprolol was administered. β-Blockers were withheld if the heart rate was <50 beats per minute or if the systolic blood pressure was <100 mmHg.

Patients were continuously monitored with a 10-electrode, 12-lead digital electrocardiography recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts), starting 1 day before surgery up to 2 days after. Recording lengths were 10 seconds every minute. The frequency response was 0.05 – 150Hz. Electrocardiographic data were processed by a technician and analyzed by 2 experienced cardiologists blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the recordings were analyzed for ST-segment deviations. A continuous ST segment trend was generated and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST-segment changes, lasting >1 minute and shifting from baseline to >0.1 mV (1 mm). The baseline ST segment level was defined as the average ST segment during a stable period (duration of 20 minutes) preceding each ischemic episode. ST segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST segment change was measured 40 ms after that point. The ischemic burden was calculated by multiplying ischemia duration with ST-segment deviation.

Troponin T levels were measured on postoperative day 1, 3, 7, before discharge and whenever clinically indicated by electrocardiographic changes, consistent with myocardial ischemia or infarction. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). For the definition of positive troponin T levels, 0.03 ng/ml was used as cut-off value, since lower values do not meet the imprecision criteria of <10%.

Mean heart rate was calculated before, during and after surgery. Heart rate variability was computed using time-domain analysis of short-term 5-minute recordings. Consecutive 5-minute recordings of 2-hour periods were obtained in a standard fashion at the evening before surgery, during the first 2-hours of surgery and at the second evening after surgery. The standard deviation of the NN intervals (SDNN (ms)) was calculated. All electrocardiographic recordings were analyzed for newly onset atrial fibrillation, monomorphic or polymorphic ventricular tachycardia and ventricular fibrillation. Non-sustained ventricular tachycardia was defined as an episode of ≥3 consecutive ventricular premature beats at a rate of ≥120 beats/min, lasting <30 seconds. Sustained ventricular tachycardia lasted >30 seconds.

During a mean follow-up of 2.3 years, outpatient visits were scheduled every 3 months after discharge. Study endpoints were all-cause mortality and major cardiac events (cardiac death and non-fatal Q-wave myocardial infarction) during hospital stay and follow-up. Non-fatal Q-wave myocardial infarction was diagnosed when at least the following were present: elevated cardiac enzyme levels, development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms), and typical symptoms of angina pectoris. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. No patients were lost to follow-up.

The study group was divided according to endovascular or open repair. Continuous data were expressed as mean (±SD) or median (interquartile range) and compared using the Student t test or Mann-Whitney test. Categorical data were analyzed using the chi-square test. Binary logistic regression analysis and Cox proportional hazard models were used for perioperative and long-term outcome analysis, respectively. A propensity score for surgical procedure was calculated, which was constructed using multiple logistic regression analysis [1]. Variables associated with the decision to perform endovascular repair were included in the multivariate propensity score. In multivariate analysis, adjustments were made for age, gender, diabetes, renal failure, coronary artery disease (history of angina or myocardial infarction or stress induced ischemia), history of cerebrovascular disease, hypertension, β-blockers, statins and propensity scores. For all tests, a p value <0.05 (two-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, Illinois).

Table 1. Baseline characteristics of the study population.

Characteristic	Abdominal aortic aneurysm (n=175)		
	Endovascular (n=49)	Open (n=126)	P value
Age >70 years	32 (65%)	65 (52%)	0.1
Men	42 (86%)	105 (83%)	0.7
Angina pectoris	12 (24%)	21 (17%)	0.2
Previous myocardial infarction	17 (35%)	54 (43%)	0.3
Previous coronary revascularization	9 (18%)	18 (14%)	0.5
Prior congestive heart failure	1 (2%)	5 (4%)	0.5
Prior cerebrovascular events	6 (12%)	20 (16%)	0.5
Renal failure	2 (4%)	5 (4%)	1.0
Diabetes mellitus	4 (8%)	19 (15%)	0.2
Hypertension	16 (33%)	50 (40%)	0.4
Hypercholesterolemia*	14 (29%)	40 (32%)	0.7
Current or past smoker	25 (51%)	81 (64%)	0.1
Aspirin	27 (55%)	53 (42%)	0.1
Angiotensin-converting enzyme inhibitors	10 (20%)	35 (28%)	0.3
β-Blockers	39 (80%)	93 (74%)	0.4
Calcium channel blockers	10 (20%)	35 (28%)	0.3
Statins	22 (45%)	59 (47%)	0.8
Stress-induced myocardial ischemia	13 (27%)	29 (23%)	0.8
Duration of operation (hours)	3.0 ± 1.1	5.6 ± 1.4	<0.001
Fluid infusion during operation (liters)	0.4 ± 0.3	2.8 ± 1.7	<0.001
Heart rate 1 day prior to surgery (beats/minute)	69 ± 11	70 ± 15	0.3

Values are expressed as mean (± SD) or number (%). * Defined as LDL-cholesterol >130 mg/dL or the use of lipid-lowering medication.

RESULTS

Out of 175 patients, open repair was performed in 126 patients and endovascular repair in 49 patients. No significant differences were observed between open and endovascular repair in terms of baseline clinical characteristics, dobutamine stress echocardiography results and cardiovascular medication (Table 1). Mean preoperative heart rate was similar between open and endovascular repair. Duration of surgery and total fluid infusion, however, were significantly higher in patients with open repair, compared to endovascular repair (Table 1). Propensity analysis demonstrated that patients were more likely to undergo endovascular abdominal aortic repair if they were older (p=0.04) and if they had a history of angina pectoris (p=0.052). Propensity score ranged from 0.35 to 0.95.

