Travelling beyond the current frontiers:

Perioperative and long-term cardiac risk assessment and management of patients undergoing major vascular surgery

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Travelling beyond the current frontiers: Perioperative and long-term cardiac risk assessment and management of patients undergoing major vascular surgery

Voorbij de bestaande grenzen:
Inschatting en behandeling van het peri-operative en lange termijn risico bij patiënten die een grote vaatoperatie ondergaan

Thesis

To obtain the degree of Doctor from the Erasmus University Rotterdam by command

of the Rector Magnificus

Prof. dr. S.W.J. Lamberts

and according to the decision of the Doctorate Board
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By

Miklos David Kertai

born in Szeged, Hungary

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In memory of Ignác Semmelweis

Contents

Preface

Patients undergoing major vascular surgery are at increased risk for perioperative and long-term cardiac complications. Despite recent advances in perioperative and long-term care, the 30-day cardiac death rate of major vascular surgery varies between 3-6%, and the cardiac event rate during long-term follow-up between 30%-40% (1, 2). The high incidence of perioperative and late cardiac complications in these patients is associated with a higher prevalence of coronary artery disease. Thirty-six percent of patients undergoing abdominal aortic aneurysm repair and in about 28% of patients undergoing infrainguinal revascularization have severe coronary artery disease, and only 6% of all vascular patients have normal coronary arteries (3).

Cardiac risk factors and noninvasive diagnostic tests for coronary artery disease may help to identify high-risk patients before major vascular surgery. Subsequent pharmacological therapy may be utilized in these high-risk individuals in order to lower their risk during and after vascular surgery. Based on the findings described in this thesis we are now able to classify patients as low-, intermediate-, or high-risk ones for cardiac complications after vascular surgery. These risk stratification tools include patients' baseline characteristics, dobutamine stress echocardiography, 12-lead electrocardiography and cardiac troponin T. Identification of these patients may help clinicians to introduce clinical measures including regular outpatient clinic visits, medication use or further evaluation and treatment of coronary artery disease.

Outline of the thesis

Part 1: Preoperative risk evaluation-clinical risk factors

Cardiac risk stratification begins with the assessment of clinical history and knowledge of the surgical and anesthesiological procedures being performed. A number of risk indices have been developed over the past decades (4-6), and baseline characteristics identified associated with adverse cardiac outcome. In this

part of the thesis after summarizing the current knowledge about cardiac risk factors and cardiac risk assessment in patients undergoing major vascular surgery we further explore the additional value of risk factors such as decreased creatinine clearance, aortic stenosis and elevated troponin T levels. Moreover, the performance of two previously developed risk models are tested, and a new risk model based on baseline characteristics, type of surgery and electrocardiographic abnormalities is proposed.

Chapter 1 is a systematic review describing the pathophysiology of perioperative cardiac complications, cardiac risk assessment and risk reduction strategies of patients undergoing major vascular surgery. This comprehensive review puts emphasis on preoperative cardiac evaluation of patients undergoing major vascular surgery, which could provide clinicians with an opportunity to reduce perioperative and late cardiac risk through prevention and optimal treatment of myocardial ischemia.

In chapter 2, a comparison is made between serum creatinine and creatinine clearance for the prediction of postoperative mortality in 852 patients undergoing major vascular surgery.

In chapter 3, the incidence of perioperative events in patients with aortic stenosis undergoing noncardiac surgery is assessed. The elevated risk of perioperative complication for 108 patients with moderate to severe aortic stenosis is compared to patients without aortic stenosis.

Subsequently, in chapter 4 the safety of performing dobutamine stress echocardiography in patients with aortic stenosis is described. Our own experience is evaluated on the basis of 75 patients with aortic stenosis who underwent either low-dose dobutamine stress echocardiography for the assessment of the severity of aortic stenosis, or a full-dose protocol for diagnostic purposes.

In chapter 5, we assessed the long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after successful major vascular surgery. Long-term mortality rates were compared for patients with and without cardiac troponin T elevations.

In chapter 6, a validation of two risk models for perioperative mortality in patients undergoing abdominal aortic aneurysm surgery is described. Using data of 361 patients who underwent abdominal aortic aneurysm surgery we compare the

performance of the so-called Leiden and the United Kingdom Small Aneurysm Trial prediction models.

Next, in chapter 7 we evaluate the perioperative cardiovascular mortality in 108,613 noncardiac surgical procedures based on the Erasmus Medical Center experience during 1991-2000. A risk model is described based on clinical risk factors, type of surgery and resting electrocardiographic abnormalities.

Part 2: Preoperative cardiac risk evaluation-noninvasive testing

Patient with multiple cardiac risk factors are often referred for further cardiac risk assessment by noninvasive testing prior to major vascular surgery. The prognostic accuracy of individual noninvasive diagnostic tests has been extensively evaluated over recent decades (6, 7). However, it is still uncertain, which of these tests shows the best prognostic accuracy. In this part of the thesis we evaluate the additional prognostic value of dobutamine stress echocardiography for the decision on the timing of abdominal aortic surgery; and to evaluate the comparative performance of different noninvasive tests for predicting perioperative cardiac risk.

In chapter 8, we propose an individualized clinical approach to perform early surgery for abdominal aortic aneurysm or institute ultrasonographic surveillance based on the combination of cardiac risk factors and dobutamine stress echocardiography.

In chapter 9, we compare the additional prognostic value of dobutamine stress echocardiography, dipyridamole stress echocardiography and dipyridamole myocardial perfusion scintigraphy on clinical risk factors in 2,204 consecutive patients undergoing major vascular surgery.

Subsequently, chapter 10 describes a meta-analysis of the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery.

Part 3: Perioperative pharmacological therapy

The efficacy of perioperative pharmacological therapy, especially beta-blocker therapy for the reduction of perioperative cardiac mortality and nonfatal myocardial infarction is well documented (8, 9). However, despite the beneficial effect of beta-blocker therapy, beta-blockers are currently underused in the perioperative setting

(10, 11). Additionally, data is emerging that other pharmacological agents, such as statins may have possible cardioprotective effect via influence on the vascular function, which results in coronary plaque stabilization and subsequently in preventing coronary plaque rupture leading to myocardial infarction (12). In this part of the thesis, we evaluate the reasons for withholding beta-blockers in the perioperative setting, beneficial effect of statin use for the reduction of perioperative mortality, and the combined effect of beta-blocker and statin use.

In chapter 11, reasons that may play role to withhold beta-blockers from high-risk patients with coronary artery disease are evaluated.

Next, in chapter 12 for the first time we describe that statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. In this case-control study, 160 patients who died during hospital stay are compared with 320 controls with regard to cardiac risk factors and statin use.

Subsequently, chapter 13 evaluates whether statins and beta-blocker are independently associated with a reduced incidence of perioperative mortality in patients undergoing abdominal aortic aneurysm surgery.

Part 4: Long-term pharmacological therapy

After major vascular surgery patients still remain at increased risk of cardiac-related death and nonfatal myocardial infarction (1, 2). The frequency of late cardiac morbidity reflects the high prevalence of underlying coronary artery disease (3). The optimal approach to the diagnosis and long-term management of coronary artery disease, which is often stable or asymptomatic in patients who underwent major vascular surgery, is unclear. This part of the thesis assesses the diagnostic utility of dobutamine stress echocardiography, and the cardioprotective effect of beta-blocker and statin use.

In chapter 14, the optimal long-term cardiac management after major vascular surgery is described based on follow-up data of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography study. The follow-up study was conducted in 1,286 patients who survived surgery for at least 30 days. The role of beta-blocker therapy, clinical characteristics, and dobutamine stress echocardiography is evaluated for the sake of long-term cardiac management.

Finally, chapter 15 deals with long-term statin use after major vascular surgery. A follow-up study describes the effects of statin use, and the additional effect of beta-blocker use on the incidence of all-cause and long-term cardiovascular mortality in patients who have undergone successful abdominal aortic aneurysm surgery.

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Chapter 1

Cardiac complications after elective major vascular surgery

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Review Article

Cardiac complications after elective major vascular surgery

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Cardiac complications are the major cause of perioperative and late mortality and morbidity in patients undergoing elective major vascular surgery. This review focuses on the pathophysiology of perioperative complications, risk assessment and risk reduction strategies, all related to cardiovascular disease. Patients without cardiac risk factors are considered to be at low risk and no additional evaluation for coronary artery disease is recommended; β-adrenergic blockers may reduce perioperative cardiac events; patients with one or more risk factors represent an intermediate to high-risk population. β-Adrenergic blockers should be prescribed to all patients and coronary revascularization should be reserved for patients who have a clearly defined need for revascularization independent of the need for vascular surgery.

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Key words: B-advenergic antagonists; cardiac complications; non-invasive tests; risk assessment; vascular surgery

CARDIAC complications are the major cause of perioperative and late mortality and morbidity in patients undergoing major vascular surgery. This is related to the presence of underlying coronary artery disease (CAD). CAD may be asymptomatic because of diabetic neuropathy, and reduced exercise capacity due to non-cardiac diseases such as a stroke or claudication. Careful pre-operative evaluation and management of cardiac risk factors offers the physician a unique opportunity to improve patients' perioperative and long-term outcomes.

The clinical problem

The burden of peripheral arterial disease (PAD) is escalating in Europe and North America. In the Netherlands, the number of patients admitted to hospital between 1980 and 1995 with PAD increased from 17,511 to 29,346, which is an increase of 36% after correction for demographic factors (1). An increase in the prevalence of abdominal aortic aneurysms was also observed in the UK Small Aneurysm Trial (2). In 1.5–3.0% of men older than 60 years of age, ultrasound screening revealed an occult aortic aneurysm with a diameter between 40 and 59 mm, and a large number of these patients will eventually require elective surgery if the diameter exceeds 55 mm (2). The reportedly high incidence of perioperative and late cardiac complications in these patients is associated with a higher prevalence of CAD. In a landmark study by Hertzer et al., haemodynamically significant CAD was reported in 36% of patients with abdominal aortic aneurysms and in 28% of patients with lower-extremity ischaemia (3). However, the frequency of adverse cardiac outcomes may vary according to the type of vascular surgery. Krupski et al. reported a similar cardiac event rate after infrainguinal procedures as after aortic operations (9% vs. 7%, respectively) (4) but late events occurred about twice as often in patients who underwent infrainguinal surgery as those who underwent aortic procedures (25% vs. 8% at 2-year follow-up). In contrast, L'Italien et al. reported a two-fold increased risk of cardiac complication rates in infrainguinal procedures compared with aortic procedures (13% vs. 6%) (5), and different non-fatal myocardial infraction (MI) rates after aortic and infrainguinal operations were reported with 2.2% and 4%, respectively (6).

Pathophysiology

The primary cause of perioperative cardiac events is myocardial ischaemia, and most of these events occur on the second or third day after surgery (7, 8).

The ischaemia may arise either from increased myocardial oxygen demand or reduced supply. Tachycardia and hypertension resulting from surgical stress, pain, interruption of β-adrenergic blockers, or the use of sympathomimetic drugs all increase myocardial oxygen demand. Decreased supply may be the result of hypotension, vasospasm, anaemia, hypoxia, or plaque rupture with thrombosis.

The location of a perioperative MI is not always related to the location of the culprit coronary lesion. In a study conducted by Dawood et al., histopathological analysis of coronary arteries and myocardium was compared in 42 patients who died of perioperative MI and 25 patients who died of non-perioperative MI (9). Evidence of plague disruption was noted in 55% of perioperative MI patients. Predicting the site of infarction based on severity of underlying stenosis would have been unsuccessful in more than half the patients in both perioperative and non-perioperative MI groups. These findings were also confirmed in a population of 32 patients who died within 30 days after major vascular surgery. In this study, the location(s) of the culprit coronary lesion was assessed preoperatively by dobutamine echocardiography (DE) and compared with the location of the MI at autopsy (10). DE showed myocardial ischaemia in 16 patients, and in seven patients in multiple coronary regions; however, DE did not predict the location of the perioperative MI in 36% of these patients. This may indicate the presence of CAD in numerous locations throughout the coronary tree in patients with fatal perioperative MI and/or the possibility that perioperative MI may result from plaque rupture and thrombosis at the site of a haemodynamically insignificant atherosclerotic plaque (11). In addition to acute plaque rupture and thrombosis, prolonged perioperative myocardial ischaemia has been suggested as the other mechanism of major cardiac complications in non-cardiac surgery. Landesberg et al. performed continuous ECG monitoring in 151 patients who underwent major vascular surgery (12). Thirteen patients had major cardiac complications including MIs, unstable angina and congestive heart failure. Overall, 85% of post-operative cardiac events were preceded by long-duration ST-segment depression, and five out of the six post-operative MIs were non-Q-wave infarctions. Similar findings were reported in studies from Fleisher et al. and Rapp et al. (13, 14). In the study of Fleisher et al., 145 high-risk non-cardiac surgery patients were also continuously monitored using ambulatory ECG during the perioperative period. Nine patients sustained a clinically apparent cardiac event; seven of whom had a cardiac event and had at least one episode of prolonged myocardial ischaemia ($\geq$30 min) either prior to or at the same time as the event. Rapp et al. used a combination of continuous ECG monitoring and repeated cardiac troponin T measurements in 20 patients who underwent elective abdominal aortic surgery (14). Eight patients (40%) had new episodes of ST-segment depression, and of these, three patients (37%) had long-lasting ST-segment depression with elevated cardiac troponin T levels. In summary, these studies indicate that patients having prolonged and repeated ischaemic episodes are at a high risk of myocardial cell injury and adverse cardiac events (15).

Pre-operative cardiac risk assessment

Identification of high-risk patients

Risk stratification begins with the assessment of clinical history and knowledge of the surgical procedure being performed. A number of risk indices have been developed over the past two decades, such as the Goldman cardiac risk index, the Detsky modified multifactorial risk index and Eagle's risk score (16–18). These risk indices stratify patients into low-, intermediate-, or high-risk groups with respect to the likelihood of cardiac complications during the perioperative period. However, the performance of these indices has been questioned. The performance of four different indices including the American Society of Anesthesiologists index, Canadian Cardiovascular Society index, the Goldman index and the modified Detsky index were prospectively compared in 2035 patients who underwent elective or urgent non-cardiac surgery (19). The results showed that these indices performed better than chance, but no index was significantly superior. Recently, Lee et al. (20) reviewed the predictive value of several clinical risk factors in patients scheduled for non-cardiac surgery. Six risk factors (high-risk surgery, stroke, diabetes mellitus, renal failure, congestive heart failure, and ischaemic heart disease) were identified in a study population of 2893 patients and later validated in a population of 1422 patients. The rate of major perioperative complications in the presence of 0, 1, 2, or $\geq$3 risk factors was 0.4%, 0.9%, 7%, and 11%, respectively. However, the limitation of this study was that only 3.8% (110 of 2893) of the study population underwent major vascular surgery and the positive predictive value of the index was low.

The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines for perioperative cardiovascular evaluation for non-cardiac

surgery provide an outline for considering cardiac risk of non-cardiac surgery in a variety of patients and surgical situations including vascular surgery (21). Although these recommendations attempt to identify low- and high-risk patients by perioperative clinical and non-invasive evaluation, few prospective or randomized studies have been performed to establish the value of different treatments on perioperative outcomes. Indeed, the validity of the guidelines has not been prospectively and adequately tested; however, there are studies evaluating the performance of the ACC/AHA guidelines in non-cardiac surgery. Bartels et al. prospectively evaluated a similar protocol to ACC/AHA guidelines in 203 patients scheduled for aortic surgery (22). According to the ACC/AHA guidelines, patients were stratified into low ($n = 101$), intermediate ($n = 79$), and high ($n = 23$) cardiac risk. In intermediate-risk patients with an estimated functional capacity <5 metabolic equivalents and in all high-risk patients, non-invasive cardiac testing and/or subsequent medical care was performed. Of these patients, 41 (20%) underwent non-invasive testing, and seven coronary angiographies and one myocardial revascularization were performed; and the perioperative cardiac death and non-fatal MI rates were 5%, respectively. The results showed that risk stratification according to the ACC/AHA guidelines provided excellent clinical outcome (total cardiac morbidity in the low-, intermediate- and high-risk categories were 9%, 14% and 24%, respectively). In a similar but retrospective study, Morgan et al. studied 85 patients who underwent DE in accordance with the ACC/AHA guidelines (23). The DE was positive for myocardial ischaemia in four, negative in 74 and non-diagnostic in seven patients. The positive predictive value of the ACC/AHA guidelines for selecting patients with a positive DE was 4.7%. Analysis of the study group revealed that no positive DEs were obtained among patients with one or more minor predictors or among those with only one intermediate clinical predictor (i.e. diabetes mellitus or mild angina). On the basis of these findings, it was concluded that the use of the current ACC/AHA guidelines for pre-operative DE testing results in a small frequency of positive tests.

Patients with no cardiac risk factors are generally at low risk and need no further evaluation or therapy (24, 25). The occurrence of ischaemia on stress testing has a low positive predictive value in such patients and may be associated with more false–positive than true–positive results (25). In the case of patients with one or more cardiac risk factors {angina pectoris, previous MI, diabetes mellitus, congestive heart failure, cardiac arrhythmias, age >70 years, renal failure [creatinine clearance >2mg/dl (180 μmol/l)]} or for patients with reduced exercise capacity, additional non-invasive testing is recommended (21). The least expensive non-invasive test for myocardial ischaemia is exercise electrocardiography (Ex-ECG), which can be safely performed in an outpatient setting. Pooled data from seven studies indicate that Ex-ECG has a sensitivity of 74% and a specificity of 69% in the prediction of cardiac death and MI (26). However, the presence of resting ECG changes (bundle branch block, left ventricular hypertrophy, ventricular pacing and digitalis effect) may preclude reliable ST-segment analysis in 40% of patients (21). Moreover, patients with occlusive vascular disease of the lower extremities often are unable to exercise because of claudication. Therefore, pharmacological rather than exercise stress testing is often required in patients undergoing major vascular surgery. In this regard, dipyridamole myocardial perfusion imaging, usually combined with clinical risk assessment, is the most extensively studied non-invasive approach to cardiac risk stratification. The test provides information beyond that available from clinical evaluation and Ex-ECG (18). Pooled data from 24 studies indicate that dipyridamole perfusion scintigraphy has sensitivity for the prediction of adverse perioperative cardiac events of 83% and a specificity of 49% (26). The frequent occurrence of false–positive results, particularly with single photon perfusion scintigraphy, is a major limitation of this test. Attenuation artefacts such as breast tissue and the diaphragm can produce apparent perfusion defects.

Dobutamine-atropine echocardiography is a new tool for pre-operative and late cardiac risk assessment. The test detects resting LV dysfunction and, most importantly, inducible myocardial ischaemia. Both of these are known predictors of perioperative ischaemic complications and late cardiac death (27). It also detects and/or quantifies the severity of co-existing valvular heart disease. Second harmonic imaging has improved the accuracy of endocardial delineation (28), and it will likely reduce intra- and interobserver variability, which is one of the major limitations of DE.

An additional benefit of DE is its safety. In a recent review of 6595 stress tests (29–31), the incidence of cardiac arrhythmias and hypotension was, respectively, 8% and 3%. Pellikka et al. (32) confirmed the safety and feasibility of DE in 98 patients with aortic aneurysms. There were no cases of aneurysm rupture or hemodynamic instability. Thus, the complication rate of DE is similar to that of dipyridamole perfusion scintigraphy (33) or Ex-ECG (34).