Myocardial ischemia during continuous 12-lead electrocardiography was detected in 60 patients (34%). A total of 109 episodes of myocardial ischemia were detected. The median duration of ischemic events was 81 minutes (interquartile range: 60-269 minutes) and the median ST-segment deviation was 1.4 mm (interquartile range: 1.0-2.7 mm). Myocardial ischemia was significantly lower in patients with endovascular repair of abdominal aortic aneurysm, compared to open repair (Table 2). The ischemic burden was also significantly lower in patients with endovascular repair (median 67 mm*min) compared to open repair (median: 209 mm*min) (p=0.003). In multivariate analysis,

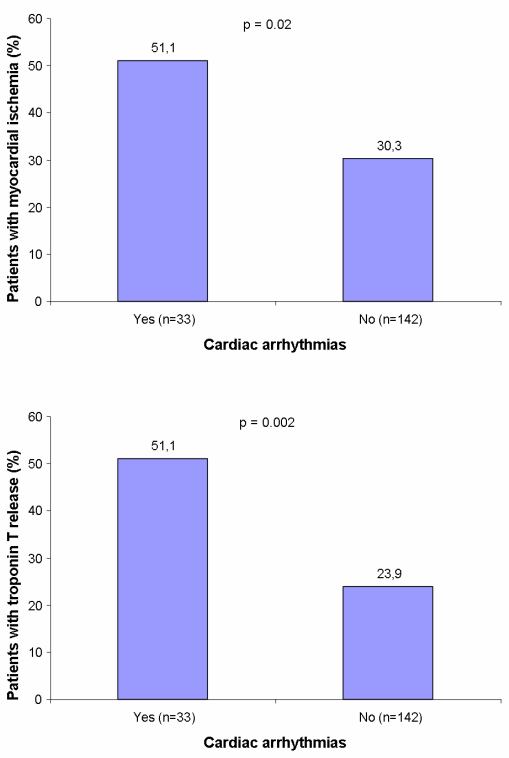

Figure 1. The incidence of perioperative myocardial ischemia (a) and troponin T release (b) in patients with and without perioperative cardiac arrhythmias.

Table 2. Myocardial ischemia, troponin T release and clinical outcome in patients with endovascular or open repair.

Variable	Abdominal aortic aneurysm (n=175)			
	Endovascular (n=49)	Open (n=126)	Relative risk (95% CI)‡	P value
Ischemia and troponin T				
ST-segment changes	5 (10.2%)	55 (43.7%)	0.14 (0.05-0.40)	<0.001
- Before operation	4 (8.2%)	7 (5.6%)	2.10 (0.50-8.61)	0.3
- During operation	5 (10.2%)	41 (32.5%)	0.24 (0.09-0.68)	0.007
- After operation	3 (6.1%)	35 (27.8%)	0.18 (0.05-0.62)	0.006
Troponin T release	3 (6.1%)	48 (38.1%)	0.10 (0.02-0.32)	<0.001
Myocardial injury*	5 (10.2%)	64 (50.8%)	0.11 (0.03-0.26)	<0.001
Outcome				
30-day all-cause mortality	0 (0%)	11 (8.7%)	-	0.03**
30-day cardiac events	0 (0%)	10 (7.9%)	-	0.04**
Long-term all-cause mortality	4 (8.2%)	17 (13.5%)	0.52 (0.17-1.63)	0.2
Long-term cardiac events	3 (6.1%)	15 (11.9%)	0.45 (0.12-1.81)	0.3

*Composite of myocardial ischemia and troponin T release. ‡ Adjusted for age, gender, diabetes, renal failure, coronary artery disease, history of heart failure, history of cerebrovascular disease, hypertension, β-blockers, statins and propensity score. ** Calculated by chi-square test.

Table 3. Perioperative heart rate, heart rate variability and arrhythmias in patients with endovascular or open repair.

Variable	Abdominal aortic aneurysm (n=175)		
	Endovascular (n=49)	Open (n=126)	P value
Heart rate (bpm)	69 ± 10	75 ± 14	0.01
- Before operation (bpm)	69 ± 11	70 ± 15	0.3
- During operation (bpm)	68 ± 9	74 ± 13	0.009
- After operation (bpm)	72 ± 13	81 ± 15	0.004
Heart rate variability (SDNN*)			
- Before operation (ms)	48 ± 20	49 ± 21	0.7
- During operation (ms)	42 ± 20	26 ± 18	0.001
- After operation (ms)	44 ± 20	28 ± 21	0.004
Arrhythmias			
- Any	7 (14.3%)	37 (29.3%)	0.04
- Non-sustained ventricular tachycardia	6 (12.2%)	23 (18.3%)	0.3
- Sustained ventricular tachycardia	0 (0%)	4 (3.1%)	0.2
- Newly onset atrial fibrillation	1 (2.0%)	8 (6.3%)	0.2
- Ventricular fibrillation	0 (0%)	2 (1.6%)	0.4

*SDNN = standard deviation of the normal-to-normal RR intervals. Values are expressed as mean (± SD) or number (%).

endovascular repair remained significantly associated with lower myocardial ischemia (Table 2).

Troponin T release was detected in 51 patients (29%). The median troponin T value was 0.45 ng/ml (interquartile range 0.08-0.75ng/ml). In univariate and multivariate analysis, endovascular repair of abdominal aortic aneurysm was significantly associated with lower troponin T release (Table 2). In patients with myocardial damage, the level of troponin T release was significantly lower after endovascular repair (median 0.17 ng/ml), compared to open repair (0.45 ng/ml) (p<0.001).

Mean preoperative heart rate and heart rate variability were comparable between open and stenting procedures. During and after surgery, however, heart rate was significantly higher and heart rate variability significantly lower in open repair, compared to endovascular repair (Table 3). Interestingly, patients with myocardial ischemia after surgery had a lower heart rate variability before (SDNN: 32±29 versus 50±26, p=0.002), during (SDNN: 23±19 versus 36±24, p=0.01) and after surgery (SDNN: 21±19 versus 46±42, p=0.008), compared to patients with no myocardial ischemia. Patients with troponin T release also had a lower heart rate variability before (SDNN: 49±25 versus 32±29, p=0.002), during (SDNN: 23±21 versus 37±23, p=0.004) and after surgery (SDNN: 21±18 versus 47±39, p<0.001), compared to patients with no troponin T release.

Newly onset atrial fibrillation, non-sustained ventricular tachycardia, sustained ventricular tachycardia and ventricular fibrillation occurred in 9 (5%), 29 (17%), 4 (2%) and 2 (1%) of patients, respectively. Patients with perioperative cardiac arrhythmias were more likely to have perioperative ischemia and troponin T release, compared to patients without arrhythmias (Figure 1). In addition, heart rate during and after surgery was significantly higher and heart rate variability during and after surgery was significantly lower in patients with cardiac arrhythmias (Figure 2). Sustained ventricular tachycardia and ventricular fibrillation were not

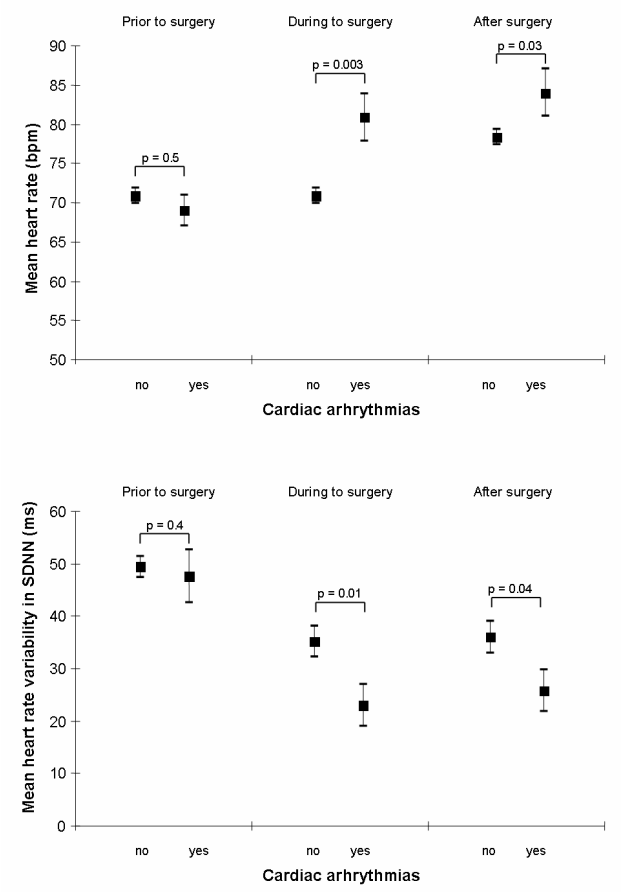

Figure 2. Mean heart rate (a) and heart rate variability (± standard error of the mean) (b) in patients with and without perioperative cardiac arrhythmias.

observed in patients with endovascular repair, but occurred in 4 (3%) and 2 patients (2%), respectively, with open surgical repair. The incidence of atrial fibrillation and non-sustained ventricular tachycardia was also non-significantly lower in patients with endovascular repair (Table 3). The cumulative incidence of cardiac arrhythmias was significantly lower in endovascular repair, compared to open surgery (Table 3).

All-cause mortality and cardiac events occurred in 11 (6.3%) and 10 (5.7%) patients, respectively, during hospital stay. In-hospital mortality and cardiac events were not observed after endovascular repair, but occurred in 11 (9%) and 10 (8%) patients with open surgical repair (Table 2). During follow-up, all-cause mortality and cardiac events occurred in 21 (12%) and 18 (10%) patients, respectively. Patients with endovascular repair were at non-significantly lower risk of long-term mortality and cardiac events, compared to open repair (Table 2).

DISCUSSION

Several studies have demonstrated that endovascular procedures can significantly decrease cardiovascular events in the perioperative period, in comparison to open repair [2-7]. Long-term studies have suggested no sustained survival benefit after the first postoperative year for endovascular stenting [8]. In a previous study, we demonstrated that endovascular stent grafting was associated with a reduced incidence of perioperative complications, but with comparable long-term cardiac outcome. [7]. In the current study, perioperative 72-hour 12-lead electrocardiographic monitoring was applied in a contemporary patient cohort. Endovascular repair was significantly associated with lower perioperative heart rate and higher perioperative heart rate variability. Patients with endovascular repair also had a lower incidence of perioperative cardiac arrhythmias, myocardial ischemia, troponin T release, mortality and cardiac events. We confirmed that long-term mortality and cardiac events were non-significantly lower in patients with endovascular repair.

In previous studies, myocardial ischemia during major vascular surgery has been observed in up to 41% of patients and has been demonstrated to be a strong predictor of subsequent clinical cardiovascular events [9]. The current study detected perioperative myocardial ischemia in 34% of patients. Myocardial ischemia in the perioperative setting may arise either from increased myocardial oxygen demand or reduced supply. Factors that increase myocardial oxygen demand are mainly tachycardia and hypertension resulting from surgical stress, postoperative pain, interruption of β-blocker use, or the use of sympathomimetic drugs. In contrast, decreased supply may be the result of hypotension, vasospasm, anemia, hypoxia, or coronary artery plaque rupture. Invasive procedures have been associated with significant changes in arterial pressure, cardiac output and increases in blood lactate, catecholamine and arterial pH [10,11]. Therefore, the higher heart rate in patients undergoing open repair is likely the result of increased surgical stress and sympathetic tone.

Heart rate variability has been used as a measure of cardiac autonomic function and mostly reflects vagal tone. Increased anesthetic depth and sympathetic tone most likely explain the lower perioperative heart rate variability in patients with open repair, compared to endovascular repair [12]. It has been suggested that decreased heart rate variability could trigger ischemic events [13,14]. Indeed, in the current study, myocardial ischemia and troponin T release was preceded by significantly lower heart rate variability.

The current results, therefore, support the view that ischemic events predominantly occur in situations with increased sympathetic activity.

This study further revealed a higher incidence of cardiac arrhythmias in patients with open repair. In addition, patients with perioperative cardiac arrhythmias had a higher incidence of myocardial ischemia and troponin T release. They also had significantly higher heart rates and lower heart rate variability during and after surgery. These results therefore suggest that surgical stress, higher heart rates and lower heart rate variability in association with myocardial oxygen supply-demand mismatch causes the higher incidence of sustained and non-sustained ventricular tachycardias, newly onset atrial fibrillation and ventricular fibrillation in patients with open repair, compared to endovascular repair.

Cardiac complications remain a leading cause of morbidity and mortality among vascular surgery patients. Due to the lack of long-term data, the choice between stenting and open repair now heavily relies on surgeon experience and patient preference. Concerns have been raised about the long-term efficacy and safety of endovascular grafts. Not only endoleaks become increasingly common as duration of follow-up is extended, aneurysm-related deaths after successful endograft therapy have also been reported [15].

The major limitation in this study is that the surgical procedures were not randomly assigned to the patients. However, baseline clinical characteristics were comparable and detailed cardiac assessment with dobutamine stress test echocardiography revealed no significant baseline differences between the two types of surgery. In addition, we used multivariate analysis and propensity analysis to adjust for known possible confounding factors. Unfortunately, no data were available regarding the incidence of repeat procedures for graft leaks in patients with endovascular surgery.