Comparison of perfusion imaging and echocardiography

There have been few comparisons of the various imaging techniques used for perioperative risk assessment. Preliminary data from 43 patients suggest that both dipyridamole echocardiography and dipyridamole perfusion imaging have a high negative predictive value (94% and 88%, respectively), but dipyridamole echocardiography has a higher positive predictive accuracy (67% vs. 37%) (35). A meta-analysis by Shaw et al. (36) compared dipyridamole perfusion imaging and DE, although not in the same patients. Both tests had similar predictive accuracy although the summed odds ratios for cardiac death and MI were greater for DE than for dipyridamole perfusion imaging. However, the confidence intervals for the DE were large because of the smaller number of patients. An earlier meta-analysis by Mantha et al. also compared the relative effectiveness of dipyridamole perfusion imaging and DE, among other tests, for the prediction of adverse cardiac outcome after vascular surgery (37). DE had a higher predictive value than dipyridamole perfusion imaging but again the data were not definitive enough in determining the optimal test as confidence intervals were overlapping. Recently, the predictive value of six non-invasive tests was compared using a novel meta-analytic approach (26). Our results demonstrated that, compared with other test modalities, DE showed higher overall sensitivity but it was only significantly higher than radionuclide ventriculography (RNV). Although the specificity of DE was also high compared with other tests but it was only significantly higher than the specificity of myocardial perfusion scintigraphy (Table 1). Other non-invasive tests including ambulatory ECG, Ex-ECG and RNV yielded lower sensitivity and reasonable specificity, with no significant difference in predictive performance (Table 2). When the prognostic accuracy of these tests was estimated through a summary receiver–operator characteristic (ROC) analysis, DE showed a positive trend for a better diagnostic performance compared with all other tests but it was only significantly better than myocardial perfusion scintigraphy (Table 2). However, DE could be the favoured test if there is an additional question about valvular and left ventricular dysfunction.

Cardiac risk reduction strategies

Risk reduction strategies aimed at reducing the incidence of perioperative cardiac complications can be grouped into two categories: perioperative medical therapy and pre-operative coronary revascularization.

Perioperative medical therapy

β-Adrenergic antagonists

The ability of β-adrenergic antagonists to reduce the perioperative incidence of cardiac death and non-fatal MI has been widely studied. The first randomized controlled study evaluating the cardioprotective effect of β-adrenergic antagonists in patients undergoing major surgery was performed by Mangano et al. (38). In this study, 200 patients who had, or were at high risk from, CAD were randomly assigned to receive atenolol or placebo during the perioperative period. Atenolol was administered intravenously or orally beginning 2 days preoperatively and continued for 7 days postoperatively. The patients were monitored perioperatively for cardiac events and then followed for 2 years after surgery. There was no difference in the incidence of perioperative MI or cardiac-related

Table 1

Meta-analysis sensitivity and specificity of pre-operative tests for perioperative cardiac death and non-fatal myocardial infarction in patients undergoing elective major vascular surgery* (26)

Non-invasive† test	No. of patients	Sensitivity (%; 95% CI)	Specificity (%; 95% CI)
A-ECG	893	52 (21–84)	70 (57–83)
Ex-ECG	685	74 (60–88)	69 (60–78)
RNV	532	50 (32–69)	91 (87–96)
MPS	3354	83 (77–89)	49 (41–57)
DiSE	850	74 (53–94)	86 (80–93)
DE	1877	85 (74–97)	70 (62–79)

* CI indicates confidence interval.
† Tests are sorted according to ascending sensitivities; A-ECG: ambulatory electrocardiography; Ex-ECG: exercise electrocardiography; DE: dobutamine stress echocardiography; MPS: myocardial perfusion scintigraphy; RNV: radionuclide ventriculography; DISE: dipyridamole stress echocardiography.

Table 2

Results of the comparison of summary receiver operating characteristic analyses between diagnostic tests* (26)

Reference test	A-ECG	Ex-ECG	RNV	MPS	DE
A-ECG		0.6 (0.2–1.8)	0.2 (0.0–1.0)	1.6 (0.5–5.0)	0.3 (0.1–1.0)
Ex-ECG	1.6 (0.5–24.5)		0.5 (0.0–6.1)	2.7 (0.3–8.2)	0.6 (0.2–1.8)
RNV	5.5 (1.1–24.5)	2.2 (0.2–30.0)		5.5 (0.8–36.6)	0.9 (0.1–18.2)
MPS	0.6 (0.2–1.8)	0.4 (0.1–30.0)	0.2 (0.0–1.2)		0.3 (0.1–0.6)†
DE	3.0 (1.2–7.4)	1.6 (0.5–4.5)	1.1 (0.1–20.1)	4.1 (1.6–10.0)†	

*A-ECG; ambulatory electrocardiography; Ex-ECG; exercise electrocardiography; RNV; radionuclide ventriculography; MPS; myo perfusion scintigraphy; DE: dobutamine stress echocardiography. The figures indicate relative diagnostic odds ratios for comp between the reference test in the column vs. the test in the row. The relative diagnostic odds ratio indicates the diagnostic performa a test, with a value larger than one indicating better discriminatory power, whereas a value equal to one no difference, and values one corresponding to reduced discriminatory ability. Figures in parenthesis are the 95% confidence intervals.
†$P < 0.01$.

death. During the follow-up period, the mortality was 10% in patients who had been previously given atenolol and 21% in the controls. The failure of atenolol to significantly alter the perioperative outcome may be related to the low incidence (3%) of serious perioperative cardiac events in the study population. The study included both patients with known CAD and those with only coronary risk factors, and patients underwent various surgical procedures.

In contrast, Poldermans et al. investigated the perioperative use of bisoprolol in elective major vascular surgery (8). Bisoprolol was started on average 30 days preoperatively with dose adjustment to achieve a resting heart rate of ≤ 60 beats per minute, and continued for 30 days postoperatively. The study was confined to a population of high-risk patients identified by the presence of both clinical risk factors and a positive DE. Patients with extensive regional wall-motion abnormalities were excluded. The overall incidence of the combined end-point of cardiac death or non-fatal MI was reduced 10-fold from 34% in the standard-care group to 3.4% in the bisoprolol group (Fig. 1).

In summary, perioperative β-blocker therapy should be started before surgery, even up to 1 month prior to the planned procedure, with a dose adjustment to achieve a resting heart rate of ≤ 60 beats per minute. Dose adjustment should take place as an outpatient procedure and up to the induction of anaesthesia. β-Blocker therapy should be continued at least through hospitalization, and longer if adequate and regular medical follow-up can be arranged (39).

Alpha2-adrenergic agonists

The effect of alpha2-adrenergic agonists has also been studied perioperatively. Randomized studies comparing clonidine and placebo failed to demonstrate that clonidine reduced the rates of MI and cardiac death (40, 41). Mivazerol, an intravenous alpha2-adrenergic agonists, was compared with placebo in a cohort of 2801 patients who were known to have CAD or risk factors for it and who underwent major vascular, thoraco-abdominal or orthopaedic procedures (42). There was no overall effect of mivazerol in the whole study population on the pre-specified combined end-point of MI and cardiac death. However, a post hoc analysis showed that in a subgroup of 904 patients with known CAD who underwent major vascular surgery, mivazerol was associated with a significantly lower incidence of MI and cardiac death.

Other agents

The prophylactic use of other agents such as nirtoglycerin or diltiazem have been studied for the prevention of cardiac complications (43, 44). However, these studies were too small to have the power to detect differences in the incidence of cardiac events.

Pre-operative coronary revascularization

Percutaneous revascularization

Pre-operative evaluation may occasionally identify a patient who would benefit from coronary revascularization. The use of percutaneous transluminal coronary angioplasty (PTCA) has been studied in patients undergoing non-cardiac surgery (45–47). The indication for PTCA most likely included the need to relieve symptomatic angina or to reduce the perioperative risk of ischaemia identified by non-invasive testing. The incidence of perioperative cardiac death and non-fatal MI was low in all three studies, but no comparison group with CAD not treated by PTCA was included. In a more recent study, Posner et al. (48) compared adverse cardiac outcomes after non-cardiac surgery among patients with prior PTCA, patients with non-revascularized CAD and normal controls.

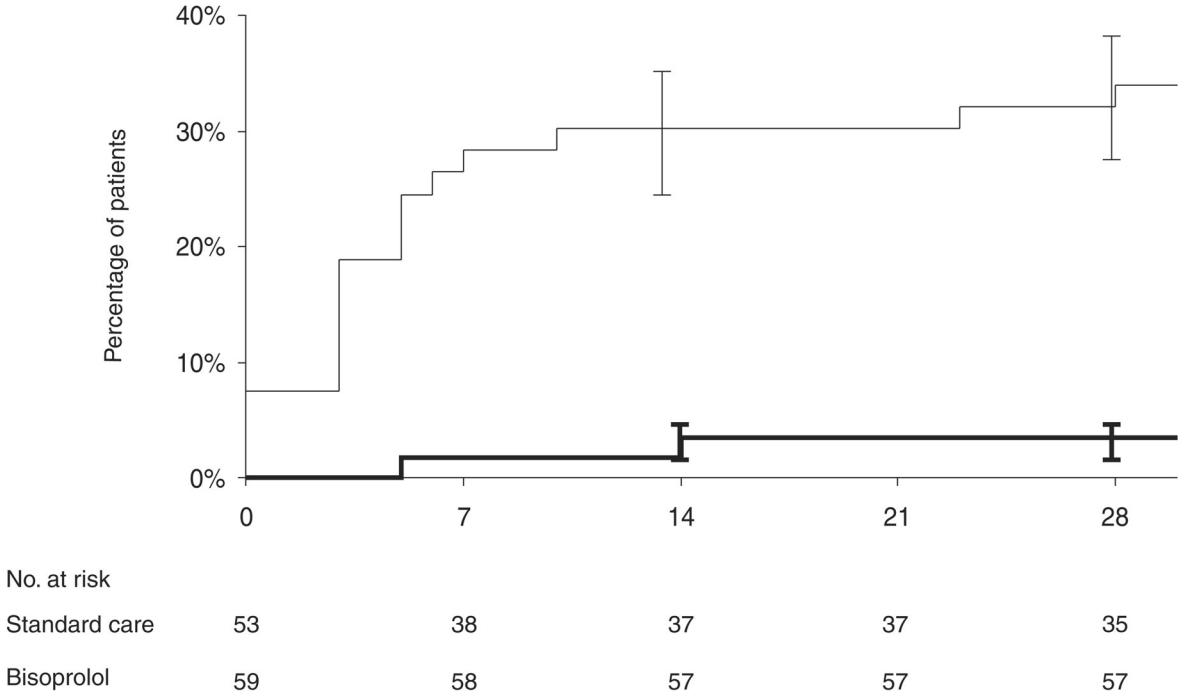

Fig. 1. Kaplan–Meier estimates of the cumulative percentages of patients who died of cardiac causes or had a nonfatal myocardial infarction during the perioperative period. Bars indicate standard errors. The difference between groups was significant ($P < 0.001$ by the log-rank test) (8).

The results of the study showed that patients revascularized by PTCA within 90 days of non-cardiac surgery had a perioperative outcome similar to matched patients with CAD who had not been revascularized. Although PTCA reduced the overall risk of perioperative cardiac events compared with non-revascularized patients with CAD, this effect was limited to a reduction in the incidence of angina pectoris and congestive heart failure. PTCA did not reduce the incidence of death and non-fatal MI. So far, these results were derived from retrospective studies and data from randomized clinical trials are lacking. Yet, the findings of the available studies, together with the inherent risk of PTCA, suggest that prophylactic use of PTCA in the weeks or months before non-cardiac surgery is not a reliable method of reducing perioperative cardiac risk.

Patient recently treated with PTCA and coronary stenting are at high risk from perioperative coronary thrombosis or major bleeding complications. Kaluza et al. studied 40 patients who underwent coronary stent placement less than 6 weeks before major non-cardiac surgery (49). In the perioperative period, there were seven MIs, 11 major bleeding episodes and eight deaths. All deaths and MIs, as well as eight of 11 bleeding episodes, occurred in patients subjected to surgery within 14 days of stenting. Stent thrombosis accounted for most of the fatal events and was caused by the interruption of antiplatelet drugs within one or two days before surgery. In contrast, serious bleeding complications occurred when antithrombotic therapy was continued until the time of surgery. In conclusion, these results suggest that PTCA with coronary stenting should be reserved for patients who have a clearly defined need for revascularization independent of the need for vascular surgery. If PTCA with coronary stenting is indicated, then elective non-cardiac surgery should be post-poned for 2–4 weeks after coronary stenting, to allow completion of the currently recommended antiplatelet therapy.

Coronary artery bypass grafting

The effectiveness of coronary artery bypass grafting (CABG) in reducing the incidence of perioperative cardiac complications has not been addressed by prospective, randomized trials. Eagle et al. have conducted the largest retrospective review to date, and their findings reveal that CABG has a protective effect prior to non-cardiac surgery (50). In this study, 3368 patients were enrolled in the Coronary Artery Surgery Study (CASS) registry and were either treated with

CABG or medical therapy. The authors found that prior CABG was protective in patients undergoing abdominal, vascular, thoracic or head and neck surgery. In this population, they noted a significant reduction in perioperative mortality (1.7% vs. 3.3%) and MI (0.8% vs. 2.7%) among patients who had undergone prior CABG, compared with those managed medically. The effect was greatest in patients with a history of advanced angina and/or multivessel CAD. Though this study suggests a protective effect of prior CABG during subsequent non-cardiac surgery, it does not account for the cumulative risks of coronary angiography and myocardial revascularization followed by non-cardiac surgery. These combined risks may exceed the risk of non-cardiac surgery alone in patients who have not undergone revascularization.

In a more recent study, a random sample of Medicare beneficiaries showed that pre-operative coronary revascularization was associated with a reduction in 1-year mortality for patients undergoing aortic surgery but had no effect on mortality among those undergoing infrainguinal surgery (51). These findings may generate a hypothesis that, successful bypass surgery may reduce the risk of perioperative and late cardiac complications among patients undergoing aortic surgery. However, this potential benefit is restricted to patients who survive revascularization.

In the Bypass Angioplasty Revascularization Investigation (BARI), coronary angioplasty was compared with CABG in 501 patients who subsequently underwent non-cardiac surgery after revascularization. Perioperative rates of cardiac death and MI were similarly low among patients with multi-vessel disease who had undergone either CABG or coronary angioplasty a median of 29 months prior to non-cardiac surgery (52).

In summary, these findings support the hypothesis that CABG, when indicated may reduce the risk of cardiac complications. However, one should take into account that the combined risks of bypass surgery and non-cardiac surgery may exceed the risk of non-cardiac surgery alone in patients who have not undergone revascularization.

Intra-operative and post-operative monitoring

Transoesophageal echocardiography and 12-lead electrocardiography

Intraoperative monitoring for myocardial ischaemia has been advocated to identify patients at high risk of perioperative ischaemic outcomes associated with non-cardiac surgery (53). However, conventional intra-operative monitoring techniques are relatively insensitive for myocardial ischemia. Therefore, there has been more reliance on sophisticated techniques such as transoesophageal echocardiography (TEE) and 12-lead ECG. Eisenberg et al. compared the routine monitoring for myocardial ischaemia with TEE or 12-lead ECG during non-cardiac surgery with clinical data and intra-operative monitoring using two-lead ECG. They concluded that TEE and 12-lead ECG had little incremental clinical value in identifying patients at high risk of perioperative ischaemic outcomes (54). The limitation of this study was that patients were under close hemodynamic control and the study was performed in a selected group of patients.

Perioperative monitoring

Isaacson et al. studied the utility of a pulmonary artery catheter or a central venous catheter for perioperative monitoring in patients undergoing abdominal aortic reconstructive surgery (55). No statistically significant difference occurred between the two groups with regard to morbidity (perioperative cardiac, pulmonary or renal sequel), mortality, and duration of intensive care, postoperative hospital stay, or cost of hospitalization. The authors concluded that the choice of central venous catheter or pulmonary artery catheter monitoring makes little difference in outcome after abdominal aortic surgery. In a later randomized clinical trial, the routine use of pulmonary artery catheters and haemodynamic optimization was studied in patients undergoing aortic surgery. The authors observed a higher number of cardiac and renal complications in the pulmonary artery catheter group compared with the standard group. The results of the study showed that the utility of pulmonary artery catheters during aortic surgery was not beneficial and may be associated with a higher rate of intra-operative complications (56). In contrast, the study of Wilson et al. showed that optimizing perioperative oxygen delivery by intense fluid therapy and vasoactive drugs guided by a pulmonary artery catheter reduced the risk of hospital mortality after major elective surgery (57). Finally, the Canadian Critical Care Clinical Trials Group (58) in a randomized study found no difference in hospital mortality in patients whom a pulmonary artery catheter was used compared with patients in the standard care group (7.8% vs. 7.7). The authors also observed a higher rate of pulmonary embolisms in the catheter group than in the standard care group (8% vs. 0%, $P = 0.004$).

Overall, there was no difference in survival rate at 6 and 12 months, and the median hospital stay was similar (10 days) in each group. The authors of this large, multicentre randomized clinical trial observed no benefit of treatment guided by a pulmonary artery catheter as compared with standard care.

Recently, Pronovost et al. related the organization characteristics of intensive care units (ICU) to outcome after abdominal aortic surgery (59). They found that daily rounds by an ICU physician were associated with a three-fold decrease in the incidence of in-hospital mortality and cardiac arrest. Similarly, the study of Dimick et al. also showed that high volume hospitals have a significantly lower death rate from abdominal aortic aneurysm repair than low volume hospitals (60). In conclusion, improved perioperative surveillance by medical staff is the only approach to monitoring in patients undergoing vascular surgery for which there is evidence of improved outcome.

Intraoperative and anaesthetic management

It has been hypothesized that intraoperative epidural anaesthesia and post-operative epidural analgesia may reduce the incidence of perioperative cardiac complications by blocking the stress response and associated hypercoagulability associated with major vascular surgery. Five randomized studies, involving over 600 patients, have examined the effect of epidural anaesthesia and/or analgesia on perioperative cardiac events in patients undergoing aortic surgery (61–65). None of these studies have demonstrated efficacy for epidural anesthesia/analgesia for the prevention of myocardial ischaemia, MI, or mortality. In contrast, a systematic review by Rodgers et al. (66) of all trials including 9559 patients with randomization to intra-operative neuraxial blockade (spinal or epidural) vs. standard care showed that overall mortality was reduced by 30% and MI by 33% in patients allocated to neuraxial blockade. Neuraxial blockade also reduced the risk of mortality by 34% in a subgroup of patients who underwent vascular surgery. The observed reduction in mortality did not differ by type of blockade or in trials in which neuraxial was combined with general anaesthesia. There are no studies that provide evidence whether neuraxial blockade is indicated or contraindicated in patients at risk from cardiac complications. It is also unclear whether the differences observed by Rodgers et al. between patients with neuraxial blockade vs. general anesthesia were due to the benefits of neuraxial blockade alone or were partially due to the avoidance of the adverse effects of general anaesthesia. The ongoing Multicenter Australian Study of Epidural Anesthesia and Analgesia in Major Surgery will provide evidence of the possible benefit of epidural anaesthesia improving outcome in high-risk patients (67). Nevertheless, serious complications (e.g. epidural haematoma) associated with neuraxial blockade are rare (68–70) and more common side-effects, such as headache or urinary retention, are not life threatening, thus the findings of this study should result in more widespread use of neuraxial anaesthesia.

A study by Frank et al. demonstrated a 55% reduction in risk of cardiac events in patients undergoing major surgery, including vascular surgery when intraoperative normothermia was maintained using forced air-warming devices and fluid warmers (71). These results imply that 20 hypothermic patients would need to be treated in order to prevent one morbid cardiac event due to hypothermia. Maintenance of normothermia would appear to be a safe and rational goal of intra-operative management.

Diagnosis of postoperative cardiac complications

In the perioperative period, sedative and analgesic drugs may mask coronary symptoms. The presence or absence of myocardial damage can be assessed objectively by several methods, including (1) measurement of myocardial proteins in the blood, (2) electrocardiographic recordings (ST-T segment changes new Q waves), and (3) imaging modalities such as myocardial perfusion imaging, echocardiography and contrast ventriculography (72).

Biochemical markers of myocardial injury and necrosis

Myocardial injury and necrosis can be diagnosed by the appearance of different proteins released into the circulation from the damaged myocytes. Myoglobin, cardiac troponins I and T, creatinine kinase (CK), creatinine kinase MB (CK-MB) fraction, and lactate dehydrogenase are the most commonly used biochemical markers of myocardial injury and necrosis (72).

The cardiac troponins have emerged as sensitive, specific and preferred biochemical markers of myocardial injury and infarction (73). Cardiac troponins T or I can be used to diagnose MI as these are not normally detectable in the blood of healthy individuals.

However, they increase after MI to levels over 20 times higher than the cut-off value (usually set only slightly above the noise level of the assay). Cardiac troponins are particularly valuable when there is clinical suspicion of either skeletal muscle injury (which often occurs during surgery) or a small MI that may be below the detection limit of CK and CK-MB measurements. Levels of cardiac troponins may remain elevated for up to 10–14 days, allowing what has been termed the retrospective diagnosis of acute MI.

Several investigations into the importance of cardiac troponin T as a marker for myocardial ischaemia have been undertaken in patients undergoing major non-cardiac surgery, including vascular surgery. In a prospective study of Lee et al., cardiac troponin T elevations occurred in 87% of patients with and in 16% of patients without MI. The rates of cardiac troponin T elevations were more common among patients with a known history of CAD and among patients undergoing high-risk operations, such vascular surgery. A ROC analysis indicated that cardiac troponin T had a similar performance for the diagnosis of acute MI similar to CK-MB, and a significantly better correlation with other major cardiac complications in patients with a definitive infarction (74). The study of Lopez-Jimenez et al. performed a 6-months follow-up of a subcohort of the same group of patients to determine whether patients who had elevated troponin levels without an overt MI were at greater risk for subsequent cardiovascular complications (75). Patients who had elevated cardiac troponin T were at almost a 5-times greater risk of cardiac complications at 6 months after adjustment was made for preoperative clinical and CK-MB data. Consistent with these studies is one conducted in patients who underwent major vascular surgery (76). In this study, blood samples were analysed for cardiac troponin I immediately after surgery and for 4 consecutive post-operative days. Twenty-eight patients (12%) had post-operative cardiac troponin I greater than 1.5 ng/ml, which was associated with a six-fold increased risk of 6-months mortality and a 27-fold increased risk of MI mortality. In conclusion, post-operative cardiac troponins provide important prognostic information, and routine cardiac troponin measurements are useful for identifying patients at increased risk from morbidity and mortality.

If cardiac troponin assays are not available, the best alternative is CK-MB (72). As with cardiac troponins, an increased CK-MB value is defined as one that exceeds the 99th percentile of CK-MB values in a reference control group. To diagnose MI, elevated values of biological markers should be recorded in two successive blood samples. Measurement of total CK is not recommended for the routine diagnosis of MI, because of the wide tissue distribution of this enzyme (72).

Electrocardiography

The ECG may show signs of myocardial ischaemia (ST-segment and T-wave changes) and/or signs of myocardial necrosis (e.g. new Q-waves). Myocardial ischaemia or necrosis may be defined from standard 12-lead ECG criteria in the absence of specific QRS changes (e.g. Bundle branch block, left ventricular hypertrophy, Wolf–Parkinson–White syndrome). However, not all patients who develop myocardial necrosis exhibit ECG changes. Therefore, a combination of sensitive biochemical markers and 12-lead ECG should be used for the verification of myocardial ischaemia or necrosis.

Imaging

There are three conventional imaging methods for diagnosing myocardial ischaemia and infarction. These are two-dimensional echocardiography, radionuclide angiography and single photon emission computed tomography (72). An advantage of echocardiography is its ability to allow for the assessment of most non-ischaemic causes of acute chest pain, such as pericarditis, valvular heart disease, pulmonary embolism and aortic pathology (77). Radionuclide techniques permit assessment of myocardial perfusion and function at the time of clinical symptoms. The quantitative analysis provided by these techniques is an attractive quality, and so too is the high accuracy when interpreted by skilled observers (78).

Nevertheless, biomarkers are more sensitive, more specific and less costly for the diagnosis of myocardial necrosis. For instance, injury involving at least 20% of myocardial wall thickness is necessary to enable the physician to detect a segmental wall motion abnormality with echocardiography. In case of radionuclide techniques more than 10 g of myocardial tissue must be injured before a radionuclide perfusion defect can be resolved (72).

Conclusions

Patients undergoing major vascular surgery without cardiac risk factors represent a low-risk population. Additional evaluation for CAD is not recommended and β-adrenergic blockers have only a marginal additional protective effect (25). However, considering the

unpredictable progression of CAD in these patients, long-term β-blocker therapy might be considered. Patients with one or more clinical risk factors represent an intermediate to high-risk population. Additional evaluation for CAD is recommended according to the ACC/AHA guideline on perioperative cardiovascular evaluation for non-cardiac surgery (21). Both nuclear tests and stress echocardiography can identify patients at risk from perioperative and late cardiac events. β-Adrenergic blockers should be prescribed to all patients and coronary revascularization should be reserved for patients who have a clearly defined need for revascularization, independent of the need for surgery. Maintenance of perioperative normothermia would appear to be a safe and rational goal of perioperative patient management. Increases in the physician-to-patient ratio in the ICU and intesivists rounding may result in a decrease in the incidence of in-hospital mortality and cardiac arrest. Pre-operative cardiac evaluation of patients undergoing major vascular surgery also provides clinicians with an opportunity to reduce perioperative and late cardiac risk through prevention and optimal treatment of myocardial ischaemia.

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Chapter 2

Comparison between serum creatinine and creatinine clearance for the prediction of postoperative mortality in patients undergoing major vascular surgery

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ORIGINAL

Comparison between serum creatinine and creatinine clearance for the prediction of postoperative mortality in patients undergoing major vascular surgery

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Key words
creatinine clearance – vascular surgery – postoperative mortality

Abstract. Background: Poor renal function prior to surgery is associated with increased risk for mortality in patients undergoing major vascular surgery. Traditionally, this function is assessed by serum creatinine concentration (SeCreat). However, SeCreat is also influenced by age, gender and body weight. Hence, creatinine clearance (C_{Cr}) is considered to be a better reflection of renal function. This study was undertaken to explore the prognostic value of preoperative calculated C_{Cr} compared to SeCreat for the prediction of postoperative mortality. Patients and methods: The study group comprised 852 consecutive patients who underwent elective major vascular surgery at the Erasmus Medical Center, Rotterdam. Preoperative C_{Cr} was calculated based on the Cockroft-Gault equation using preoperative SeCreat, age, body weight and gender. Univariable logistic regression analyses were used to study the relation between preoperative SeCreat, C_{Cr} and postoperative mortality. Furthermore, multivariable logistic regression analysis was applied to evaluate the additional predictive value of age, body weight and gender additional to SeCreat. The receiver operating characteristic (ROC) curve was determined to evaluate the predictive power of several regression models for perioperative mortality. Results: Postoperative mortality was 5.9% (50/852) within 30 days of surgery. In a univariable analysis, 10 μmol/l increment of SeCreat were associated with a 20% increased risk of postoperative mortality (OR = 1.2, 95% CI, 1.1 – 1.3) with an area under the ROC curve of 0.64 (95% CI, 0.56 – 0.71). If age, gender and body weight were added, the area under the ROC curve increased to 0.70 (95% CI, 0.63 – 0.77; $p < 0.001$), indicating that these risk factors had additional prognostic value. Indeed, in a separate regression analysis 10 ml/min decrease in C_{Cr} was associated with a 40% increased risk of postoperative mortality (OR = 1.4, 95% CI, 1.2 – 1.5; ROC area: 0.70, 95% CI, 0.63 – 0.76). ROC curve analysis showed that the cut-off value of 64 ml/min for C_{Cr} yielded the highest sensitivity/specificity to predict postoperative mortality. Conclusion: Preoperative SeCreat was strongly associated with postoperative mortality, and adding age, gender, and body weight to the model showed improved predictive power indicating that preoperative C_{Cr} calculated with these data has additional prognostic value.

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Introduction

Patients with peripheral vascular disease frequently have underlying renal disease [Mangano 1990]. These patients have a higher prevalence of comorbidities such as hypertension and diabetes mellitus, which may further aggravate the renal dysfunction or cause renal insufficiency [Mangano 1990]. Superimposed on these, intraoperative aortic cross clamping, fluctuations in intravascular volume and cardiac output can compromise renal perfusion during intraoperative and postoperative periods [Cronenwett and Lindenauer 1977, Gamulin et al. 1986]. Hence, major vascular surgery patients are at increased risk for perioperative deterioration of renal function or acute renal failure leading to excess mortality. For instance, acute renal failure occurs in 3% of patients undergoing infrarenal aortic reconstruction, and mortality resulting from acute renal failure is greater than 40% [Gelman 1995]. Appropriate patient management prior to surgery then includes identification of patients at risk for renal dysfunction as well as strategies to reduce this risk.

Preoperative renal function measured as serum creatinine concentration (SeCreat) or creatinine clearance (C_{Cr}) has been shown an independent risk factor for postoperative mortality in patients undergoing cardiac surgery [Chertow et al. 1997, Mangano et al. 1998]. However, the predictive value of preoperative C_{Cr} and its additional value compared to SeCreat have not been studied for the prediction of postoperative mortality in patients undergoing major non-cardiac vascular surgery. Therefore, this study was undertaken to compare the additional prognostic value of preoperative C_{Cr} to SeCreat to predict postoperative mortality in patients undergoing major vascular surgery.

Subjects and methods

Patients

We retrospectively reviewed medical records of 900 patients who participated in a single center study (n = 296) [Poldermans et al. 1997] or in the Dutch Echocardiography Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) study (n = 604) [Boersma et al. 2001] and underwent major vascular surgery between 1991 and 1999 at the Erasmus Medical Center, Rotterdam. Of the 900 patients selected, 48 were excluded from analysis because of patients on dialyses (n = 25) or preexisting renal dysfunction (serum creatinine level > 180 μmol/l; n = 23). Therefore, the final cohort comprised 852 patients. Individual patient characteristics, medical history and laboratory data were routinely assessed in all patients undergoing surgery. The surgical management of all patients included preoperative evaluation and intraoperative and postoperative care. Two hundred and fifteen (25%) patients underwent abdominal aortic surgery (tube prosthesis or aortoiliac graft) with clamping of the suprarenal aorta in 51 (24%) cases, and 637 (75%) infrainguinal reconstructions. Perioperative anesthetic management included general anesthesia for abdominal aortic surgery and/or regional anesthesia for infrainguinal procedures. Patients were inserted an intra-arterial catheter for continuous monitoring of systemic blood pressure, and, if necessary, either central venous or pulmonary artery pressure monitoring was applied. The choice of anesthetic agents, technique and clinical management was based on the judgment of the attending anesthesiologists. After surgery, all patients were admitted to the postoperative surgical intensive care unit until their condition was judged to be satisfactory for transfer to the ward. Outcome was defined as overall postoperative mortality occurring within 30 days of surgery. The cause of postoperative death was retrieved from hospital records or autopsy results.

Definitions of risk factors

Risk factors considered for postoperative mortality were age, gender, a history of cardiac, renal or pulmonary disease, hypertension and diabetes mellitus. Cardiac disease included current stable angina or prior angina (AP), a history of myocardial infarction (MI) and a history of symptoms of congestive heart failure (CHF). Current stable angina or prior angina was characterized according to the definition of the Canadian Cardiovascular Society [Campeau 1976]. History of myocardial infarction was defined as a documented history of an MI or a finding of pathologic Q waves on electrocardiography. Congestive heart failure was defined according to the presence of a history of symptoms or signs of pulmonary congestion, signs of left or right ventricular failure and chest radiographic findings suggestive of heart failure. Hypertension was defined as a history of regular use of antihypertensive medication, and/or a blood pressure > 140/90 mmHg at 3 separate measurements. Patients were characterized as having diabetes mellitus if they met one of the following criteria:

- treated with insulin or oral hypoglycemic agents,
- a history of diabetes mellitus and a preoperative plasma glucose = 200 mg/dl (11.1 mmol/l),
- a fasting plasma glucose = 126 mg/dl (7.0 mmol/l).

Pulmonary comorbidity was defined to be present if forced expiratory volume in 1s was = 75% of normal, corrected for age and gender.

Assessment of preoperative renal function

The preoperative C_{Cr} was calculated to assess the baseline renal function using the Cockroft-Gault equation [Cockroft and Gault 1976]. Age, body weight and preoperative SeCreat were available from the medical records and computerized database of the patients. In order to investigate the relation between clinical risk factors and preoperative C_{Cr}, patients were classified into quartiles as follows: < 57.1, 57.1 – 73.3, 73.3 – 92.0 and > 92.0 ml/min.

Statistical analysis

Univariable association between postoperative mortality and clinical risk factors were evaluated by independent t-test or the Chi-square test, as appropriate. The Chi-square test for linear trend was used for comparisons of clinical risk factors across quartiles of preoperative C_{Cr} for categorical variables, and analysis of variance for continuous variables. Univariable logistic regression analyses were used to study the relation between preoperative SeCreat, C_{Cr}, and postoperative mortality. Furthermore, multivariable logistic regression analyses were applied to evaluate the additional predictive value of age, body weight and gender (additional to SeCreat), and corrected for clinical variables that are potentially associated with increased risk. We compared the –2Log likelihood of the separate models with SeCreat and with C_{Cr} to test the hypothesis that preoperative C_{Cr} has better predictive value than preoperative SeCreat. The receiver operating characteristic (ROC) curve was determined to evaluate the predictive power of several models for perioperative mortality. Furthermore, the ROC curve was used for determination of the optimal cutoff value of C_{Cr} for postoperative mortality, defined as that providing the maximal sum of sensitivity/specificity. Sensitivity and specificity are based upon their standard definitions. For all tests, a p value was < 0.05 considered significant.

Table 1. Cause of postoperative mortality in 50 patients who underwent major vascular surgery.

Cause of death	n = 50*
Cardiac death	15 (30)
Respiratory failure	8 (16)
Acute renal failure	7 (14)
Bleeding	6 (12)
Bowel ischemia	5 (10)
Pancreatitis or liver insufficiency	3 (6)
Infected prosthesis	2 (4)
Mesenterial thrombosis	2 (4)
Cerebrovascular accident	2 (4)

* = values in parenthesis are percentages.

Results

Of the 852 patients undergoing major vascular surgery, 50 (5.9%) patients died within 30 days of surgery. The most common immediate cause of death was cardiac, with respiratory and renal failure being the next 2 leading causes (Table 1).

The overall mean age was 66.8 ± 10.4 years (range 21 – 92). The mean age of men exceeded that of women (67.3 ± 9.5 vs 65.0 ± 13.3 year; p = 0.029). Table 2 shows the relation between clinical baseline characteristics and postoperative mortality. Patients who died due to any cause during the postoperative period were significantly older than those who survived, and more often had a history of CHF and pulmonary disease. However, there was no significant association between postoperative mortality and gender, AP, history of MI, hypertension and diabetes mellitus (Table 2). There was a strong relation between type of surgery (abdominal aorta vs. infrainguinal procedure) and postoperative mortality. In patients undergoing abdominal aortic surgery with clamping of the suprarenal aorta, there was no difference in postoperative mortality compared to those who underwent the same procedure but without clamping of the suprarenal aorta (12% vs. 8%; p = 0.41). Preoperative renal function, as assessed by SeCreat, was significantly higher in patients who died, as well as C_{Cr} was substantially lower in those who subsequently died during the postoperative period (Table 2).

In univariable analysis, lower preoperative levels of C_{Cr} were associated with older age, female sex, congestive heart failure and

Table 2. Relation between clinical baseline characteristics and postoperative mortality (n = 852)*.

Risk factor**	Died (n = 50)***	Survived (n = 802)***	Odds ratio (95% confidence interval)	Wald χ^2	p value
Demographics					
Age at operation (years)	70.8 ± 7.3	66.6 ± 10.6	1.05 (1.01 – 1.08)	7.6	0.006
Male sex	39 (78)	630 (79)	0.9 (0.5 – 1.9)	0.01	0.926
History					
Current stable or prior angina	7 (14)	165 (21)	0.6 (0.3 – 1.4)	1.3	0.262
Prior myocardial infarction	24 (48)	295 (37)	1.6 (0.9 – 2.8)	2.5	0.116
Congestive heart failure	7 (14)	39 (5)	3.2 (1.3 – 7.4)	6.8	0.009
Hypertension	26 (52)	326 (41)	1.6 (0.8 – 2.8)	2.4	0.123
Diabetes mellitus	5 (10)	95 (12)	0.8 (0.3 – 2.1)	0.2	0.692
Pulmonary disease	18 (36)	117 (15)	3.3 (1.8 – 6.1)	14.7	< 0.001
Type of surgery					
Abdominal aortic surgery	19 (38)	196 (24)	1.9 (1.1 – 3.4)	4.5	0.035
Preoperative renal function					
Serum creatinine level (μmol/l)	103.8 ± 29.7	90.3 ± 24.9	1.2 (1.1 – 1.3)	12.6	< 0.001
C_{Cr} (ml/min)	59.8 ± 18.0	77.4 ± 26.4	1.4 (1.2 – 1.5)	20.8	< 0.001

* = numbers may not add to 852 due to missing data, ** = for definition of risk factors see *Methods* section; values in parenthesis are percentages; Continuous variables are given as means ± SD.

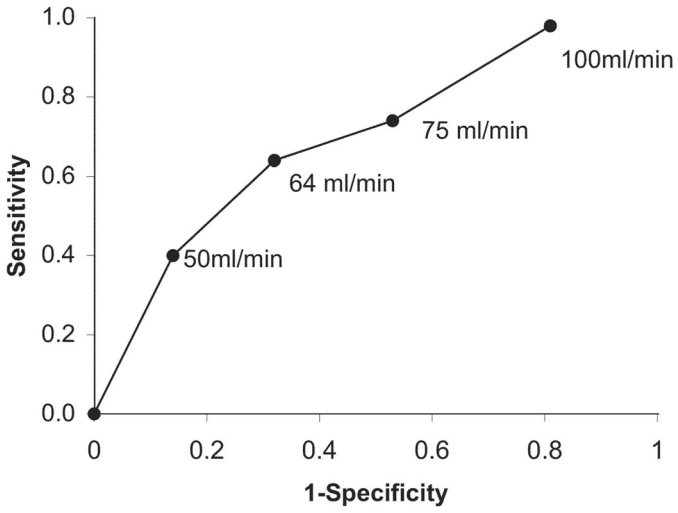

Figure 1. Receiver operating characteristic curve showing sensitivity and (1-specificity) of different preoperative C_{Cr} levels to predict postoperative mortality.

type of surgery (Table 3). There was no consistent relation between the level of C_{Cr} and AP, a history of MI, hypertension, diabetes mellitus and pulmonary disease. The proportion of patients with hypertension and diabetes mellitus increased only slightly with lower quartiles of C_{Cr}, from 36% to 47% for hypertension and from 12% to 15% for diabetes, whereas it did not change for pulmonary disease (Table 3). There was a graded increase from 16% to 30% in the frequency of abdominal aortic surgery in patients from the highest to the lowest quartile of C_{Cr}.

In a univariable logistic regression analysis each 10 μmol/l increase in SeCreat was associated with a 20% increased risk of postoperative mortality (OR = 1.2, 95% CI, 1.1 – 1.3) with an area under the ROC curve of 0.64 (95% CI, 0.56 – 0.71). If age, gender and body weight were added, the area under the ROC curve significantly increased to 0.70 (95% CI, 0.63 – 0.77), indicating that these risk factors had significant additional prognostic value (difference in –2Log likelihood: 14.02; $p < 0.001$). Indeed, in a separate regression analysis each 10 ml/min decrease in C_{Cr} was associated with a 40% increased risk of perioperative mortality (OR = 1.4, 95% CI, 1.2 – 1.5) with the same area under the ROC curve: 0.70, (95% CI, 0.63 – 0.76). ROC curve analysis showed that the cut-off value of 64 ml/min for C_{Cr} yielded the highest sensitivity/specificity to predict postoperative mortality (area under the curve 0.70); 32 of 50 patients who died had C_{Cr} below 64 ml/min level, while 543 of 802 who survived had C_{Cr} above the cut-off value of 64 ml/min. Using this cutoff level, C_{Cr} had a sensitivity of 64% and a specificity of 68%. When sensitivity was improved to 74% (by shifting the optimal

Table 3. Baseline clinical risk factors according to the quartile of C_{Cr} (n = 852)*.