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Summary and Conclusions

IN THE NEXT FEW DECADES, cardiovascular disease will remain the dominant cause of death and disability in the world. Until recently, atherosclerotic disease of the lower extremities has been regarded as a local problem, which required local treatment. Now, the association between peripheral arterial disease and cardiovascular mortality is well appreciated and treatment strategies focus on the systemic nature of atherosclerosis. Strategies include primary prevention of atherosclerotic disease, secondary prevention of disease complications and tertiary prevention in patients with established disease. This thesis proposes strategies to improve management and outcome in patients with peripheral arterial disease.

The recognition of risk factors in patients with peripheral arterial disease is important since many of these risk factors can be modified. In patients with peripheral arterial disease, the following risk factors were associated with increased 10-year mortality: renal dysfunction, heart failure, ST-changes, age above 65, hypercholesterolemia, ankle-brachial index values below 0.60, Q-waves, diabetes, cerebrovascular disease and pulmonary disease (Chapter 2). A risk index based on these variables can provide an overall framework for risk assessment and medical decision making (Chapter 2). In addition to these classic risk factors, low post-exercise ankle-brachial index values (Chapter 3), stress-induced myocardial ischemia and left ventricular dysfunction during dobutamine stress echocardiography (Chapter 4) are correlated with poor outcome. During follow-up, patients with declining ankle-brachial index values, i.e. progressive atherosclerotic disease, will experience more mortality, cardiac events and kidney dysfunction, compared to patients with no declines in ankle-brachial index (Chapter 5).

Fortunately, mortality and morbidity in these patients can be reduced by cardioprotective medication, such as statins, aspirin, beta-blockers and angiotensin-converting enzyme inhibitors (Chapter 6). Especially intensified lipid-lowering therapy with low target LDL-cholesterol levels will improve the prognosis of peripheral arterial disease (Chapter 7). Renal dysfunction is both a major risk factor and complication in patients with peripheral arterial disease. Improved renal outcome can be accomplished with statins and angiotensin converting enzyme-inhibitors; both are associated with less progression towards end-stage renal disease (Chapter 8). Diabetes is another major risk factor in peripheral arterial disease and poor glycemic control contributes to mortality and morbidity (Chapter 9). The beneficial effect of statins in patients with peripheral arterial disease can be attributed to both improved lipid metabolism and improved glycemic control (Chapter 9).

Patients with advanced peripheral atherosclerotic disease can present with many symptoms including claudication, gangrene, angina pectoris, stroke and myocardial infarction. These patients are also at increased risk of abdominal aortic aneurysms, renal artery stenosis and carotid stenosis, which may present without any symptoms. Patients may require surgery for symptomatic relief or for preventive purposes in order to increase overall survival. Unfortunately, surgery is associated with substantial perioperative myocardial ischemia and cardiac events (Chapter 10). Therefore, the indication for surgery should outweigh its risk. A substantial proportion of patients have perioperative ST-elevation, which can occur in non-culprit related coronary arteries (Chapter 10). This finding complicates its prediction and may explain why preoperative preventive coronary artery revascularization does not improve perioperative outcome.

Risk assessment is an essential step in perioperative management. Risk factors in addition to traditional risk factors are unrecognized myocardial infarction and silent myocardial ischemia (Chapter 11), impaired fasting glucose and poor glycemic control (Chapter 12), marginal troponin T elevations (Chapter 19) and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (Chapter 13 and 14). The positive correlation between elevated NT-proBNP with the extent of stress induced myocardial ischemia during dobutamine stress echocardiography (Chapter 15) and with perioperative ischemia (Chapter 16) provides addition support for its use as marker of coronary artery disease. NT-proBNP levels also reflect left ventricular function and functional status after cardiac surgery (Chapter 17).

Perioperative risk stratification is important, since it guides perioperative management (Chapter 18 and 20). For example, high risk patients with left ventricular dysfunction should receive angiotensin-converting enzyme-inhibitors, statins and beta-blockers in order to improve not only long-term outcome, but also perioperative outcome (Chapter 21). Although the benefit of perioperative beta-blockers in high-risk patients has been established by large randomized trials, recent studies have demonstrated conflicting results and have questioned its routine use. Chapter 22 argues an

individual patient approach, in which cardioprotection can be achieved by tight heart rate control with adequate beta-blocker dosage (Chapter 22). The benefit of beta-blockers in patients with left ventricular dysfunction is suggested in Chapter 23. In addition to beta-blockers, statins have emerged as promising drugs with cardioprotective properties. Chapter 25 shows that statins have perioperative cardioprotective effects, which go beyond its lipid-lowering properties.

With recent advances in perioperative management, higher-risk patients, such as the (very) elderly, are now considered for major surgery (Chapter 26 and 27). Surgical procedures with minimal cardiac stress should be appreciated. Chapters 29 and 30 study cardiac outcome in patients who are undergoing less invasive surgical procedures, such as carotid stenting or endovascular abdominal aortic repair. These studies show that less-invasive procedures correlate with lower cardiac events, compared to more invasive surgery.

Samenvatting en Conclusies

WERELDWIJD blijven hart- en vaat- aandoendingen de komende jaren de primaire oorzaak voor morbiditeit en mortality. Perifeer atherosclerose van de onderste extremiteiten werd ooit beschouwd als locaal probleem. Op dit moment is het welbekend dat perifeer atherosclerotisch vaatlijden een systemisch probeem is dat een systemische behandeling vergt. Met name coronaire vaataandoeningen zijn geassocieerd met perifeer atherosclerotisch vaatleiden. Behandeling is gericht op primaire preventie, secundaire preventie van ziektecomplicaties en tertiaire preventie in patiënten die reeds ziektecomplicaties hebben. In dit proefschrift worden verschillende strategien voorgesteld die tot doel hebben een verbetering te brengen in de prognose van patienten met perifeer en coronair atherosclerotische vaataandoeningen.

Identificatie van risicofactoren in patiënten met perifeer atherosclerotische aandoeningen is belangrijk zodat deze risicofactoren aggressiev behandeld kunnen worden. De volgende risicofactoren zijn geassocieerd met verhoogde mortaliteit: nierinsufficiëncie, hartfalen, ST-segment afwijkingen, leeftijd boven 65 jaar, hypercholesterolemie, enkel-arm index kleiner dan 0.60, Q's op de electrocardiogram, diabetes mellitus, cerebrovasculaire aandoeningen en longaandoeningen (hoofdstuk 2). Deze risicofactoren kunnen samengevat worden in een risico-index dat gebruikt kan worden om het risico op mortaliteit te schatten. Op basis van deze index kan vervolgens een optimaal preventief beleid bepaald worden (hoofdstuk 2). Naast de traditionele risicofactoren zijn een lage enkel-arm index na inspanning (hoofdstuk 3), stress-geïnduceerd myocardischemie en linker ventrikel dysfunctie (hoofdstuk 4) geassocieerd met een slechte prognose. Een verslechtering in enkle-arm index gedurende de tijd is ook geassocieerd met een verhoogd risico op mortaliteit, cardiale complicaties en nierfalen (hoofdstuk 5).