Risk factors**	Quartile 1 (92.0 ml/min)	Quartile 2 (73.4 – 92.0 ml/min)	Quartile 3 (57.2 – 73.3 ml/min)	Quartile 4 (57.1 ml/min)	p value***
Number of patients	210	214	214	214	
Demographics					
Age, years	57.6 ± 10.3	65.9 ± 8.4	70.2 ± 7.7	73.4 ± 7.9	< 0.001
Male sex	170 (81)	182 (85)	170 (79)	147 (69)	< 0.001
History					
Current stable angina and prior angina	47 (23)	40 (19)	39 (18)	46 (22)	0.641
Prior myocardial infarction	62 (32)	88 (41)	73 (34)	91 (43)	0.064
Congestive heart failure	4 (2)	9 (4)	17 (8)	16 (18)	0.011
Hypertension	76 (36)	85 (40)	91 (43)	100 (47)	0.181
Diabetes mellitus	26 (12)	25 (12)	17 (8)	32 (15)	0.151
Pulmonary disease	31 (15)	35 (16)	34 (16)	35 (16)	0.965
Type of surgery					
Abdominal aortic	34 (16)	53 (25)	63 (29)	65 (30)	0.002

* = numbers may not add to 852 due to missing data, ** = for definition of risk factors see *Methods* section, values in parenthesis are percentages, continuous variables are given as means ± SD; *** = p value corresponds to the independent t-test for continuous variables and Chi-square test for categorical, all p values are 2-tailed and considered significant at < 0.05 level.

Table 4. Multivariable analyses between clinical baseline characteristics and perioperative mortality corrected for serum creatinine concentration in model I and for C_{Cr} in model II.

Risk factors*	Wald χ^2	Odds ratio (95%, confidence Interval)	p value
Model I			
Serum creatinine	9.6	1.2 (1.1 – 1.3)	0.002
Current stable angina and prior angina	2.0	0.54 (0.23 – 1.26)	0.155
Prior myocardial infarction	0.7	1.31 (0.70 – 2.50)	0.397
Congestive heart failure	3.6	2.52 (0.97 – 6.56)	0.057
Hypertension	1.9	1.51 (0.83 – 2.76)	0.173
Diabetes mellitus	0.1	0.89 (0.33 – 2.41)	0.822
Pulmonary disease	11.6	3.07 (1.61 – 5.87)	0.001
Abdominal aorta vs infrainguinal surgery	3.4	1.81 (0.96 – 3.41)	0.066
Model II			
C_{Cr}	18.0	1.4 (1.2 – 1.5)	< 0.001
Current stable angina or prior angina	2.7	0.48 (0.20 – 1.15)	0.101
Prior myocardial infarction	1.1	1.41 (0.74 – 2.66)	0.287
Congestive heart failure	2.9	2.30 (0.88 – 5.94)	0.088
Hypertension	1.9	1.52 (0.83 – 2.78)	0.171
Diabetes mellitus	0.1	0.92 (0.34 – 2.50)	0.822
Pulmonary disease	11.3	3.04 (1.60 – 5.80)	0.001
Abdominal aorta vs infrainguinal surgery	3.3	1.80 (0.95 – 3.42)	0.071

* = for definition of risk factors see *Methods* section.

cutoff value of Ccr to 75 ml/min) the specificity declined to 47%. Figure 1 provides sensitivity and 1-specificity for various C_{Cr} values.

In multivariable logistic regression analyses, the relation between clinical risk factors and renal function showed that preoperative SeCreat and presence of pulmonary disease were the only significant risk factors for postoperative mortality. When the same relation was studied but correcting for preoperative C_{Cr}, similar results were found, i.e. C_{Cr} and pulmonary disease were the only significant risk factors for postoperative mortality (Table 4). The area under the ROC curve for the

models, one with SeCreat and the other one with C_{Cr} showed a slightly better discrimination for the model with C_{Cr} (0.74 (95% CI, 0.67 – 0.81) vs 0.78 (95% CI, 0.72 – 0.84); difference in –2Log likelihood: 12.6; $p < 0.01$).

Discussion

This study confirmed that preoperative poor renal function as assessed by C_{Cr} is a significant risk factor for postoperative mortality and has additional prognostic value compared to SeCreat.

There have been numerous studies that identified renal dysfunction as a risk factor for postoperative mortality in patients undergoing major vascular surgery [Brady et al. 2000, Chertow et al. 1997, Katz et al. 1994]. However, no large-scale studies using preoperative C_{Cr} instead of SeCreat as a measure of renal function have been reported.

The association between increasing age and poor renal function was obvious in the present study and more pronounced in the groups with the lowest C_{Cr} levels. The observed changes in renal function with increasing age are due to progressive loss of renal mass, change in renal blood flow and age-related decline in the glomerular filtration rate (GFR). Since muscle mass falls with age at approximately the same rate as GFR, the rather striking age-related loss of renal function is not reflected by an increase in SeCreat. Thus, SeCreat underestimates the decline in GFR in the elderly, whereas C_{Cr} retains a good correlation with it [Levi and Rowe]. Therefore, the use of C_{Cr} gives a better reflection of renal function.

The impact of baseline comorbidities across the quartiles of C_{Cr} was evident. Patients with more severe renal dysfunction had more often a history of MI, CHF, hypertension and diabetes, but compared to earlier studies it reached significance only for CHF [Lee et al. 1999, Mangano 1990]. This finding can reflect a changing population or improved perioperative management although it may also be a matter of a relatively low number of events. Infrainguinal procedures were more frequent across the renal strata, however, the rate of patients undergoing abdominal aortic surgery increased with a more pronounced renal dysfunction. The later finding could be due to the fact that atherosclerotic disease in the abdominal aorta often involves the renal arteries which can compromise renal blood flow and renal function [Levi and Rowe]. There was no association between clamping of the suprarenal aorta and increased rate of postoperative mortality. This observation may reflect improved surgical technique and restoration of renal blood flow during surgery but it can be again a matter of a relatively low number of cases.

The rate of postoperative death (5.9%) in the present study was similar to that reported in other studies [Brady et al. 2000, Katz et al. 1994]. A multivariable logistic regression analysis showed that preoperative poor renal function measured, as either SeCreat or C_{Cr} was strongly associated with postoperative mortality. However, C_{Cr} showed additional value compared to SeCreat resulting in a model with improved predictive power.

There have been many attempts to improve or preserve the renal function in patients undergoing surgery. These have been improved surgical and anesthetic management, and use of renal protective pharmacological agents that may help to preserve or improve the renal function during the perioperative period [Brown et al. 1981, Hanley and Davidson 1981]. Preoperative renal artery stenting [Sullivan and Hertzer 1998], reduction in duration of aortic cross clamping may restore or prevent the interruption in renal blood flow. The choice of less invasive techniques, i.e. endovascular procedures may help to avoid aortic cross clamping and fluctuations in systemic blood pressure. There are also other more important factors to consider, such as adequate fluid repletion and allowing contrast-induced nephropathy to resolve before proceeding with elective surgery. However, future clinical trials are necessary to evaluate the potential role of interventions like these in patients undergoing major vascular surgery.

There are some limitations to this study. The single measure of preoperative SeCreat could have been influenced by the degree of hydration and renal perfusion. Use of the Cockroft-Gault equation to estimate C_{Cr} may have led to misclassification of some subjects. Because adjustment for body weight alone may not indicate differences in creati-

nine generation among patients who are obese, muscular or wasted. A more precise measure of renal function, such as a 24-hour collection or radioisotope study, would be preferable. However, it has been demonstrated that C_{Cr} calculated from the Cockroft-Gault equation is also a reliable method for measuring C_{Cr} compared to a 24-hour urine collection [Toto 1995]. Other limitation to the present study is that information on the change in intra- and postoperative volume loading strategies over time was not available. Despite these limitations, the present study demonstrated that calculating C_{Cr} using SeCreat, body weight, age and gender provides a reasonable and clinically useful bedside measure of renal function.

In conclusion, preoperative C_{Cr} derived from SeCreat, age, body weight and gender has additional prognostic value compared to SeCreat to predict postoperative mortality in patients undergoing major vascular surgery. Future studies are required on the role of improvement in renal function prior to surgery to reduce postoperative mortality in this high-risk patient population.

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Chapter 3

Aortic stenosis: an underestimated risk factor for perioperative complications in patients undergoing noncardiac surgery

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Aortic Stenosis: An Underestimated Risk Factor for Perioperative Complications in Patients Undergoing Noncardiac Surgery

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PURPOSE: To determine the incidence of perioperative events in patients with aortic stenosis undergoing noncardiac surgery.
METHODS: We studied 108 patients with moderate (mean gradient, 25 to 49 mm Hg) or severe (mean gradient, ≥50 mm Hg) aortic stenosis and 216 controls who underwent noncardiac surgery between 1991 and 2000 at Erasmus Medical Center. Controls were selected based on calendar year and type of surgery. Details of clinical risk factors, type of surgery, and perioperative management were retrieved from medical records. The main outcome measure was the composite of perioperative mortality and nonfatal myocardial infarction.
RESULTS: There was a significantly higher incidence of the composite endpoint in patients with aortic stenosis than in patients without aortic stenosis (14% [15/108] vs. 2% [4/216], $P < 0.001$). This rate of perioperative complications was also substantially higher in patients with severe aortic stenosis compared with patients with moderate aortic stenosis (31% [5/16] vs. 11% [10/92], $P = 0.04$). After adjusting for cardiac risk factors, aortic stenosis remained a strong predictor of the composite endpoint (odds ratio = 5.2; 95% confidence interval: 1.6 to 17.0).
CONCLUSION: Aortic stenosis is a risk factor for perioperative mortality and nonfatal myocardial infarction, and the severity of aortic stenosis is highly predictive of these complications. **Am J Med. 2004;116:8–13.**

Aortic stenosis is the most common valvular heart disease affecting 2% to 9% of adults over 65 years of age (1,2). Aortic stenosis is also considered to be a risk factor for perioperative cardiac complications in patients undergoing noncardiac surgery. The study by Goldman et al in 1977 was the first to show that patients with aortic stenosis were at increased risk of life-threatening or fatal cardiac complications (3), and this characteristic was also reported in the subsequent study by Detsky et al (4). Although three later studies reported that selected patients with aortic stenosis who were not candidates for, or refused, aortic valve replacement could undergo noncardiac surgery with a reasonably low event rate of 0% to 7% (5–7), Rohde et al (8) recently reported that increased peak instantaneous aortic gradients were associated with increased cardiovascular morbidity. The present study was designed to determine the incidence of perioperative mortality and nonfatal myocardial infarction over time in a large group of patients with moderate to severe aortic stenosis who were undergoing elective noncardiac surgery.

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METHODS

Study Design

Between January 1991 and December 2000, a total of 123,802 consecutive patients over 18 years of age underwent noncardiac surgery at the Erasmus Medical Center, Rotterdam, The Netherlands. The hospital electronic database was reviewed for medical records of patients with a diagnosis of aortic stenosis who had undergone elective noncardiac surgery. One hundred and eight patients were identified as having moderate or severe aortic stenosis and as having undergone elective noncardiac surgery. From the same database, 2 controls were selected for each patient with aortic stenosis; controls had to have undergone surgery immediately before or after the patients with aortic stenosis, and were stratified according to the type of elective surgery (9). We studied a 10-year period with a strict control for the calendar year as surgical and anesthesiological techniques may have changed over this time.

Data Collection

For all patients with aortic stenosis and controls, medical records, anesthesiological charts, and discharge letters were manually reviewed for information on cardiac risk factors, chronic medication use, type of noncardiac oper-

ation, and cause and type of perioperative complications. The medical records of patients with aortic stenosis were also reviewed for the most recent echocardiogram and signs of symptomatic aortic stenosis, such as syncope or presyncope, angina, and dyspnea.

Details of intraoperative course included the American Society of Anesthesiologists classification (10), choice of anesthetic technique, intraoperative hemodynamic changes, and the management of those changes. The duration of anesthesia, intraoperative blood loss, intraoperative fluid administration, and use of invasive pressure monitors were recorded. Each anesthetic technique was classified as follows: balanced or intravenous general anesthesia, central neural blockade, combination of general anesthesia and central neural blockade, and conscious sedation. Postoperative admission to the intensive care unit and duration of stay were also noted.

Elective noncardiac operations were classified as follows: major vascular (infrarenal abdominal aortic and infrainguinal procedures), other vascular (carotid endarterectomy, peripheral vascular embolectomy), abdominal (gastrointestinal and renal surgery), orthopedic (total hip or knee arthroplasty, arthroscopy, or lower limb amputation), genitourinary (hysterectomy and operations involving the urinary bladder), head and neck surgery (thyroidectomy, procedures involving the larynx), and other (ear, eye, nose, throat, or breast surgery).

Definition of Perioperative Events

The study outcome was a composite of perioperative death and nonfatal myocardial infarction, occurring before discharge or within 30 days after surgery, whichever came first. Two of the investigators (MDK, DP) reviewed all available medical records, laboratory values, electrocardiograms, echocardiograms, and clinical events. The cause of perioperative death was obtained from hospital records or autopsy results. The diagnosis of myocardial infarction was made by measurement of a serum creatine kinase level >110 U/L with a myoglobin isoenzyme fraction of more than 10% or troponin T level >0.1 μg/L, and by new electrocardiographic Q waves ≥ 1 mm or >30 ms.

Evaluation of the Aortic Valve

In patients with documented aortic stenosis, the transvalvular aortic gradient and severity of aortic stenosis were determined by continuous-wave Doppler echocardiography. Patients were included in the study if echocardiography was performed within 3 months before noncardiac surgery, and if patients had moderate aortic stenosis on echocardiography defined as an aortic valve area between 0.7 and 1 cm^2 or a mean gradient between 25 and 49 mm Hg, or severe aortic stenosis defined as an aortic valve area index <0.7 cm^2 or a mean gradient ≥ 50 mm Hg.

Statistical Analysis

Continuous variables are presented as means ($\pm$ SD) or medians (interquartile range), and categorical variables are presented as percent frequencies. Comparisons were made using the *t* test, Mann-Whitney test, or chi-squared test, as appropriate. The number of outcome events in the study was limited. Therefore, to avoid overfitting and to enable assessment of the relation between clinical risk factors and the composite endpoint, we used the Revised Cardiac Risk Index (11). Univariable logistic regression analyses were used to study the relation between aortic stenosis and the composite endpoint. Multivariable logistic regression analysis was also performed to evaluate the additional predictive value of aortic stenosis, adjusting for baseline clinical characteristics. Odds ratios and corresponding 95% confidence intervals are reported. In order to reveal possible heterogeneity between aortic stenosis and clinical risk factors, an interaction term was evaluated. For all tests, a P value ≤ 0.05 was considered significant. All analyses were performed using SPSS statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Patients with aortic stenosis were older, and had a higher prevalence of cardiac risk factors, including angina pectoris, myocardial infarction, heart failure, stroke, diabetes mellitus, renal failure, and hypertension, compared with patients without aortic stenosis (Table 1). More patients with aortic stenosis had a cardiac risk index of 1 or more compared with controls. Use of angiotensin-converting enzyme inhibitors, diuretics, and nitrates was also more common among patients with aortic stenosis. There were no differences between the two patient groups with regards to sex, pulmonary disease, and smoking.

Characteristics of Patients with Aortic Stenosis

On two-dimensional echocardiography, 92 patients had moderate aortic stenosis and 16 had severe aortic stenosis. Twenty-two patients (20%) had one or more cardiac symptoms related to aortic stenosis: history of syncope (n = 2), angina pectoris (n = 7), and exertional dyspnea (n = 19). Of these patients, 14 had moderate aortic stenosis and 8 had severe aortic stenosis. Aortic valve replacement was not performed for various reasons, including the presence of coexisting medical illness, advanced age, relative emergency of the noncardiac operation, and patient refusal. All patients (n = 93) who survived noncardiac surgery as a routine procedure were seen regularly at the cardiology outpatient clinic at Erasmus Medical Center, of whom 29 underwent aortic valve replacement an average of 2 years later.

Patients with severe aortic stenosis more often had reduced or severely reduced left ventricular function as compared with patients with moderate aortic stenosis

Table 1. Characteristics of Patients with Aortic Stenosis and Controls

Characteristic	Patients with Aortic Stenosis (n = 108)	Patients without Aortic Stenosis (n = 216)	*P* Value
	Number (%) or Mean ± SD		
Age (years)	69.0 ± 10.3	56.6 ± 18.0	<0.001
Age >70 years	61 (57)	62 (29)	<0.001
Male sex	55 (51)	119 (56)	0.47
History of angina	26 (24)	24 (11)	<0.01
History of myocardial infarction	27 (25)	29 (13)	0.01
History of heart failure	30 (28)	6 (3)	<0.001
History of cerebrovascular disease	20 (19)	18 (8)	0.01
Diabetes mellitus	26 (24)	20 (9)	<0.001
Renal failure (serum creatinine ≥2 mg/dL)	22 (20)	13 (6)	<0.001
Revised Cardiac Risk Index ≥1*	90 (83)	115 (53)	<0.001
Hypertension	66 (61)	66 (31)	<0.001
Pulmonary disease	22 (20)	29 (13)	0.10
Smoking	30 (29)	70 (33)	0.52
Medication			
Aspirin	15 (14)	26 (12)	0.72
ACE inhibitor	55 (51)	51 (24)	<0.001
Beta-blocker	31 (29)	43 (20)	0.09
Diuretic	35 (32)	26 (12)	<0.001
Nitrates	22 (20)	16 (7)	0.001
Statin	18 (16)	21 (10)	0.10

* Derived by assigning 1 point to each of the following characteristics: high-risk type of surgery, ischemic heart disease, history of heart failure, history of cerebrovascular disease, insulin therapy for diabetes, and preoperative serum creatinine level >2.0 mg/dL.
ACE = angiotensin-converting enzyme inhibitor.

(Table 2). Other hemodynamic parameters such as the mean valve area was lower in patients with severe aortic stenosis, whereas the mean transvalvular aortic velocity and mean derived instantaneous gradient were higher in these patients. Of the 108 patients with aortic stenosis, left ventricular hypertrophy on echocardiography was evident in 49 patients (45%), left ventricular dilation was evident in 17 (16%), and left ventricular wall motion abnormality was evident in 29 (27%). Concomitant mild or moderate valve abnormality was detected in 26 patients (24%). Aortic regurgitation was noted in 11 patients, mitral valve regurgitation in 8, mitral valve stenosis in 7, tricuspid valve regurgitation in 7, and pulmonary regurgitation in 3.