Ondanks dit somber perspectief kan mortaliteit aanzienlijk verbeterd worden door het voorschrijven van verschillende cardiovasculaire medicaties, zoals statines, aspirine, beta-blokkers en ACE-remmers (hoofdstuk 6). Intensief statine gebruik en lage LDL-cholesterol waardes verbetert de prognose aanzienlijk (hoofdstuk 7). Hoofdstuk 8 laat zien dat statines en ACE-remmers ook een verlaging kunnen geven in de incidentie van nierfalen. Hoofdstuk 9, tenslotte, suggereeert dat het effect van statines gerelateerd is aan een verbeterde glucosemetabolisme.

Patiënten met gevorderd atherosclerotisch vaatleiden kunnen zich symptomatisch presenteren of zich presenteren met asymptomatische aandoeningen zoals abdominale aneurysmata, nierslagader-vernauwingen en halsslagadervernauwingen. Zowel het verlichten van symptomen als het verbeteren van prognose zijn indicatoren voor chirurgisch ingrijpen. Helaas zijn hoog-risico operaties geassocieerd met perioperatieve ST-afwijkingen en cardiale complicaties, met name in hoog-risico patiënten (hoofdstuk 10). Volgens de resultaten in hoofdsuk 11 correleert de locatie van ST-elevatie slecht met de locatie van de kritieke coronairvernauwing. Deze observatie kan verklaren waarom preventieve coronaire revascularisatie geen verbeterde perioperatieve prognose geeft.

Een weloverwogen beslissing moet gemaakt worden tussen de voor- en nadelen van chirurgie. Bekende risicofactoren voor het ontwikkelen van perioperatieve complicaties zijn diabetes mellitus, cerebrovasculaire aandoeningen, nierfunctiestoornissen, coronair atherosclerotische aandoeningen en hartfalen. Ook een stil mycardinfarct en asymptomatisch coronair atherosclerotische aandoeningen (hoofdstuk 11), slechte glucoseregulatie (hoofdstuk 12), een verhoging in het natriuretisch hormoon (hoofdstuk 13 en 14) en marginale perioperative troponinestijgingen (hoofdstuk 19) hebben prognostische waarde. De positieve associatie tussen verhoogde natriuretisch hormoon concentraties en stress-geïnduceerd myocardischemie tijdens dobutamine stress echocardiografie (hoofdstuk 15) en myocardischemie tijdens operatie (hoofdstuk 16) ondersteund de hypothese dat verhoogde natriuretisch hormoon concentraties gebruikt kunnen worden als prognostisch middel. Ook kan het natriuretisch hormoon een indicator zijn voor linkerventrikel functie en functionele status na mitraalklepchirurgie (hoofdstuk 17).

Risicostratificatie bepaalt het perioperatieve beleid (hoofdstuk 20). Chirurgische patiënten met linkerventrikeldysfunctie kunnen hun overlevingskans vergroten door het gebruik van perioperatieve ACE-remmers, statines en beta-blokkers (hoofdstuk 21). Hoofdstuk 22 suggereert dat het voorschrijven van beta-blokkers een individuele patiëntenbenadering vereist waarin cardioprotectie verkregen wordt door stricte hartslagfrequentiecontrole en adequate beta-blokkerdosering. De effectiviteit van beta-blokkers in patienten met hartfalen word verondersteld in hoofdstuk 23. Naast beta-blokkers hebben ook statines een positief effect in het voorkomen van cardiale complicaties (hoofdstuk 24).

Door verbeteringen in perioperatief beleid komen patiënten met een hoger risico, zoals patiënten met een hogere leeftijd, in aanmerking voor chirurgie. In hoog-risico patiënten kan een voorkeur gegeven worden aan chirurgische ingrepen met minimale cardiale stress. Hoofdstukken 29 en 30 laten zien dat minimaal invasieve chirurgische ingrepen, zoals het gebruik van endoscopische procedures en stents, een vermindering kunnen geven in myocardcelschade en cardiale complicaties, in vergelijking tot meer invasieve ingrepen.

Addendum: Perioperatieve risicostratificatie en beleid in vaatchirurgische patiënten

Harm H.H. Feringa, MD

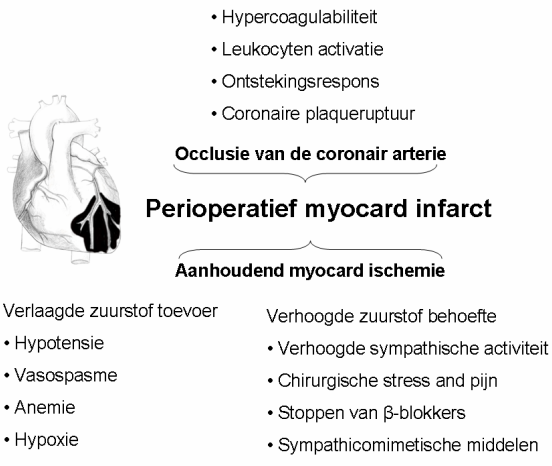
Het risico op cardiale complicaties is hoog bij patiënten die een vaatchirurgische operatie ondergaan. Deze complicaties ontstaan door aanhoudende myocardischemie of door ruptuur van de coronaire plaque in de perioperatieve periode. Preoperatieve risico-inschatting in deze patiënten is belangrijk voor het bepalen van een optimaal medisch beleid dat gericht is op risicoreductie. β-Blokkers verminderen dit risico aanzienlijk, waarbij adequate dosering van de β-blokker, nauwkeurige perioperatieve controle van de hartslag en continuering van de β-blokker na ontslag uit het ziekenhuis belangrijk zijn. Recent is ook bewezen dat ook statines een perioperatief cardioprotectief effect hebben. Het perioperatief beleid dient niet alleen gericht te zijn op kortetermijnuitkomsten, elke poging om langetermijnprognose te verbeteren moet worden verwelkomd.

HET PROBLEEM

IN NEDERLAND ONDERGAAT jaarlijks 3.8% van de bevolking een niet-cardiaal chirurgische ingreep (www.prismant.nl). Ongeveer 6% van deze ingrepen bestaat uit vaatchirurgische operaties [1]. Jaarlijks overlijden er ongeveer 1.500 patiënten tijdens of na een vaatchirurgische operatie, uitgaande van de schatting dat de perioperatieve sterfte in Nederland 4.4% is [1]. Meer dan de helft van deze sterftegevallen is het gevolg van primaire of secundaire cardiale complicaties [2]. Daarmee kent de vaatchirurgie het hoogste risico op cardiovasculaire sterfte, in vergelijking met andere niet-cardiaal chirurgische ingrepen [2]. De incidentie van perioperatieve cardiovasculaire complicaties op mondiaal niveau is vergelijkbaar: 2.5% van de patiënten die een niet-cardiale niet-vaatchirurgische operatie ondergaan en 6.2% van de patiënten die een perifeer vaatchirurgische operatie ondergaan [3]. De hoge incidentie van cardiovasculaire complicaties weerspiegelt de hoge prevalentie van onderliggend coronairlijden. Volgens de Wereld Gezondheids Organisatie zal de wereldwijde epidemie van hartziekte niet alleen toenemen in de westerse wereld, maar zal deze zich ook uitbreiden naar onderontwikkelde landen. Verder zullen door nieuwe chirurgische technieken, zoals endovasculaire ingrepen, patiënten met een hogere leeftijd en een hoger risicoprofiel in aanmerking komen voor vaatchirurgie. Ondanks de verbetering in perioperatieve zorg gedurende de laatste decennia, blijft het daarom noodzakelijk aandacht te geven aan reductie van perioperatieve morbiditeit en mortaliteit. In deze beschouwing zal ingegaan worden op de pathofysiologie van perioperatieve cardiale complicaties. Verder zullen de preoperatieve beoordeling van het cardiale risicoprofiel en de risicoreductie door middel van medicamenteuze therapie aan bod komen.

PATHOFYSIOLOGIE

Perioperatieve cardiale complicaties kunnen ontstaan door aanhoudende myocardischemie of door ruptuur van een atherosclerotische plaque in een van de coronair arteriën (Figuur 1) [4]. Aanhoudende perioperatieve ischemie van het myocard ontstaat door een locaal toegenomen behoefte aan zuurstof of een verlaagde zuurstoftoevoer. Verhoogde zuurstofbehoefte kan ontstaan door de stress van de operatie (pijnsensaties, tachycardie, hypertensie) of door de toediening van sympathicomimetische geneesmiddelen. Een verlaagd



Figuur 1. Pathologie van een perioperatief myocardinfarct.

aanbod van zuurstof aan het myocard kan ontstaan door hypotensie, vasospasme, anemie, hypoxie of een significante coronaire stenose of obstructie. Verschillende studies hebben aangetoond dat

Tabel 1. Een schematisch stappenplan voor perioperatief beleid.

Stap		Omschrijving	Bewijs klasse
1.	Identificeer cardiale risicofactoren	Ischemische hartziekte, hartfalen, cerebrovasculaire aandoening, diabetes mellitus, nierfunctiestoornissen (Lee-score)	I-B
2.	Schat risico in van de betreffende chirurgische ingreep	Laag risico: gynaecologie, oogheelkunde, carotischirurgie, mammachirurgie; Intermediair-laag risico: orthopedie, urologie; Intermediair-hoog risico: abdominale chirurgie, keel-, neus-, oorheelkunde, neurochirurgie, longchirurgie; Hoog-risico: aortachirurgie, perifere vaatchirurgie.	I-B
3.	Elektrocardiografie	Ritme- en geleidingsstoornissen voorspellen perioperatieve cardiale complicaties.	I-B
4.	Bloedserum analyse	Verhoging in concentraties van natriuretisch hormoon, glucose, geglycosyleerd hemoglobine en creatinine voorspellen cardiale complicaties.	I-B
5.	Overweeg rust echocartografie	Linkelventrikelfunctie bepaling bij hartfalen. Diagnostiseren van hartklepafwijkingen.	I-B
6.	Overweeg stress echocartografie	Screening voor ischemische hartziekte in hoogrisico patiënten.	I-B
7.	Optimaliseer medisch beleid	β-Blokkers in adequate dosis and van zekere duur (start minimaal 1 maand voor de operatie tot minimaal 1 maand na de operatie) bij patiënten met een hoog risico. Overweeg statines bij patiënten met een hoog risico.	I-A I-B
8.	Overweeg coronair revascularisatie	Nut van preoperatieve coronair revascularisatie is controversieel.	IIb-A
9.	Perioperatieve ischemie detectie	(Sub)klinische myocardischemie en myocardcelschade bepaald door middel van perioperatieve Holter registratie of troponine T metingen is geassocieerd met een verhoogde korte en lange-termijn mortaliteit.	I-B
10.	Optimaliseer postoperatief beleid	Overweeg continuering van β-blokker en statine na ontslag uit het ziekenhuis. Overweeg cardiologisch consult bij complicaties.	I-B

*Klasse I: Er is bewijs of algemene overeenstemming dat de procedure of behandeling effectief en nuttig is
Klasse II: Er is tegenstrijdig bewijs en/of uiteenlopende mening dat de procedure of behandeling effectief en nuttig is.
Klasse IIa: Er is gunstig bewijs voor effect en nut
Klasse IIb: Er is minder gunstig bewijs voor effect en nut
Klasse III: Er is bewijs of algemene overeenstemming dat de procedure of behandeling niet effectief en nuttig is en in sommige gevallen zelfs schadelijk
A: Data verkregen door middel van meerdere gerandomiseerde onderzoeken
B: Data verkregen door middel van een gerandomiseerd onderzoek of ongerandomiseerde onderzoeken
C: Gebaseerd op de opinie van experts of case studies

aanhoudende ischemie van het myocard kan leiden tot myocardcelschade en vervolgens tot cardiale complicaties [5]. Pathologische studies laten zien dat bijna alle patiënten met een fataal perioperatief myocardinfarct significante afwijkingen hebben in de coronair arteriën en dat ongeveer de helft een ruptuur van de coronaire plaque heeft gehad [6]. Perioperatief beleid bestaat zowel uit het inschatten van het risico van deze complicaties als uit interventies gericht om het pathologische proces positief te beïnvloeden.