Perioperative Course

Patients with aortic stenosis were more often classified as having an American Society of Anesthesiologists classification score of 2 or higher, as compared with controls, and had slightly lower hemoglobin and hematocrit

Table 2. Hemodynamic Characteristics of Patients, by Severity of Aortic Stenosis

Variable	Patients with Moderate Aortic Stenosis (n = 92)	Patients with Severe Aortic Stenosis (n = 16)
	Number (%) or Mean ± SD	
Left ventricular ejection fraction		
≥50%	55 (60)	14 (40)
35%–49%	31 (34)	11 (31)
<35%	6 (6)	10 (29)
Aortic valve gradient (mm Hg)	37.2 ± 8.1	67.8 ± 11.3
Valve area (cm^2)	0.9 ± 0.1	0.6 ± 0.1
Transvalvular velocity (ms)	3.0 ± 0.4	4.2 ± 0.6

Table 3. Perioperative Characteristics of Patients with Aortic Stenosis and Controls

Characteristic	Patients with Aortic Stenosis (n = 108)	Patients without Aortic Stenosis (n = 216)	*P* Value
	Number (%), Mean ± SD, or Median (Interquartile Range)		
Preoperative period			
American Society of Anesthesiology score			<0.001
1	9 (8)	64 (30)	
2	72 (67)	119 (55)	
3	27 (25)	33 (15)	
Laboratory values			
Hemoglobin (g/L)	132 (116–141)	137 (124–148)	0.01
Hematocrit (%)	39 (35–42)	41 (37–43)	0.04
Serum creatinine (mg/dL)*	1.0 (0.8–1.3)	0.8 (0.7–1.1)	0.001
Intraoperative period			
Type of anesthesia			<0.01
Balanced or intravenous general	82 (76)	126 (58)	
Central neural blockade	7 (7)	28 (14)	
Combined technique	8 (7)	41 (19)	
Conscious sedation	11 (10)	21 (9)	
Type of surgery			1.0
Major vascular	41 (38)	82 (38)	
Other vascular	9 (8)	18 (8)	
Abdominal	13 (12)	26 (12)	
Orthopedic	23 (21)	46 (21)	
Genitourinary	7 (7)	14 (7)	
Head and neck	2 (2)	4 (2)	
Other	13 (12)	26 (12)	
Swan-Ganz catheter	26 (24)	5 (2)	<0.001
Intra-arterial blood pressure monitoring	15 (14)	25 (12)	0.15
Central venous pressure monitoring	54 (50)	51 (24)	<0.001
Blood pressure drop during induction (mm Hg)†	30 (20–40)	20 (10–30)	<0.01
Dose of phenylephrine (bolus) (μg)	40 (20–50)	40 (30–50)	0.05
Blood loss (mL)	400 (225–1450)	600 (300–1700)	0.22
Number of packed cells given (unit)	2.0 (1.2–5.3)	2.0 (1.3–4.0)	0.90
Total intraoperative fluid administered (mL)	2000 (1000–3500)	2000 (1500–4000)	0.16
Operation time (h)	2.4 (1.2–4.1)	2.0 (1.1–3.3)	<0.01
Anesthesia time (h)	3.0 (1.3–4.1)	2.3 (1.3–4.1)	0.04
Postoperative period			
Intensive care unit admission	24 (22)	59 (27)	0.35
Number of days in intensive care unit (days)	3.0 (2–3)	3.0 (2–4)	0.70

* To convert from mg/dL to μmol/L, multiply by 88.4.
† Defined as a drop in systolic blood pressure compared with baseline.

levels, but higher serum creatinine levels, before surgery (Table 3). There was an overall difference in the type of anesthesia used. Patients with aortic stenosis were more likely to undergo balanced or general anesthesia than were controls. Indeed, only half of patients with aortic stenosis received epidural or spinal anesthesia and only one third underwent general anesthesia combined with central neural blockade. However, after stratified selection of patients without aortic stenosis, no difference in type of surgery was observed between the two groups (Table 3).

There were no differences between patients with aortic stenosis and controls in terms of intraoperative blood loss, number of packed cells received, and total intraoperative intravenous fluid administration (Table 3). However, patients with aortic stenosis were more likely to have undergone invasive hemodynamic monitoring by Swan-Ganz catheter or central venous pressure monitoring.

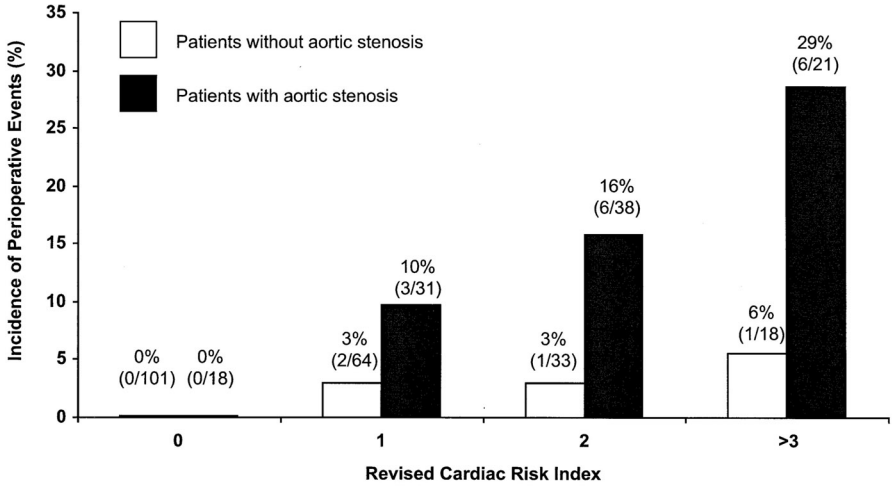

Figure. Incidence of perioperative mortality and nonfatal myocardial infarction in patients with aortic stenosis and controls. Results are based on the absence or presence of aortic valve stenosis, and on the Revised Cardiac Risk Index, which assigns 1 point to each of the following characteristics: high-risk type of surgery, ischemic heart disease, history of heart failure, history of cerebrovascular disease, insulin therapy for diabetes, and preoperative serum creatinine level >2.0 mg/dL.

The median operation and anesthesia times were also slightly longer in patients with aortic stenosis. Similar percentages of patients from both groups were admitted to the intensive care unit, with no substantial differences in the length of stay.

Relation between Aortic Stenosis and Perioperative Outcome

Perioperative death or myocardial infarction occurred in 19 patients (6%): 13 cardiac deaths, 4 noncardiac deaths (2 due to sepsis, 1 renal failure, and 1 intestinal ischemia), and 2 nonfatal myocardial infarctions. Autopsy was performed in 15 patients (79%).

Fifteen (79%) of the 19 patients who died or had a myocardial infarction were from the aortic stenosis group. The rate of perioperative complications was substantially higher in patients with severe aortic stenosis than in those with moderate aortic stenosis (31% [5/16] vs. 11% [10/92], $P = 0.04$). Patients with aortic stenosis had an 8.5-fold increased risk of perioperative complications compared with patients without aortic stenosis (95% confidence interval [CI]: 2.8 to 26.5). This association persisted even after adjusting for clinical risk factors (odds ratio [OR] = 5.2; 95% CI: 1.6 to 17.0). A 1-point increase in the cardiac risk index was also associated with adverse perioperative outcomes in both univariable (OR = 2.2; 95% CI: 1.5 to 3.2) and multivariable (OR = 1.8; 95% CI: 1.2 to 2.7) analyses.

Association between Aortic Stenosis and the Cardiac Risk Index

Based on the number of clinical risk factors and the presence of aortic stenosis, the incidence of perioperative mortality and nonfatal myocardial infarction was estimated. In patients with aortic stenosis and controls who had a risk index of 0, no adverse perioperative outcomes were observed (Figure). However, if patients with aortic stenosis had a risk index of 1 or higher, there was a higher risk of an adverse perioperative outcome, compared with in controls. Test for heterogeneity revealed no association among the number of risk factors, aortic stenosis, and perioperative adverse outcome ($P = 0.78$).

DISCUSSION

Our results suggest that patients with aortic stenosis have a fivefold increased risk of perioperative mortality and nonfatal myocardial infarction, regardless of the presence of risk factors for coronary artery disease, such as angina, previous myocardial infarction, heart failure, renal dysfunction, and stroke. The severity of aortic stenosis was also highly predictive of perioperative adverse outcome.

These findings are in agreement with prior research and guidelines, based initially on the study by Goldman et al, who in 1977 reported major cardiac complications in 13% of 23 patients with important aortic stenosis (3). The persistent prognostic value of aortic stenosis was also established by Rohde et al (8) in 67 patients with aortic stenosis who underwent noncardiac surgery and who had a sevenfold increased risk of perioperative cardiac complications. In contrast to these studies and our results, other investigators have found that selected patients with aortic stenosis who were not candidates for, or refused, aortic valve replacement could undergo noncardiac surgery with a reasonably low risk (5–7). However, the 122

patients with aortic stenosis in these studies commonly underwent minor procedures.

Our results showed that cardiac complications were the major cause of perioperative death in all patients (76% [13/17]). Patients with aortic stenosis more often had a clinical history of coronary artery disease than did patients without aortic stenosis. The association between aortic stenosis and coronary artery disease has been confirmed in previous studies (12,13). Half of the 123 patients with aortic stenosis studied by Otto et al showed coronary artery disease as assessed by coronary angiography (13). Clinical factors that were associated with aortic stenosis were similar to those associated with coronary artery disease, and include advanced age, and a history of angina, previous myocardial infarction, heart failure, or stroke. In addition, the perioperative risk attributed to aortic stenosis is also independent of coronary artery disease. Patients with aortic stenosis are prone to developing hypotension and low cardiac output, which may also increase the risk of perioperative complications (14).

In symptomatic patients with aortic stenosis, valve replacement should be considered before surgery (15). In patients with aortic stenosis and in those with a history of coronary artery disease, signs of coronary artery disease should be evaluated. Patients without coronary artery disease can be considered candidates for elective surgery provided that strict hemodynamic control is effected and hypotension is recognized early and treated adequately. In patients with signs of both coronary artery disease and aortic stenosis, further evaluation and subsequent coronary revascularization with valve replacement should be considered. In patients who are not candidates for aortic valve replacement or in whom surgery cannot be delayed sufficiently for valve replacement to be performed, the use of balloon aortic valvuloplasty may be more appropriate.

This study has several limitations. The study was retrospective, and adverse events may have been missed. However, we used hard endpoints, such as all-cause mortality and nonfatal myocardial infarction. Additionally, we used a combination of matching and multivariable regression analysis to adjust for potential confounders. We selected and adjusted for clinical characteristics that have been described in the literature as important prognostic factors for perioperative complications. Still, there is always a possibility that unknown clinical risk factors were missed.

In conclusion, patients with aortic stenosis undergoing elective noncardiac surgery remain at an increased risk of perioperative mortality and nonfatal myocardial infarction similar to that during the last few decades. Furthermore, our data showed that the severity of aortic stenosis was also highly predictive of perioperative complications.

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Chapter 4

Safety of dobutamine stress echocardiography in patients with aortic stenosis

Bountioukos M, Kertai MD, Schinkel AFL, Vourvouri EC, Rizello V, Krenning BJ, Bax JJ, Roelandt JRTC, Poldermans D

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Safety of Dobutamine Stress Echocardiography in Patients with Aortic Stenosis

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Background and aim of the study: **Aortic valve disease is becoming one of the most important cardiac diseases in western society. Low-dose dobutamine stress echocardiography (DSE) is recommended in patients with low-gradient aortic stenosis (AS) and severe left ventricular (LV) dysfunction. DSE is also used in patients with AS and moderately reduced or normal LV function for diagnostic purposes. The study aim was to assess the safety of DSE in the setting of AS and various degrees of LV dysfunction.**

Methods: **A total of 75 patients with AS who underwent DSE at the authors' center between 1997 and 2001 was reviewed. Group A patients (n = 20) had severely reduced mean LV ejection fraction (LVEF) of 25 ± 6% and underwent low-dose DSE; group B patients (n = 55) had moderate to normal LV function (LVEF 51 ± 8%) and underwent high-dose DSE. The mean pressure gradient, valve area and side effects after DSE were evaluated.**

Results: **Serious cardiac arrhythmias occurred in 10 patients. In group A, four patients (20%) developed non-sustained ventricular tachycardia. In group B, two patients (4%) had non-sustained ventricular tachycardia (VT), four (7%) had paroxysmal supraventricular tachycardias, and two (4%) severe symptomatic hypotension. Among the 20 patients with evidence of ischemia on DSE, three developed adverse side effects (no difference compared with patients without ischemia; p = 0.922). Fourteen patients received atropine during DSE, and 1 of these developed non-sustained VT after atropine administration.**

Conclusion: **Serious cardiac arrhythmias occur frequently during both low-dose and high-dose DSE in patients with AS. Adverse side effects do not relate to stress-induced ischemia or atropine addition.**

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Low-dose dobutamine stress echocardiography (DSE) is a recommended investigation in patients with low-gradient aortic stenosis and reduced left ventricular function to assess whether the aortic stenosis is fixed or dynamic (i.e. flow-dependent) (1-3). Despite a high number of reported side effects, the test has been claimed to be safe in patients with 'low-gradient' aortic stenosis (4-6). According to Carabello (7), "the clinician can be confident that, in a given patient, the symptoms are due to aortic stenosis if the mean aortic-valve gradient exceeds 50 mmHg or if the aortic-valve area is no larger than 1 cm^2".

Patients with aortic stenosis and normal or mildly reduced left ventricular function may be referred for DSE for the diagnosis of coronary artery disease, or for risk stratification before non-cardiac surgery. Currently, few data are available relating to the safety of DSE in these patients.

Hence, the present study was initiated to evaluate retrospectively the current authors' experience with a patient population with aortic stenosis who underwent either low-dose DSE for the assessment of the severity of aortic stenosis, or a full-dose protocol for diagnostic purposes.

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Clinical material and methods

Patients

The study population comprised 75 consecutive patients with aortic stenosis and a mean gradient ≥15 mmHg who had been referred for DSE. Patients with severe aortic insufficiency or severe concomitant valvular heart disease were excluded. All patients were included in an electronic registry accumulated over the course of daily clinical care. Among these patients, 20 (group A) with a poor left ventricular ejec-

tion fraction (LVEF) (mean 25 ± 6%; range: 18 to 35%) and low transvalvular pressure gradient were tested in order to assess the severity of aortic stenosis. A second group of 55 patients (group B) with mild or moderate aortic stenosis and moderate to normal left ventricular function (LVEF 51 ± 8%; range: 40 to 69%) underwent high-dose DSE for the diagnosis of coronary artery disease, or for risk stratification before non-cardiac surgery. Group B patients underwent DSE only if their LVEF was ≥40%, and if aortic stenosis was not severe at baseline (mean pressure gradient ≤40 mmHg and/or aortic valve area ≥1 cm^2).

Echocardiography

All patients with a suspected aortic stenosis underwent a complete echocardiographic study at rest prior to DSE, using commercially available equipment (Sonos 5500, Andover, Massachusetts, USA). Two-dimensional (2D) images were acquired from three apical views (four-chamber, two-chamber and three-chamber) and two parasternal views (short-axis and long-axis).

Assessment of global left ventricular function

The LVEF was determined off-line using the 2D biplane disk method with the modified Simpson's rule. The endocardial borders of the two- and four-chamber apical views were digitally traced at end-diastole and end-systole. Subsequently, the left ventricular end-diastolic and end-systolic volumes were measured and the LVEF was calculated. Left ventricular hypertrophy was defined as an end-diastolic thickness of the anterior septum ≥12 mm when measured by M-mode in the parasternal long axis view.

Evaluation of the aortic valve

Aortic valves were evaluated off-line for the purpose of the study. Observers were blinded to the development of side effects during dobutamine infusion. A multiwindow approach was used to obtain the maximal transaortic velocity with a continuous-wave Doppler technique. The peak instantaneous gradient was calculated using the modified Bernoulli equation from three to five consecutive beats. The mean pressure gradient was assessed using appropriate software after tracing the velocity time integral. The diameter of the left ventricular outflow tract was measured from the parasternal long-axis view, in proximity to the aortic valve. The mean pressure gradient of the outflow tract was obtained using pulsed-wave Doppler from the apical three-chamber view, by placing the Doppler sample volume just under the aortic valve and planimetering the signal. Calculations of the aortic valve area were derived using the continuity equation. The measurements of mean pressure gradient and aortic valve area were repeated at the time of the maximum heart rate. Aortic valve insufficiency was qualitatively assessed using a four-grade scale. Left ventricular function, aortic valve area, mean pressure gradient, hemodynamic response to stress, and side effects during dobutamine infusion were evaluated separately in both patient groups.

DSE protocol

DSE was carried out following the acquisition of images at rest. The baseline, low-dose, peak stress and recovery images were displayed as a cineloop format. In patients with a severely reduced LVEF and a low transvalvular gradient (group A), dobutamine was infused at a starting dose of 5 μg/kg/min for 5 min followed by 10 μg/kg/min for 5 min (low-dose stage), up to 20 μg/kg/min for a further 3-min period. In patients undergoing high-dose DSE (group B), the dobutamine dose was increased by 10 μg/kg/min every 3 min to a maximum dose of 40 μg/kg/min. Atropine (up to 2 mg) was added at the end of the last stage if the target heart rate had not been achieved. End-points for interruption of the test in group B were: (i) achievement of the target heart rate; (ii) mean pressure gradient >50 mmHg during the test; and (iii) maximal dose of both dobutamine and atropine. The test end-points for both groups were: (i) extensive stress-induced ischemia (severe new wall motion abnormalities); (ii) horizontal or downsloping ST-segment depression (0.2 mV at 80 ms after the J-point compared with baseline); (iii) severe angina; (iv) severe and symptomatic reduction in systolic blood pressure >40 mmHg from baseline; (v) hypertension (blood pressure >240/120 mmHg); (vi) significant arrhythmias (paroxysmal supraventricular tachycardias, non-sustained ventricular tachycardia (more than three consecutive beats for less than 30 s), sustained ventricular tachycardia (duration of ≥30 s) and ventricular fibrillation; or (vii) any side effect regarded as being due to dobutamine. Metoprolol was available to reverse the (side) effects of dobutamine and atropine.

Wall motion analysis

A 16-segment model for left ventricular wall motion analysis was used, as recommended by the American Society of Echocardiography (8), and visually scored by two experienced reviewers (D.P. and M.B.). Each segment was scored as follows: 1 = normal; 2 = mildly hypokinetic; 3 = severely hypokinetic; 4 = akinetic; and 5 = dyskinetic. For each patient, a wall motion score index (total score divided by the number of segments scored) was calculated at rest, at low-dose dobutamine, and at peak heart rate. Reduction of wall thickening and new wall motion abnormalities during the stress test were considered to be hallmarks of

Table I: Baseline patient characteristics.

Parameter	Group A (n = 20)	Group B (n = 55)
Male:female ratio	15:5	34:21
Age (years)*	64 ± 13	69 ± 12
Prior revascularization	4 (20)	10 (18)
Prior myocardial infarction	6 (30)	20 (36)
Heart failure (NYHA class III/IV)	13 (65)	4 (7)
Syncope/presyncope	2 (10)	2 (4)
LVEF (%)*	25 ± 6	51 ± 8
Echocardiographic LVH+	12 (33)	24 (67)
Resting electrocardiogram		
Q-waves	5 (25)	17 (31)
LVH	3 (15)	2 (4)
LBBB	4 (20)	5 (9)

*Values are mean ± SD.
+End-diastolic thickness of the anterior septum ≥12 mm.
Values in parentheses are percentages.
LBBB: Left bundle branch block; LVEF: Left ventricular ejection fraction; LVH: Left ventricular hypertrophy.

ischemia. The transition of akinesia to dyskinesia was considered a mechanically induced phenomenon (9).

Statistical analysis

Results were expressed as mean ± SD, and percentages were rounded. The statistical analysis was performed using the SPSS program (version 11.0.1 for Windows). Changes in continuous variables in the same group were tested for significance by a paired two-tailed *t*-test, whilst an independent-samples *t*-test was used to compare continuous variables in different groups. Significant differences in categorical variables were assessed using the Pearson chi-square test. A p-value <0.05 was considered to be statistically significant.

Results

Baseline patient characteristics are shown in Table I. Left ventricular hypertrophy (assessed echocardiographically) was present in 36 patients (48%), the majority of whom (n = 24; 67%) had preserved left ventricular function (group B). Patients in both groups showed no evidence of cardiac arrhythmias before DSE. Syncope or presyncope were present in 10% and 4% of patients in group A and B, respectively (Table I). In group A, increases from baseline to peak infusion were seen in both the mean pressure gradient (from 25 ± 11 mmHg to 36 ± 15 mmHg) and aortic valve area (from 0.9 ± 0.3 cm^2 to 1.1 ± 0.4 cm^2). Likewise, in group B, increases from baseline to peak infusion were seen in both the mean pressure gradient (from 23.5 ± 12.0

Table II: Aortic valve indexes and dobutamine stress results in patients of group A (n = 20) and group B (n = 55).

Parameter	At rest			Dobutamine infusion		
	Group A	Group B	p-value	Group A	Group B	p-value
MPG (mmHg)	25 ± 11	23.5 ± 12	NS	36 ± 15	31.5 ± 14	
AVA (cm^2)	0.9 ± 0.3	1.0 ± 0.2	NS	1.1± 0.4	1.1 ± 0.3	NS
Heart rate (beats/min)	76 ± 11	75 ± 17	NS	87 ± 23	118 ± 23	
SBP (mmHg)	125 ± 34	138 ± 28	NS	125 ± 31	126 ± 32	
DBP (mmHg)	67 ± 16	71 ± 13	NS	65 ± 14	66 ± 15	
Rate-pressure product	9542 ± 3295	10310 ± 3010	NS	11013 ± 4789	14958 ± 4938	
WMSI	2.7 ± 1.0	1.5 ± 0.8	<0.001	2.3 ± 1.0	1.4 ± 0.7	
LVEF (%)	25 ± 6	51 ± 8	<0.001	37 ± 8	75 ± 12	<0.001

Values are mean ± SD.
AVA: Aortic valve area; DBP: Diastolic blood pressure; LVEF: Left ventricular ejection fraction; MPG: Mean pressure gradient; NS: Not significant; SBP: Systolic blood pressure; WMSI: Wall motion score index.

Table III: Significant side effects during dobutamine stress echocardiography in groups A and B.

Side effect	Group A n (%)	Group B n (%)
Arrhythmias		
NSVT		
>10 complexes	2 (10)	-
≤10 complexes	2 (10)	2 (3.6)
SVT	-	4 (7.2)
Hypotension*	-	2 (3.6)

*Symptomatic decrease of systolic blood pressure ≥40 mmHg compared to resting value.
NSVT: Non-sustained ventricular tachycardia; SVT: Supraventricular tachycardia.

mmHg to 31.5 ± 14.0 mmHg) and aortic valve area (from 1.0 ± 0.2 cm^2 to 1.1 ± 0.3 cm^2). Aortic valve indexes and DSE results are presented in Table II.

Side effects

The mean rate of dobutamine infusion was 15.5 ± 5.0 μg/kg/min in group A, and 32.0 ± 11.0 μg/kg/min in group B. Serious cardiac arrhythmias occurred in 10 patients (Table III). Four patients (20%) in group A developed non-sustained ventricular tachycardia, two of which contained more than 10 continuous complexes. In group B, two patients (4%) developed non-sustained ventricular tachycardia with less than 10 continuous complexes, and four experienced paroxysmal supraventricular tachycardia (7%), including one patient with atrial fibrillation. All patients who developed non-sustained ventricular tachycardia in group A had fixed aortic stenosis and a LVEF ≤30%. The two patients with non-sustained ventricular tachycardia in group B developed arrhythmias at peak dose dobutamine infusion. At that time, stress-induced ischemia was evident echocardiographically in both patients. In group B, two patients had severe stress-induced hypotension; both developed dizziness and nausea, but the symptoms resolved after intravenous fluid administration and passive leg elevation. The characteristics of the 12 patients who developed serious side effects are listed in Table IV.

Interestingly, patients with stress-induced ischemia did not differ with respect to the incidence of side effects, compared to patients without ischemia on DSE (three patients with side effects out of 20 with stress-induced ischemia versus nine patients with side effects out of 55 without ischemia, p = 0.922). In addition, among patients in group B who received atropine in order to reach the target heart rate, only one patient developed non-sustained ventricular tachycardia (p = 0.637 for the comparison with patients without atropine administration). Medical treatment, cardioversion or hospitalization were unnecessary as all

Table IV. Patients with serious side effects.

Patient no.	Age (years)	At rest			Maximum dobutamine rate			Side effect
		MPG (mmHg)	AVA (cm^2)	LVEF (%)	MPG (mmHg)	AVA (cm^2)	LVEF (%)	
Group A								
1	57	16	1.2	25	27	1.3	32	NSVT
2	66	35	0.8	23	42	0.7	28	NSVT
3	70	15	0.8	15	24	0.9	19	NSVT
4	64	35	0.9	28	47	0.9	34	NSVT
Group B								
1	77	18	1.2	66	25	1.2	78	SVT
2	80	18	1.1	62	20	1	80	SVT
3	68	28	1	56	35	1.1	69	SVT
4	72	24	1.3	58	29	1.7	76	SVT
5	69	21	1.2	60	20	1.2	78	HT*
6	79	15	1.3	50	23	1.5	72	HT*
7	56	22	1	40	24	1	68	NSVT
8	60	23	1.2	40	35	1.3	60	NSVT

*Symptomatic decrease of systolic blood pressure ≥40 mmHg compared to resting value.
AVA: Aortic valve area; HT: Hypotension; LVEF: Left ventricular ejection fraction; MPG: Mean pressure gradient; NSVT: Non-sustained ventricular tachycardia; SVT: Supraventricular tachycardia.

side effects completely resolved within minutes after cessation of dobutamine infusion.

Discussion

In the present study, a high number of incidents of cardiac arrhythmia and symptomatic hypotension developed in the patients. The high incidence of potentially life-threatening arrhythmias - especially in those patients with a low LVEF - suggests that poor left ventricular function and a fixed aortic stenosis can further lead to sustained ventricular tachycardia or ventricular fibrillation. Hence, these patients should be closely observed and there must be advanced cardiac life support-trained personnel available in close proximity.

Because of the aging population and degenerative changes in the aortic valve, aortic stenosis is currently the third most important cardiac disease in western society (10). Although low-dose DSE is recommended and is claimed to be safe in patients with aortic stenosis and reduced left ventricular function to distinguish a fixed from a flow-dependent stenosis, cardiac arrhythmia is frequently induced (5,6). The mechanisms responsible for cardiac arrhythmia in patients with aortic stenosis are complex. Stress increases cardiac output by both positive inotropic and chronotropic effects, whilst peripheral vascular resistance decreases. The resulting vasodilation is discordant to the fixed stroke volume in patients with aortic stenosis (11). Cardiac output at rest usually remains within normal limits, but often fails to increase sufficiently during stress, resulting in an acute elevation of pulmonary pressure. This mechanism can cause dyspnea and a drop in systolic arterial blood pressure, leading to symptomatic hypotension which, together with the increase in wall stress, results in subendocardial hypoperfusion and ischemia (12). However, subendocardial ischemic foci may be present and missed by visual wall motion scoring. These foci may serve as a substrate for arrhythmia, especially in the presence of epicardial coronary artery disease and ischemic cardiomyopathy. In the present study, a number of patients had known coronary artery disease (prior revascularization, and/or myocardial infarction). In group A (the low LVEF group), three of the patients had undergone previous coronary artery bypass surgery, and revascularization had been performed at least three years before the dobutamine stress test. It is likely that, at the time of the surgery, there was no indication for simultaneous aortic valve replacement. After the test, five patients in group A underwent coronary angiography, and this revealed two patients with three-vessel disease, one patient with one-vessel disease, and one with significant stenosis in a vein graft. In group B, 18 patients with stress-induced ischemia on dobutamine stress testing underwent coronary angiography; of these patients, two had normal coronary arteries, 13 had severe stenosis in at least one vessel, and three had stenoses in one or more vein grafts.

Previous studies

DSE was found to be quite safe in patients with poor left ventricular function, without aortic stenosis (13). However, an increased incidence of serious cardiac arrhythmia and hypotension in patients with aortic stenosis has been reported in previous studies. Lin et al. (5) studied 27 patients with an aortic valve area <1 cm^2 and reported four cases of atrial tachyarrhythmia (15%), four cases of hypotension (15%), and no ventricular tachycardia. In the study of Plonska et al. (6), symptomatic hypotension occurred in 16 patients (10%), and ventricular and supraventricular tachyarrhythmia (including premature ventricular contractions) in 33 (21%). The present study confirms these observations, as a quite large proportion of the patients in group A (20%) and group B (11%) developed tachycardias. In addition, 4% of the patients in group B had severe symptomatic hypotension. A large study performed at the present authors' center included 1,737 patients with proven or suspected coronary artery disease who underwent DSE between 1989 and 1997. The incidence of cardiac arrhythmias in this large population was 5% (ventricular fibrillation in three patients, sustained ventricular tachycardia in 13, ventricular tachycardia with less than 10 complexes in 44, and atrial fibrillation in 27). Severe symptomatic hypotension occurred in 0.4% of patients, although the total percentage of hypotensive episodes was 4% (14).

In contrast to DSE studies, single-photon emission computed tomography with adenosine, a vasodilator, was not associated with cardiac arrhythmias in a group of 35 patients with moderate to severe aortic stenosis (15).

Study limitations

In patients studied with low-dose dobutamine (group A), the presence of ischemia was difficult to assess, and some of the arrhythmias observed may have been ischemic in origin. Moreover, the mean dobutamine infusion rate in group A exceeded the normally used low-dose rate of 10 μg/kg/min, and this may have contributed to the high incidence of arrhythmia in these patients.

In conclusion, during DSE patients with low-gradient aortic stenosis and left ventricular dysfunction are susceptible to potentially life-threatening arrhythmias. When the results of DSE are likely to influence the patient's management, then low-dose DSE should be

performed under close monitoring. In patients with mild or moderate aortic stenosis, and with normal or mildly reduced left ventricular function, DSE is relatively safe, but arrhythmias and hypotension can occur during a high-dose dobutamine challenge. In these patients an alternative non-invasive test for the diagnosis of coronary artery disease, such as adenosine perfusion scintigraphy, should be considered.

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Chapter 5

Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after successful major vascular surgery

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Abstract

Background: Cardiac troponin T (cTnT) is a sensitive and specific marker for myocardial injury, but elevations of cTnT without clinical evidence of ischemia and persistent or new electrocardiographic (ECG) abnormalities are common in patients undergoing major vascular surgery. We explored the long-term prognostic value of cTnT levels in these patients.

Methods: A follow-up study was conducted between 1996-2000 in 393 patients who underwent successful aortic or infrainguinal vascular surgery and routine sampling of cTnT. Patients were followed until May 2003 (median of four years [25^{th}-75^{th} percentile, 2.8-5.3 years]. Total creatine kinase (CK), CK-MB, and cTnT were routinely screened in all patients, and included sampling after surgery and the mornings of postoperative days 2, 3 and 7. Electrocardiograms were also routinely evaluated for sign of ischemia. An elevated cTnT was defined as serum concentrations $\geq$0.1 ng/mL in any of these samples. All-cause mortality was evaluated during long-term follow-up.

Results: Eighty patients (20%) had late death. The incidence of all-cause mortality (41% vs. 17%; $p<0.001$) was significantly higher in patients with an elevated cTnT level compared to patients with normal cTnT. After adjustment for baseline clinical characteristics, the association between an elevated cTnT level and increased incidence of all-cause mortality (adjusted hazard ratio, 1.9; 95% CI, 1.1-3.1) persisted. Elevated cTnT had significant prognostic value in patients with and without renal dysfunction, abnormal levels of CK-MB, and in patients with transient ECG abnormalities.

Conclusions: Elevated cTnT levels are associated with an increased incidence of all-cause mortality in patients undergoing major vascular surgery.

Introduction

In patients undergoing major vascular surgery myocardial ischemia is the most common cause of perioperative and late morbidity and mortality.[1-4] However, symptoms of myocardial ischemia may be masked by perioperative use of sedative and analgesic drugs, and detection of perioperative myocardial ischemia may be hampered by false positive elevations of MB creatine kinase levels attributed to skeletal muscle injury occurring during surgery.[5] Recently, cardiac troponins have emerged as new risk stratification tools for prediction of perioperative and short-term cardiac complications. Cardiac troponins (T or I) are highly sensitive and specific markers for myocardial injury.[6] It has been shown that routine surveillance for cardiac troponins can be useful for identifying patients without clinical evidence of myocardial ischemia who are at increased risk of perioperative myocardial infarction and death.[5, 7-9] However, these studies are limited by relatively small numbers of patients, mixture of surgical populations, and by a short duration of follow-up. Accordingly, the aim of the present study was to explore the long-term prognostic value of cardiac troponin T (cTnT) levels after successful major vascular surgery in patients without clinical evidence of ischemia or new electrocardiographic changes consistent with ischemia.

Methods

Study population

We retrospectively reviewed the hospital electronic database for all patients who underwent major vascular surgery between May 1996 and December 2000 at the Erasmus Medical Center, Rotterdam, the Netherlands. This database holds information on demographic data, clinical records, and information on the perioperative course of all patients. During this period, the hospital protocol recommended serial blood sampling for cardiac enzymes and electrocardiograms (day 2, 3 and 7 or discharge) in patients undergoing major vascular surgery. As a result of this protocol serial sampling of cardiac enzymes and electrocardiograms were taken in 402 patients who underwent major elective vascular surgery. Of these 402 patients, nine patients with elevated cTnT died or developed nonfatal myocardial infarction after surgery and subsequently were excluded from the analyses. The remaining 393 patients who survived at least 30 days after surgery
formed the base of the present study.

Measurement of CK, CK-MB, and cardiac troponin T

Total creatine kinase and creatine kinase MB activities were measured until December 1998 (n=242 patients) by means of a N-acetylcysteine-activated optimised ultraviolet test (Merck; Darmstadt, Germany). Creatine kinase MB activity was determined by immunoinhibition. After December 1998, a mass assay for CK and CK-MB, utilizing a monoclonal antibody, was performed on the Roche/Hitachi 747 analyser. The upper levels of the reference intervals of CK was 190 IU/L, and for CK-MB activity above 24 IU/L, or the CK-MB activity fraction exceeding 6% of total CK.

Cardiac troponin T during the entire study period was measured qualitatively using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany).[10] The cut-off value for an abnormal cTnT test result was $\geq$0.1 ng/mL.

Data collection

The computerized hospital database, medical files, nurses reports, surgical records, postoperative charts, discharge letters and records of the outpatient clinic visits were manually screened to collect information on the presence of clinical risk factors and chronic cardiac medication use. Medical records were screened for the following clinical risk factors including age, gender, current or prior stable angina, previous MI, congestive heart failure, chronic pulmonary disease, renal dysfunction, diabetes mellitus, stroke, and hypertension. Additionally, postoperative 12-lead electrocardiograms were evaluated for abnormalities consistent with sign of ischemia, myocardial infarction or conduction abnormalities.

Follow-up

In May 2003 a follow-up was performed of all 393 patients who survived major vascular surgery for at least 30 days. The primary endpoint chosen for the present study was all-case mortality in order to avoid misclassification among cardiac, arrhythmic and noncardiac mortality. Information about patients' vital status was requested by approaching the Office of Civil Registry. For patients who died at the Erasmus MC during follow-up, hospital records and autopsy results were retrieved and reviewed. For patients who died outside of Erasmus MC, general practitioners were approached to ascertain the cause of death. If no autopsy was performed, medical information provided by general practitioners was used to ascertain the cause of death.

Statistical analysis

Dichotomous variables were compared by means of Fisher's exact test, and continuous variables were compared by means of Kruskal-Wallis test. The Kaplan-Meier method was used to evaluate the prognostic value of cTnT with respect to event-free survival. Differences in survival curves were compared by the log-rank test. Univariable Cox proportional hazard regression models were used to assess the independent association between cTnT, baseline clinical characteristics, and all-cause mortality. In order to avoid model over-fitting we applied a clinical risk model (3) that was developed elsewhere, and the clinical risk assessment was summarized in 1 index variable. Multivariable regression models were constructed by backward stepwise deletion of the least significant characteristics. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported. For all tests, a P value was $\leq$0.05 considered significant. All analyses were performed using SPSS statistical software (SPSS Inc., Chicago, Illinois, version 11.0).

Results

Patient characteristics

The characteristics of the study population are described in Table 1. Fourteen percent of patients had elevated ($\geq$0.1 ng/mL) cTnT levels postoperatively. Patients with abnormal cTnT levels were older, more often had a history of angina pectoris, renal dysfunction, and more often underwent acute or elective abdominal aortic aneurysm repair than patients with normal cTnT levels (Table 1). Furthermore, Ca-channel blocker and nitrate use, and elevated serum creatinine levels, abnormal elevations of postoperative creatine kinase and creatine kinase MB isoenzyme, and abnormal electrocardiograms were also more often observed in patients with abnormal levels of cTnT compared to patients with normal levels of cTnT (Table 1).

Table 1. Baseline characteristics

	Cardiac Troponin T Level		
Characteristics	**Abnormal* n=54, (%)**	**Normal n=339, (%)**	**P-value†**
Demographics			
Age ≥70 years	34 (63)	154 (45)	0.02
Male sex	45 (83)	268 (79)	0.60
Medical history			
Current stable or history of angina pectoris	23 (43)	65 (19)	0.001
Previous myocardial infarction	22 (41)	102 (30)	0.15
Congestive heart failure	4 (7)	14 (4)	0.29
Diabetes mellitus	6 (11)	46 (14)	0.83
Prior cerebrovascular accident	6 (11)	45 (13)	0.82
Renal dysfunction	16 (30)	42 (12)	0.003
Chronic pulmonary disease	15 (28)	68 (20)	0.21
Hypertension	23 (43)	132 (39)	0.65
Prior CABG	6 (11)	34 (10)	0.81
Prior PTCA	1 (2)	14 (4)	0.70
Type of surgery			0.04
Acute abdominal aortic repair	6 (11)	11 (3)	
Thoracoabdominal aneurysm repair	2 (4)	12 (4)	
Abdominal aortic aneurysm repair	25 (46)	131 (39)	
Aortoiliac repair	9 (17)	51 (15)	
Infrainguinal bypass	12 (22)	134 (40)	
Chronic cardiac medication			
ACE inhibitors	24 (44)	127 (38)	0.37
Aspirin	25 (46)	133 (39)	0.37
ß-blockers	30 (56)	169 (50)	0.47
Ca-channel blockers	20 (37)	59 (17)	0.02
Nitrates	21 (39)	49 (15)	<0.001
Statins	21 (39)	137 (40)	0.88
Electrocardiogram			
Left ventricular hypertrophy	14 (26)	59 (14)	0.14
Q waves consistent with previous myocardial infarction	12 (23)	38 (11)	0.03
ST-segment changes consistent with ischemia	15 (28)	45 (13)	0.007

Table 1. Baseline characteristics [cont]

Characteristics	Cardiac Troponin T Level		
	Abnormal*	**Normal**	**P-value†**
	n=54 (%)	**n=339 (%)**	
Laboratory findings			
Serum creatinine, mmol/L [median, IQR]	98.5 [80.8-143.5]	82 [67-104]	<0.001
Abnormal levels of creatine kinase	30 (56)	108 (32)	0.001
Abnormal levels of creatine kinase, MB isoenzyme	9 (17)	22 (7)	0.03

*All data are presented as number (percentage) unless otherwise indicated; IQR, indicates interquartile range; CABG, coronary artery bypass surgery; PTCA, percutaneous transluminal coronary angioplasty; For definition of risk factors see "Methods" section.