PREOPERATIEVE RISICOSTRATIFICATIE

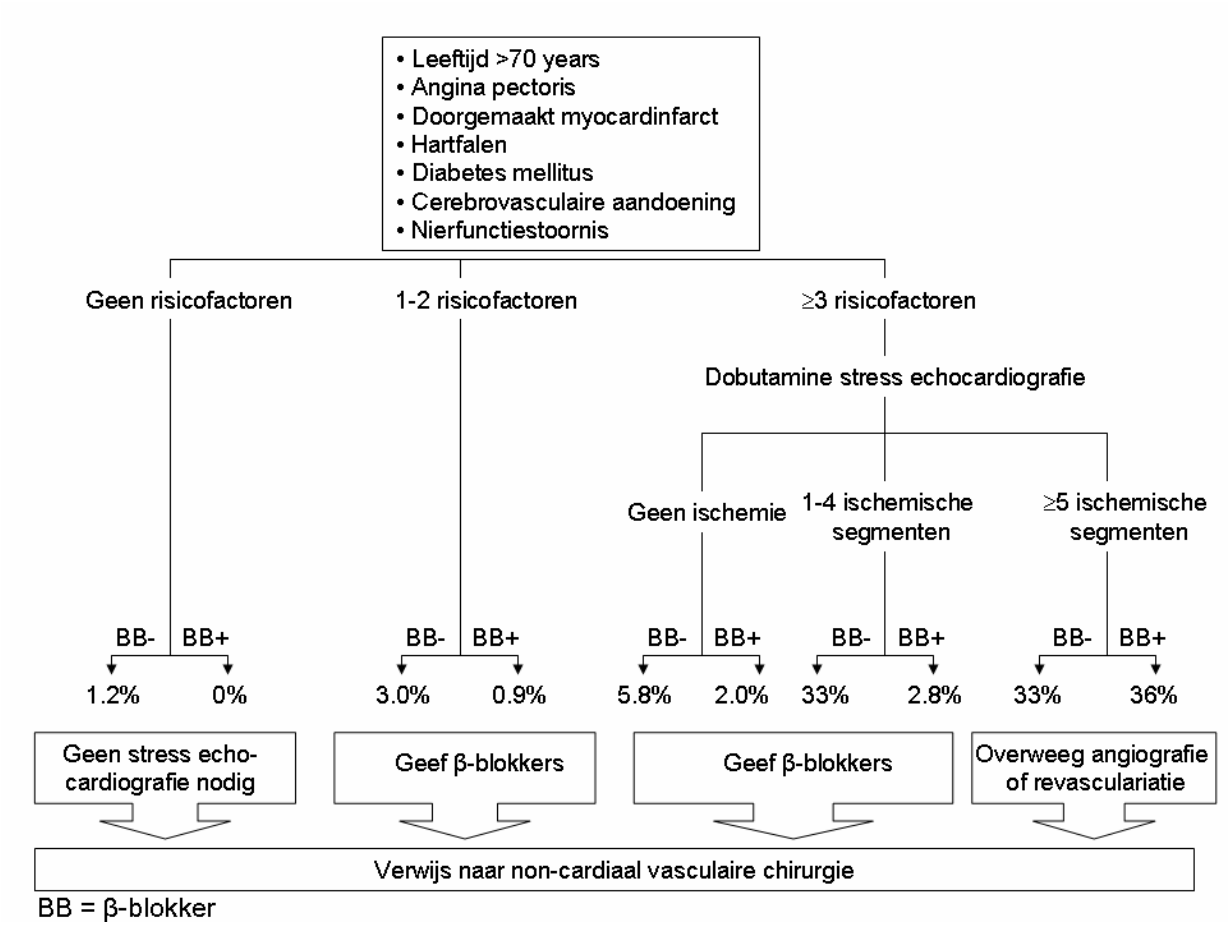
Verschillende risico-indicatoren zijn ontwikkeld om het risico op perioperatieve complicaties te kunnen inschatten. Lee's gereviseerde cardiale risico-index wordt het meest gebruikt [7]. Deze risico-index was ontwikkeld bij patiënten ≥50 jaar die een niet-cardiale, electieve chirurgische ingreep ondergingen waarvan de verwachte ziekenhuis duur twee dagen of langer was. Deze index gebruikt 6 voorspellers voor cardiale complicaties: 1) hoogrisico chirurgie, 2) ischemische hartziekte, 3) hartfalen, 4) cerebrovasculaire aandoeningen, 5) diabetes mellitus en 6) een gestoorde nierfunctie. De geschatte prevalentie van cardiale complicaties bij aanwezigheid van 0, 1, 2, of ≥3 van deze voorspellers was respectievelijk 0.4%, 0.9%, 7% en 11%. Recente studies hebben aangetoond dat inschatting van het risico verbeterd kan worden door preoperatieve bepaling van het natriuretisch hormoon [8-11]. Verder is rust echocardiografie geïndiceerd voor

het detecteren van linkerventrikeldysfunctie bij patiënten met hartfalen. Ook kunnen hartklepaandoeningen opgespoord worden, zoals aortaklepstenose, welke geassocieerd zijn met verhoogde perioperatieve sterfte. [12]. Richtlijnen adviseren verder een niet-invasieve cardiale stress test bij patiënten met een hoog risico [13]. Gezien de prognostische nauwkeurigheid kan in dit verband een voorkeur gegeven worden aan farmacologische stress echocardiografie [14]. Een schematische stappenplan voor het perioperatief beleid is weergegeven in Tabel 1.