†Fisher exact 2-sided test, independent t-test or Kruskal-Wallis test

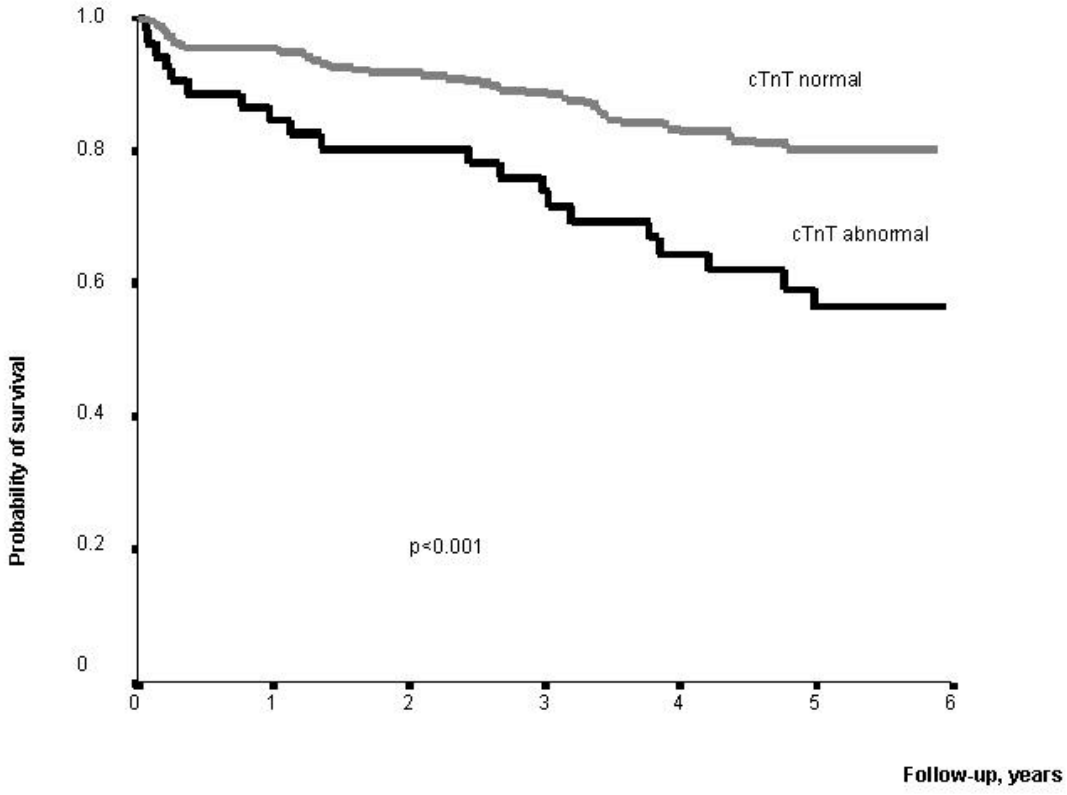
Follow-up

The median follow-up was 4.3 years (25^{th}-75^{th} percentile, 2.8-5.3 years). Eighty (20%) patients died during follow-up, among whom 49 died of cardiac causes. The cause of non-cardiac death was respiratory insufficiency in 10, cancer 10, sepsis secondary to infected prosthetic grafts 7, renal failure 2 and other causes in 2. Additionally, five (1.3%) patients had late coronary revascularization because of progression of angina pectoris, six patients suffered non-fatal cerebrovascular accident, and there were five patients who developed symptoms of congestive heart failure.

Relation between abnormal cTnT levels and long-term outcome

Survival of patients with abnormal and normal cTnT levels is shown in Figure 1.

Figure 1. Kaplan-Meier estimates of all-cause mortality according to normal and elevated levels of cardiac troponin T.



Abnormal levels of cTnT were associated with a significant increased risk of all-cause mortality in univariable analysis. Compared with patients with normal cTnT levels, patients with abnormal cTnT levels had a more than two-fold increase in risk of all-cause mortality (crude HR, 2.4; 95%CI, 1.5-4.0). Other variables that were associated with all-cause mortality in our dataset included chronic pulmonary disease and type of surgery. Patients who underwent acute abdominal aortic repair, thoracoabdominal and abdominal aortic aneurysm repairs had relatively high long-term mortality rates (Table 2).

Table 2. Univariable predictors and estimated risk of long-term all-cause mortality

Variables*		**Unadjusted**	
	Patients who died, n (%)	**HR (95% CI)**	*P-value*
Demographics			
Age≥70 years	46 (24.5)	1.6 (1.0-2.4)	0.05
Male gender	64 (20.4)	1.1 (0.6-1.8)	0.82
Medical history			
Current stable or history of angina pectoris	24 (27.3)	1.3 (0.8-2.2)	0.20
Previous myocardial infarction	30 (24.2)	1.3 (0.8-2.1)	0.22
Congestive heart failure	6 (33.3)	1.9 (0.8-4.3)	0.15
Diabetes mellitus	11 (21.2)	1.1 (0.6-2.2)	0.67
Prior cerebrovascular accident	14 (27.5)	1.6 (0.9-3.0)	0.10
Renal dysfunction	13 (22.4)	1.3 (0.7-2.3)	0.43
Chronic pulmonary disease	26 (31.3)	1.7 (1.1-2.8)	0.02
Hypertension	33 (21.2)	1.0 (0.7-1.6)	0.90
Prior CABG	10 (25.0)	1.1 (0.5-2.1)	0.85
Previous PTCA	1 (6.7)	0.4 (0.1-2.6)	0.31
Type of surgery, compared with infrainguinal bypass	20 (13.7)		
Acute abdominal aortic repair	6 (35.3)	3.8 (1.5-9.6)	0.004
Thoracoabdominal aneurysm surgery	7 (50.0)	6.5 (2.7-15.5)	<0.001
Abdominal aortic aneurysm repair	40 (25.6)	1.9 (1.1-3.3)	0.01
Aortoiliac repair	7 (11.7)	0.8 (0.3-1.8)	0.60
Chronic cardiac medication			
ACE-inhibitors	30 (20.0)	0.9 (0.6-1.4)	0.70
Aspirin	23 (14.6)	0.6 (0.4-0.9)	0.03
ß-blockers	34 (17.1)	0.7 (0.4-1.0)	0.05
Ca-channel blockers	19 (24.1)	1.0 (0.6-1.7)	0.95
Nitrates	20 (28.6)	1.5 (0.9-2.6)	0.10
Statins	14 (8.9)	0.3 (0.2-0.5)	<0.001
Electrocardiogram			
Left ventricular hypertrophy	20 (27.4)	1.7 (1.0-2.8)	0.05
Q waves consistent with previous MI	13 (26.0)	1.3 (0.7-2.7)	0.40
ST segment changes consistent with ischemia	17 (28.3)	1.6 (0.9-2.8)	0.08
Laboratory findings			
Abnormal CK-MB/CK index	8 (25.8)	1.6 (0.7-3.4)	0.20
Abnormal cardiac troponin T	22 (40.7)	2.4 (1.5-4.0)	0.001

*For definition of risk factors and laboratory findings see “Methods” section; HR, hazard ratio; CI, confidence interval

In contrast, aspirin, beta-blocker and statin use were associated with reduced all-cause mortality. Additionally, no association was observed between abnormal CK-MB levels and long-term mortality. The association between increased cTnT levels and the incidence of all-cause mortality persisted in multivariable analyses after correcting for other clinical risk factors, and electrocardiographic changes consistent with myocardial ischemia (Table 3).

Table 3. Multivariable predictors and estimated risk of long-term all-cause mortality (N=393)

Variables*	**Adjusted**	
	HR (95% CI)	*P-value*
Abnormal cardiac Troponin T	1.9 (1.1-3.1)	0.02
ST segment changes consistent with ischemia	1.8 (1.0-3.1)	0.05
Risk factors†, compared with no risk factors		
≥3	5.5 (1.8-16.5)	0.002
1 to 2	2.8 (1.0-8.1)	0.05
Type of surgery, compared with infrainguinal bypass		
Acute abdominal aortic repair	2.4 (0.8-7.0)	0.1
Thoracoabdominal aneurysm surgery	8.5 (3.4-20.1)	<0.001
Abdominal aortic aneurysm repair	2.4 (1.4-4.3)	0.003
Aortoiliac repair	1.3 (0.5-3.2)	0.6
Chronic cardiac medication		
Statins	0.3 (0.2-0.5)	<0.001
ß-blockers	0.5 (0.3-0.8)	0.004
Aspirin	0.6 (0.3-0.9)	0.04

*For definition of variables see “Methods” section; HR, hazard ratio; CI, confidence interval

†Risk score was composed by assigning 1 point to each of the following characteristics: age>70 years, angina pectoris, prior myocardial infarction, heart failure, prior cerebrovascular event, diabetes mellitus, renal dysfunction and chronic pulmonary disease

In separate analyses we also studied the prognostic value of cTnT levels in different subgroups of patients. There were no significant differences observed in the prognostic value of abnormal cTnT levels in subgroup of patients with renal dysfunction, elevated levels of CK-MB or in patients with ischemic ST-segment changes on electrocardiogram (Table 4).

Table 4. Prognostic value of abnormal cTnT levels according to subgroups of patients*

	Abnormal cTnT	Normal cTnT	HR (95% CI)	Abnormal cTnT	Normal cTnT	HR (95% CI)	P value†
	Normal renal function			***Renal dysfunction***			
Total	38	297		16	42		
Death	18 (47.4%)	49 (16.5%)	3.0 (1.8-5.2)	4 (25%)	9 (21.4%)	0.9 (0.3-3.3)	0.08
	Normal CK-MB levels			***Abnormal CK-MB levels***			
Total	44	304		9	22		
Death	19 (43.2%)	50 (16.4%)	2.6 (1.6-4.5)	3 (33.4%)	5 (22.7%)	1.4 (0.3-5.9)	0.23
	No ST segment changes			***ST segment changes***			
Total	37	294		15	45		
Death	14 (37.8%)	48 (16.3%)	2.1 (1.1-3.8)	7 (46.7%)	10 (22.3%)	2.1 (0.8-5.4)	0.98

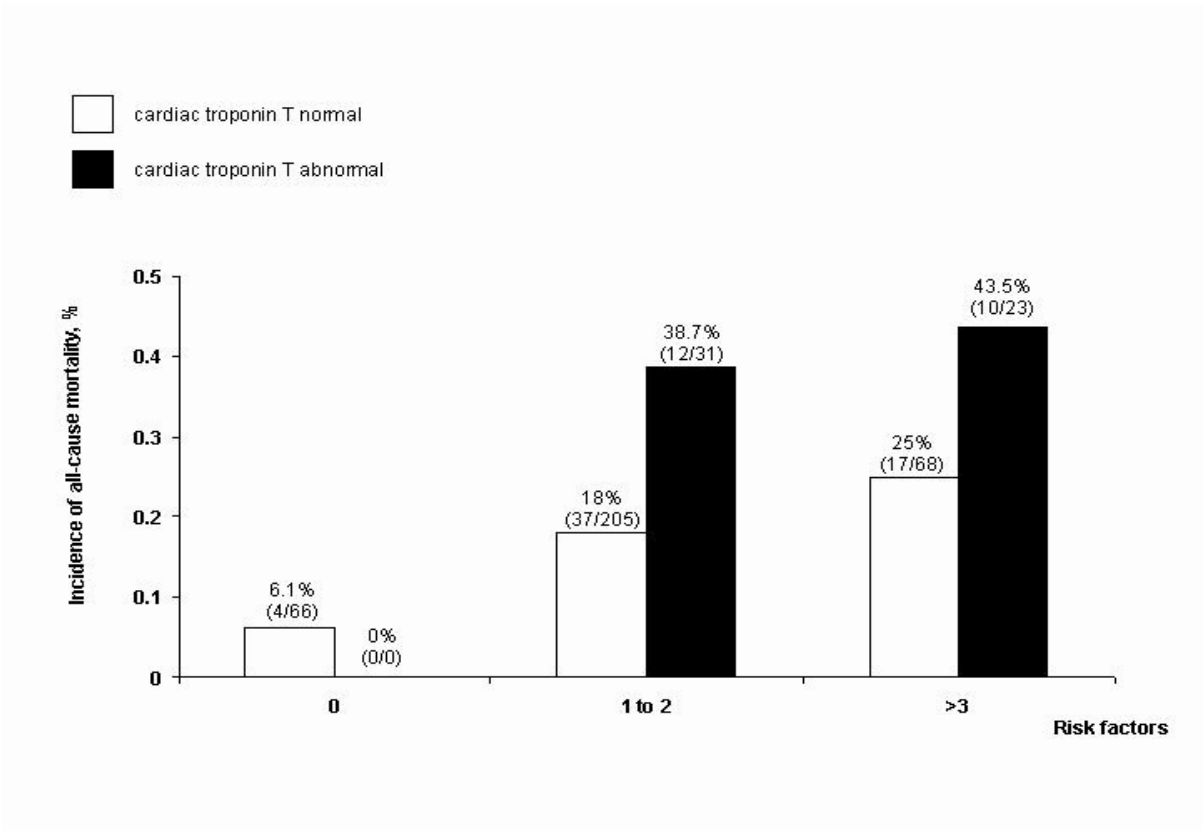
*Numbers may not add up to 393 due to missing data; HR, hazard ratio; CI, confidence interval

†P value for interaction represents a level of statistical evidence for heterogeneity in the prognostic value of cTnT in subgroup of patients with renal dysfunction, abnormal levels of CK-MB and ST segment changes on electrocardiograms consistent with ischemia

Prognostic value of cTnT levels according to cardiac risk factors

Based on the number of cardiac risk factors and the presence of abnormal cTnT levels the incidence of all-cause mortality was estimated. If patients had a risk index of 0 no patients had abnormal cTnT levels and the incidence of all-cause mortality was 6.1% in patients with normal cTnT (Figure 2). In contrast, patients with a risk index of 1 to 2 and 3 or more risk factors and with abnormal cTnT levels were at substantially higher risk of adverse perioperative outcome compared to patients with normal cTnT levels.

Figure 2. Incidence of all-cause mortality according to cardiac risk factors and normal and elevated levels of cardiac troponin T.



Results are based on the number of clinical risk factors (age>70 years, current angina, prior myocardial infarction, heart failure, prior cerebrovascular event, diabetes mellitus, renal insufficiency and pulmonary disease), and normal and abnormal levels of cardiac troponin T.

Discussion

Asymptomatic cardiac troponin T elevations were associated with an almost two-fold increased risk of long-term mortality in patients undergoing successful major vascular surgery, independent of the presence of risk factors for coronary artery disease, renal dysfunction, cardiac medication use, elevated CK-MB levels and ST-changes consistent with myocardial ischemia.

These findings are consistent with the results of previous studies on cardiac troponins as markers of myocardial injury in noncardiac surgery setting. Several investigations have shown that abnormal levels of cardiac troponins identify patients at increased risk of perioperative and short-term cardiac complications.[5, 7-9] Lopez-Jimenez et al.[9], showed that abnormal levels of cTnT in patients undergoing noncardiac surgery was associated with a more than four-fold increased risk of cardiac events during a six-month follow-up period. Kim et al. later confirmed these

findings[7], in 229 patients who underwent serial measurements of cardiac troponin I levels after vascular surgery. Twenty-eight (12%) patients had abnormal postoperative cardiac troponin I levels, which was associated with a six-fold increased risk of six-month mortality. In a more recent study similar to our findings, Landesberg et al, also found a positive association between abnormal levels of cardiac troponin I after vascular surgery and all-cause mortality during on average of two an half years of follow-up.[11]

Patients undergoing noncardiac surgery with or at high risk of coronary artery disease have an incidence of perioperative myocardial ischemia exceeding 40% with an associated nine-fold increased risk for cardiac death and myocardial infarction.[12, 13] Patients with events related to myocardial ischemia and surviving the perioperative period still remain at high risk for long-term cardiac complications.[14] In this regard, patients undergoing major vascular surgery are particularly at very high risk for perioperative and long-term mortality and morbidity related to myocardial ischemia.[2, 15-17] Detection of myocardial ischemia during and after major vascular surgery could be difficult as a result of altered pain perception, false positive elevations of CK-MB levels or due to presence of pre-existing electrocardiographic abnormalities.[18] Cardiac troponins, on the other hand may help to identify patients at increased risk for perioperative and short-term adverse events. It contrast, it has been observed that many patients without cardiac complications or symptoms related to myocardial ischemia may have elevated cTnT levels [8], raising the question whether or not these abnormal values are false positive results, or indeed evidence of asymptomatic myocardial injury. The findings of our study provide evidence that asymptomatic patients with elevated cTnT levels remain also at increased risk for long-term mortality.

In earlier reports it was described that renal dysfunction may interfere with the prognostic value of cTnT because of its clearance may be decreased. In contrast, Aviles et al.[19], showed that cTnT levels predicted short-term prognosis in acute coronary syndrome patients regardless of the presence or absence of renal dysfunction. Consistent with these findings we found that abnormal cTnT levels independently predicted long-term all-cause mortality regardless of renal dysfunction. Similarly to previous studies the prognostic value of abnormal cTnT levels was superior to that of CK-MB elevations. In fact, patients with abnormal cTnT levels experienced adverse long-term mortality more often than patients with elevated CK-

MB levels.[8, 9, 20-22] These data are consistent with findings for surgical and nonsurgical populations indicating that abnormal cTnT levels is a marker for myocardial injury, even if that myocardial injury is not sufficient to cause CK-MB release and clinical symptoms. Furthermore, the findings of our study indicate that abnormal levels of cTnT independently predicted long-term mortality in patients with and without ECG abnormalities consistent with myocardial ischemia. These results are consistent with the hypothesis that elevated cTnT levels in these patients may reflect a degree of myocardial ischemia, which is not sufficient to cause ECG abnormalities that would be detected by routine 12-lead ECG recordings.[9] These findings indicate that cTnT may further facilitate identification of high-risk patients.

There are no clinical studies about the long-term optimal treatment strategy to patients with asymptomatic cardiac troponin T elevations after successful major vascular surgery. However, previous reports of medical patients show that a relationship between elevated levels of cardiac troponin and incidence of cardiac complications may help to guide risk stratification practices, and as a screening test, cardiac troponins have been shown to improve clinical management and subsequently improve survival of patients presenting to emergency room with acute chest pain.[23] Recently, a marked reduction in adverse cardiac events were reported among patients with elevated cardiac troponins and acute coronary syndromes if they were randomized to an early invasive treatment.[24] Our data suggest that inclusion of cTnT in the long-term management of patients with asymptomatic elevations of cTnT may have clinical utility for developing optimal treatment strategies.

Several limitations of this study should be considered when interpreting the results. Since this study was observational, adverse outcome events could potentially have been missed. However, we used all cause specific mortality data as the primary outcome measure for this study. Additionally, during the study period a qualitative test was used for detecting elevated levels of cTnT, which did not allow us to investigate the relation between different cTnT levels and incidence of cardiac complications.

In conclusion, abnormal levels of cTnT after successful major vascular surgery are associated with a higher incidence of long-term all-cause mortality, and provide additional prognostic information to clinical risk factors and CK-MB levels. Clinical

studies are required to determine the most optimal approach and management for patients with abnormal cTnT levels to improve their long-term outcome.

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Chapter 6

Validation of two risk models for perioperative mortality in patients undergoing abdominal aortic aneurysm surgery

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Validation of Two Risk Models for Perioperative Mortality in Patients Undergoing Elective Abdominal Aortic Aneurysm Surgery

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The authors validated 2 clinical risk models for perioperative mortality in patients scheduled for elective open abdominal aortic aneurysm surgery (AAA surgery). They studied 361 patients who underwent elective AAA surgery between 1991 and 1999 (validation population). Two clinical risk models were validated. The first was developed in 238 patients from Leiden University Hospital (Leiden risk model). The Leiden risk model was modified to provide predictions for the validation population based on 6 predictors including age, gender, a history of previous myocardial infarction, congestive heart failure, renal disease, and pulmonary disease. The second was a recently published simpler risk model developed in 820 patients in the UK Small Aneurysm Trial (UK risk model) and included 3 predictors (age and renal and pulmonary comorbidity). Logistic regression was used to quantify the relationship between predictors and outcome (mortality within 30 days of surgery). Validation further included the concordance statistic (c-statistic) for discriminative ability and the Hosmer-Lemeshow test for model reliability. The perioperative mortality in the validation population was 6.6% (24/361). Predictors had similar odds ratios, with particularly strong effects of congestive heart failure, pulmonary disease, and renal impairment. The Leiden risk model had reasonable good ability (c-statistic 0.72) and showed adequate calibration ($\chi^2 = 3.3$, $p = 0.97$). It could particularly identify a low-risk group. The UK risk model did not perform well (c-statistic 0.60), showing statistically significant lack of fit ($\chi^2 = 64.9$, $p < 0.001$). This study showed similar predictive ability of previously identified predictors for perioperative mortality. The Leiden risk model could identify a low-risk group, while the UK risk model showed a relatively poor performance. The current study supports the use of the Leiden model for preoperative risk assessment.