β-BLOKKERS

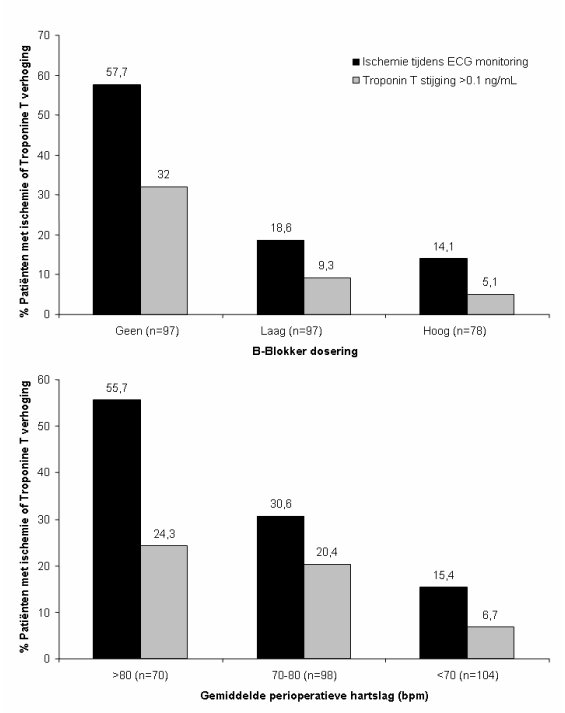
Meerdere studies hebben aangetoond dat β-blokkers de incidentie van perioperatieve myocardischemie en cardiale complicaties kunnen reduceren [15,16,17]. Het stroomdiagram (figuur 2) bijvoorbeeld laat de incidentie in perioperatieve cardiale complicaties zien in laag-, intermediair- en hoogrisico patiënten met of zonder β-blokkers. Overtuigend zijn twee gerandomiseerde studies bij hoogrisico patiënten. De eerste studie evalueerde het effect van atenolol bij 200 hoogrisico patiënten die een niet-cardiale ingreep ondergingen. Hoewel er geen verschil was in perioperatieve sterfte, was er een significant lager sterftecijfer 6 maanden na ontslag (0 vs. 8%, $P < 0.001$), in het eerste jaar (3 vs. 14%, $P = 0.005$) en na 2 jaar follow-up (10 vs. 21%, $P = 0.2$) [16]. De tweede studie toonde bij 112 hoogrisico patiënten met stressgeïnduceerde myocardischemie aan dat het gebruik van bisoprolol geassocieerd was met een 10-voudige reductie in de gecombineerde eindpunten perioperatieve cardiale sterfte en het optreden van myocardinfarct, in vergelijking met placebo [17].

Recent gepubliceerde studies vermelden echter tegenstrijdige resultaten [18,19]. In een studie waarbij



Figuur 2. Incidentie van perioperatieve cardiale sterfte of niet-fataal myocardinfarct in vaatchirurgische patiënten [zie referentie 15].

metoprolol of placebo gegeven werd aan vasculair chirurgische patiënten 2 uur voor operatie tot een maximum van 5 dagen na de operatie werd geen verschil waargenomen in cardiale complicaties na 30 dagen en 6 maanden [18]. In een studie waarbij 1 dag voor operatie tot maximaal 8 dagen erna metoprolol of placebo gegeven werd aan chirurgische patiënten met diabetes mellitus werd ook geen verschil waargenomen [19]. Deze negatieve resultaten kunnen verklaard worden door een onvoldoende dosering in β-blokker en een onvoldoende verlaging in hartslagfrequentie (Figuur 3) [20]. Ook kunnen deze resultaten verklaard worden door de relatief korte duur van β-blokker toediening. Een studie heeft laten zien dat de prognose significant verbeterd wordt wanneer β-blokkers gecontinueerd worden na ontslag uit het ziekenhuis [21]. Tevens zijn er aanwijzingen dat kortwerkende β-blokkers (zoals metoprolol) minder cardioprotectief zijn dan langwerkende β-blokkers (zoals atenolol) [22]. Toekomstige studies zullen moeten uitwijzen of β-blokkers de perioperatieve sterfte verminderen in laag-intermediair risico patiënten.



Figuur 3. Incidentie van perioperatieve myocardischemie en troponine T stijging in relatie tot β-blokker dosering en hartslagfrequentie [zie referentie 20].

STATINES

Recente studies hebben laten zien dat statines de kans op perioperatieve cardiovasculaire complicaties kunnen verlagen [23]. De gunstige eigenschappen van statines kunnen naast het lipide-verlagend effect verklaard worden door de zogenoemde pleiotrope effecten, zoals oxidatieve stress reductie, ontstekingsreductie en plaque stabilisatie [24]. Ook zijn er aanwijzingen dat perioperatieve toediening van statines de verblijfsduur in het ziekenhuis verkorten en postoperatieve nierfunctieverslechtering na suprarenale afklemming van de aorta kan voorkomen [25,26]. De DECREASE III studie is een gerandomiseerd onderzoek in vaatchirurgische patiënten dat het effect van statines op onstekingsparameters en perioperatieve mortaliteit evalueert. De DECREASE IV studie is een gerandomiseerd onderzoek in laagintermediair risico patiënten met een niet-cardiaal, niet-vasculair chirurgische ingreep dat het effect van β-blokkers en statines op perioperatieve sterfte evalueert [27]. Deze studies zullen meer inzicht geven in het effect van statines op perioperatieve ontstekings-mediatoren en op cardiovasculaire uitkomst in niet-cardiaal chirurgische patiënten.

OVERIGE MEDICATIE

Andere middelen met potentieel cardioprotectieve effecten zijn calcium antagonisten (dihydropyridines en non-dihydropyridines), nitroglycerine en a_2-receptor agonisten (clonidine, dexmedetomidine, mivazerol). Er zijn enkele studies met relatief weinig patiënten verricht die gekeken hebben naar de effecten van non-dihydropyridines (diltiazem) in de perioperatieve periode [28]. Hoewel bradycardie relatief vaker voor kwam in patiënten met diltiazem, leek het de perioperatieve incidentie op myocardinfarct niet te reduceren [28]. α_2-Receptor agonisten lijken perioperatief wel cardioprotectieve eigenschappen te hebben. Het is aangetoond dat zowel mivazerol als clonidine de incidentie van perioperatieve cardiovasculaire complicaties kan reduceren [29,30]. α_2-Receptor agonisten verminderen het vrijkomen van endogeen noradrenaline. Hierdoor zou cardiale ischemie tijdens chirurgie voorkomen kunnen worden. Het bewijs ten gunste van α_2-receptor agonisten is echter nog gebaseerd op te weinig onderzoek, waardoor een eventuele gunstige invloed op de lange termijn vooralsnog onopgehelderd blijft. Verder is het de vraag of α_2-receptor agonisten superieur zijn in vergelijking met β-blokkers en statines en of deze medicamenten elkaar in werking kunnen complementeren.

CONCLUSIE

Vaatchirurgische patiënten hebben een hoog risico op cardiale complicaties. Risico-inschatting in deze patiënten is belangrijk zodat optimaal medisch beleid

toegepast kan worden voor risicoreductie. β-Blokkers worden geadviseerd in hoogrisico patiënten en statines zouden overwogen moeten worden. Risico reductie moet gericht zijn zowel op de korte-termijn als lange-termijn periode.

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