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Introduction

Patients undergoing elective open abdominal aortic aneurysm surgery (AAA surgery) are at increased risk for perioperative mortality. Despite recent advances in perioperative care the 30-day mortality rate of elective AAA surgery still varies from 5% in selected series, up to 8% in population-based studies.[1,2] Identification of preopera-

tive factors associated with increased risk of mortality may initiate preoperative interventions and influence decisions about the type (ie, endovascular procedures) and also the timing of the elective surgical repair.[3]

A number of risk factors of perioperative mortality in elective AAA surgery have been identified, including age, female gender, history of previous myocardial infarction (MI), congestive heart failure (CHF), electrocardiographic abnormalities, and pulmonary and renal disease.[4-12] These risk factors have been incorporated in clinical risk models such as developed in a cohort of patients from the Leiden University Hospital ("Leiden risk model").[4] This risk model then provides predictions of the risk of perioperative death in individual patients. However, the Leiden risk model was developed in a limited number of patients and was not prospectively validated.

In a recent study similar risk factors for perioperative death were studied in patients of the UK Small Aneurysm Trial, and a simpler risk model was proposed, the "UK risk model."[3] This includes age, pulmonary disease, and impaired renal function as risk factors. This study also externally validated the Leiden risk model and found a poor performance for patients at low and intermediate risk.

The objective of the present study was to evaluate the performance of the Leiden and UK risk models in a group of recently operated on patients who underwent elective AAA surgery.

Materials and Methods—Clinical Risk Models

Leiden Risk Model

The Leiden risk model was developed in 238 patients from the Leiden University Hospital combined with a metaanalysis of published risk factors.[4,13] In the present study we had access to the original data in which the Leiden risk model was developed (Leiden population). In that risk model a risk score was allocated to age (age < 60, −4; age = 70, 0; age > 80, +4), female gender (+4), history of MI (+3), CHF (+8), electrocardiographic evidence of ischemia (+8), renal disease (preoperative creatinine cutoff value of 160 μmol/L, +12), and pulmonary disease (chronic obstructive pulmonary disease, emphysema, dyspnea, or previous pulmonary surgery, +7). The scores added up to a sum score for each patient, which was translated into a probability of perioperative death p: $p = 1/(1 + \exp[-([\text{sumscore}/10] - 6.14)])$. In the present study, however, because the variable "evidence of resting ischemia on electrocardiography" was often missing in the validation dataset, the model was reestimated by using the Leiden population, which resulted in a revised risk model with 6 determinants instead of 7.

The UK Risk Model

We also evaluated a recently published simpler risk model developed in 820 patients in the UK Small Aneurysm Trial (the UK risk model).[3] This model comprises 3 risk factors dichotomized around their median value: age, lung function, and renal function, as assessed by the forced expiratory volume in 1 *s* (FEV_1) and serum creatinine level, respectively. The probability of perioperative mortality was predicted for 8 categories of patients according to the presence of risk factors.

Validation Population

To validate these 2 risk models we collected data on 369 consecutive patients who underwent elective AAA surgery between 1991 and 1999 at the Erasmus Medical Center or were participating in a multicenter study (validation population).[14,15] Of 369 patients who underwent elective surgery, 361 had no missing value on any of the selected risk factors. Statistical analyses were based on these 361 patients. Perioperative mortality was defined as mortality within 30 days after surgery. Risk factors according to the Leiden risk model considered for perioperative mortality in the validation population were age, sex, and a history of cardiac, renal, and pulmonary disease. Cardiac disease included only 2 factors (ie, history of myocardial infarction and congestive heart failure), because the third risk factor "evidence of resting ischemia on electrocardiography" was often missing. History of myocardial infarction in the validation population was defined as a documented history of a myocardial infarction or, if electrocardiography was available, a finding of pathologic Q waves. Congestive heart failure was defined according to the presence of a history of symptoms or signs of pulmonary congestion, signs of left or right ventricular failure, and chest radiographic findings suggestive of heart failure. Impaired renal function was defined categorically by using a preoperative creatinine cutoff value of 180 μmol/L (2.0 mg/dL). Pulmonary comor-

bidity was present if FEV_1 was 75% of normal, corrected for age and gender.

Statistical Analysis

Multivariable logistic regression analyses were performed to reestimate the coefficients for each risk factor. We compared the multivariable coefficients for each risk factor in the validation population with those of the Leiden and UK populations by using t tests. We hypothesized that overall multivariable effects of the risk factors would not differ between the validation population and the other populations. This hypothesis was tested in the validation population by comparing the log-likelihood of the Leiden and UK risk models with the log-likelihood of the risk models with the same predictors but with reestimated coefficients.

The performance of the Leiden and UK risk models was studied with respect to discrimination and calibration.[16] Discrimination is the ability of the risk model to distinguish patients who survived from those who died. The discriminative ability of the risk models was quantified with the concordance statistic (c-statistic), which is identical to the area under the receiver operating characteristic curve.[17] The c-statistic represents the probability that for a random pair of patients a patient who died had a higher predicted probability of dying than a patient who survived.

Calibration indicates to what extent the predicted perioperative risks agree with the observed perioperative mortality. Calibration was assessed graphically by plotting the observed frequencies against the predicted risks. Calibration was further assessed with the Hosmer-Lemeshow goodness-of-fit test.[18]

All analyses were performed with SPSS for Windows version 10.0 and S-plus version 2000 software, using the Design library.[19]

Results

Comparison of Patient Populations

The main patient characteristics of the 3 populations are described in Table I. The patients in the validation population were of similar age as those

Table I. Characteristics of patients in the validation, Leiden and UK populations.

Characteristics	Validation Population n = 361	Leiden Population n = 238	UK Population‡ n = 820
Demographics			
Age at operation (years)*	68.8 ±8.8	66.4 ±7.5	70.0 ±6.1
Female gender, n (%)	54 (15)	21 (9)	136 (17)
History†‡			
Prior myocardial infarction, n (%)	127 (35)	58 (24)	–
Congestive heart failure, n (%)	22 (6)	80 (34)	–
Pulmonary disease, n (%)	44 (12)	45 (19)	371 (45)
Impaired renal function, n (%)	22 (6)	15 (6)	380 (46)
Outcome			
Perioperative mortality, n (%)	24 (6.6)	18 (7.6)	46 (5.6)

*Values are mean ± SD; All data are presented as number (percentage) unless otherwise indicated.
†For definitions of risk factors, see "Methods" section. ‡Data for some of the risk factors in the UK Small Aneurysm Trial were not retrievable.

in the other populations (average 69 years), and women constituted a similar fraction as in the UK population (average 15%). Clinical risk factors were different in prevalence, in particular, pulmonary disease and impaired renal functions were less often noted than in the UK population (12% versus 45% and 6% versus 46%, respectively). The perioperative mortality was similar in the validation and Leiden populations (6.6% and 7.6%, respectively), whereas it was slightly lower in the UK Small Aneurysm Trial patients (5.6%).

Comparison of Predictive Effects

Table II shows the results of the multivariable analyses of the preoperative risk factors for perioperative mortality, with the corresponding 95% confidence intervals (CIs). Multivariable odds ratios (ORs) were in the same direction as those calculated in the Leiden population. However, age and a history of MI had virtually no predictive value (OR close to 1). Gender, a history of pulmonary disease, and impaired renal function had greater effects than in the Leiden population. These differences were, however, no greater than they would be expected based on chance (overall test, $p = 0.26$).

The results of the multivariable analyses of the 3 predictors as specified by the UK risk model are shown in Table II. The effect of age was greater in the UK population (OR > 2), while pulmonary disease and renal impairment had stronger effects in the validation population.

Comparison of Predictive Performance

The Leiden risk model showed good discriminative ability (c-statistic 0.80) within the Leiden population. Overall goodness-of-fit was adequate, indicating that the multivariable logistic regression model reliably fitted the Leiden data (Hosmer-Lemeshow test; $\chi^2 = 3.2$, $p = 0.92$; Table III). The c-statistic decreased to 0.72 when the Leiden risk model was applied to the validation patients.

Figure 1 shows the relation between predicted risks derived from the modified Leiden risk model and observed frequencies in the validation population. There was a good agreement at risk lower than 5%, where the observed frequencies were similar to the predicted risks. However, at higher predicted risk, the observed frequencies became higher than the predicted probabilities. The goodness-of-fit of this risk model was ade-

Table II. Predictive effects of patient characteristics included in the Leiden and UK risk models. Multivariable odds ratios are shown for the validation, Leiden, and UK populations.

Risk Models	Risk Factors*	Validation Population	Leiden Population	p Value
Leiden	Age per decade	1.0 (0.6–1.7)	1.9 (0.9–4.2)	0.13
	Female gender	2.8 (1.0–7.8)	1.5 (0.3–7.7)	0.49
	Prior myocardial infarction	1.1 (0.4–2.9)	2.9 (0.9–8.2)	0.20
	Congestive heart failure	3.1 (0.8–12.0)	3.5 (1.1–11)	0.90
	Pulmonary disease	3.2 (1.2–8.7)	1.8 (0.7–13)	0.45
	Impaired renal function	5.1 (1.6–17)	2.9 (0.6–5.5)	0.55
UK	Age per decade	1.0 (0.6–1.7)	2.1 (1.1–4.2)	0.17
	Pulmonary disease	3.8 (1.6–9.8)	1.3 (0.7–2.4)	0.06
	Impaired renal function	6.0 (2.0–18)	2.6 (1.3–5.1)	0.19

*For definitions of risk factors, see "Methods" section; CI: 95% confidence interval; p value corresponds to the t test for comparison of odds ratios between 2 populations for each risk factor.

Table III. Performance of the Leiden and UK prediction rules in the validation, Leiden, and UK populations.

Risk Model	Population	N	Reliability†	Discriminative Ability‡
Leiden	Leiden	238	3.2 (p=0.92)	0.80 (0.60–0.91)
	Validation	361	3.3 (p=0.97)	0.72 (0.60–0.83)
	UK*	820	–	0.55 (–)
UK	UK*	820	–	0.65 (–)
	Validation	361	64.9 (p<0.001)	0.60 (0.47–0.77)
	Leiden	238	17.2 (p=0.016)	0.65 (0.60–0.80)

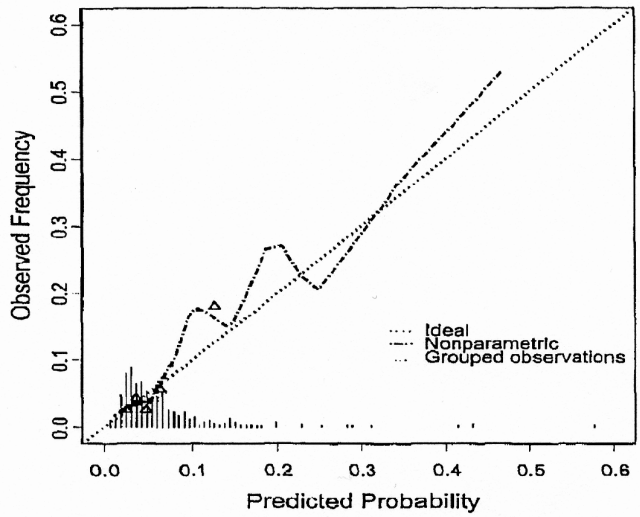
*Individual patient data were not available for the UK Small Aneurysm Trial patients; from the published report only the c-statistic was retrievable. †Reliability: indicates to what extent predicted perioperative risk agrees with the observed perioperative mortality, quantified by chi-square statistic. ‡Discriminative ability: an ability to distinguish patients who survived from those who died, quantified by c-statistic and corresponding 95% confidence interval.

Table IV. Predicted perioperative risk of death by age, pulmonary disease, and impaired renal function as developed on patients in the UK Small Aneurysm Trial[3] and observed risks in the UK and validation populations.

Age, years	Pulmonary Disease	Impaired Renal Function	Predicted Risk (%)	Observed Risk (%) UK Population*	Observed Risk (%) Validation Population*
60–69	No	No	2.7	0.9 (1/116)	5.0 (5/99)
		Yes	3.2	5.0 (5/100)	40.0 (4/10)
	Yes	No	4.1	2.2 (2/89)	19.0 (3/20)
		Yes	5.7	6.1 (4/66)	0.0 (0/2)
70–80	No	No	3.8	4.0 (3/76)	3.0 (4/133)
		Yes	5.2	8.9 (10/112)	25.0 (1/4)
	Yes	No	6.0	5.3 (6/114)	18.8 (3/16)
		Yes	7.8	9.8 (10/102)	50.0 (1/2)

*Numbers in the denominator may not add up to the total population sizes in the UK population owing to missing values, and in the validation population owing to some patients who were not classified, for they were younger than 60 years (n=49), as well as older than 80 years (n=26).

Figure 1. Calibration of the modified Leiden risk model in the validation population. The dashed line is a nonparametric smoothed curve representing the relation between observed frequency and predicted probability. Perfect calibration is represented by the dotted line through the origin with slope equal to 1. Triangles indicate incidence of perioperative death in 10 groups of patients with similar predicted probabilities. The distribution of predicted probabilities is shown above the x-axis (vertical lines).



quate (Hosmer-Lemeshow test; $\chi^2 = 3.3$, $p = 0.97$; Table III).

Perioperative mortality for different risk categories according to the UK risk model[3] is presented in Table IV. In most categories, the observed perioperative mortality for the validation population was somewhat higher than expected based on the UK risk model. The disagreement was statistically significant ($\chi^2 = 64.9$, $p < 0.001$, respectively; Table III). After correction for this disagreement the goodness-of-fit was reasonable ($\chi^2 = 4.8$, $p = 0.68$), which indicates that the poor goodness-of-fit of the original UK risk model could largely be explained by the difference in average outcome incidence between the UK and validation populations. The UK risk model showed relatively poor discrimination in the validation and Leiden populations (c-statistic 0.60 and 0.65, respectively), in agreement with the moderate performance in the UK patients (c-statistic 0.65).

Discussion

The novelty of the present study is that it provides insight into the applicability of the Leiden risk model over time in this unique patient population. We have shown that previously identified risk factors for perioperative mortality of elective open AAA surgery have similar prognostic impact in a contemporary group of patients. A slightly modified Leiden model showed good discrimination and has the ability to identify a low-risk group of patients. Conversely, the simpler UK model seemed to perform poorly in the validation population.

The original Leiden risk model was slightly modified such that of "evidence of resting ischemia on ECG" was often missing in the validation population. We observed a diminished but still reasonable discriminative ability of the preoperative risk factors in the validation population (c-statistic 0.72) compared to the Leiden population (c-statistic 0.80). This difference in c-statistic may be partially explained by chance and/or true differences in the prognostic impact of preoperative risk factors but also by differences in the distribution of predictors in the 2 populations.

Unlike the validation population, the positive association of age and perioperative mortality was observed both in the Leiden and UK populations. Yet, age had an association with mortality when adjusted for pulmonary and renal comorbidities in the Leiden and UK populations. The ob-

served weakening of the evidence for an age effect across all populations after adjusting for important prognostic variables is explained by the fact that other risk factors for perioperative mortality increase with age. Therefore, elective surgical repair should not be postponed on grounds of advanced age alone.

Similar to previous studies, women in all 3 populations were at slightly higher risk for perioperative death compared to men.[4,20] The reasons for higher mortality rates among women are unclear; however, it has been suggested that women are at an advanced stage of the disease when they are referred for operation.

Indicators of coronary artery disease such as history of MI, CHF, and ECG evidence of ischemia have been shown to be important risk factors for perioperative mortality,[4,8,9,21] and in the original Leiden model were included. In contrast, in the UK population, evaluation of suitability for surgery and cardiac function was based on local clinical judgment as the proxies for coronary artery disease. Histories of CHF and MI were not used for perioperative risk assessment in the UK model; however, both histories of MI and CHF were strong predictors for perioperative death in both Leiden and validation populations. The only cardiac risk factor selected and assessed in the UK population was evidence of ischemia on ECG, which was not a strong risk factor for perioperative mortality. We found that the UK risk model would not have performed well when applied to the validation nor the Leiden populations. Therefore, inclusion of information on CHF and previous MI might have refined the prognostic ability of the UK risk model.

In the UK population,[3] poor pulmonary and renal function were strongly and linearly related to perioperative death, and as such they were included in the UK model. Indeed, these risk factors were also significant predictors for perioperative mortality in the validation population. However, patients in the validation population with poor pulmonary function had an almost fourfold increased risk for perioperative mortality, and patients with poor renal function had a sixfold increased risk for perioperative mortality compared to the UK population. The differences in effect measures for these risk factors were higher in the validation population, but there was no significant difference between the odds ratios of the 2 populations for each risk factor. The observed differences in the prognostic value of these risk factors may be explained by slightly different criteria used to define poor pulmonary and renal function between the populations.

While similar perioperative mortality was observed in the validation and Leiden populations, the UK population experienced slightly lower perioperative mortality. The difference may be explained by the use of prespecified study criteria in the UK population, whereas the validation and Leiden populations were made up of consecutive patients.

The identification of high-risk patients may facilitate the timely initiation of treatment strategies to reduce perioperative mortality. The present study showed that cardiac, pulmonary, and renal comorbidities remain important as risk factors for perioperative mortality. Indeed, the most common cause of death in AAA surgery is cardiac-related, with pulmonary and renal insufficiencies being the next 2 leading causes.[4,8,9,22,23] Preoperative cardiac evaluation of these patients should incorporate steps, such as a clinical evaluation of baseline characteristics and diagnostic information to determine the patient's likelihood of significant coronary disease and perioperative cardiac event risk, and selective use of noninvasive testing to further refine risk assessment.[24] The study of Boersma et al[15] confirmed that a combination of cardiac risk factors and a noninvasive test such as dobutamine stress echocardiography may help to identify patients in whom surgery can still be performed while receiving cardiac medication and those in whom cardiac revascularization should be considered.

Poor pulmonary and renal function have been observed as strong risk factors for perioperative mortality in the present study as well as in the literature.[4,8,9,20,22] Combination of different perioperative strategies including bronchodilators, physiotherapy, glucocorticoid administration, cessation of smoking, shorter duration of surgery, avoidance of the long-acting neuromuscular blocker pancuronium, and postoperative physiotherapy and pain control may reduce the risk of postoperative pulmonary complications.[25] There have been many attempts to improve or preserve the renal function in patients undergoing surgery including improved surgical and anesthetic management, and use of renal protective pharmacological agents.[26,27] Reduction in duration of aortic cross-clamping may restore or prevent the prolonged interruption of renal blood flow. The choice of less invasive techniques, such as endovascular procedures, may help to avoid aortic cross-clamping and fluctuations in systemic blood pressure.

There are also other important factors to consider, such as adequate fluid repletion and allowing contrast-induced nephropathy to resolve before proceeding with elective surgery. Selection of some additional risk factors may further improve the identification of patients at higher preoperative risk. Risk factors, such as diabetes mellitus, not only increase the likelihood and extent of coronary artery disease but may also promote endothelium dysfunction and prothrombotic activity and predispose the patient to increased perioperative and long-term cardiac complications.[22,28,29] However, in a recent study diabetes mellitus was not a statistically significant predictor in a multivariable analysis for surgical complications.[15] A prior cerebrovascular accident has also been shown to be an important risk factor for adverse perioperative cardiac outcome and cardiac mortality[15] but not for overall mortality.[24]

Conclusion

This study shows that 6 previously identified preoperative risk factors of perioperative mortality for elective open AAA surgery had predictive ability in a contemporary group of patients. The Leiden risk model could identify a low-risk group of patients. The UK risk model had only relatively poor performance and, hence, was not a suitable alternative to the Leiden risk model. The current study provides evidence that may support the use of the Leiden model in practice.

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Chapter 7

Perioperative cardiovascular mortality in 108,613 noncardiac surgical procedures. The Erasmus MC experience during 1991-2000

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Submitted for publication

Abstract

Background: The classical preoperative cardiovascular risk evaluation scores for non-cardiac surgery date from the 1970s and 1980s, and are based on relatively small samples and a few outcome events.

Methods and Results: We studied the 108,613 non-cardiac surgical procedures that were performed in 75,581 adult patients during 1991-2000 in the Erasmus MC, Rotterdam, the Netherlands. Consistent with clinical practice the surgical procedure was taken as unit of analysis. Perioperative mortality occurred in 1,877 cases (1.7%), of which 543 were due to cardiovascular complications (0.5% of the population; 29% of deaths). The incidence of cardiovascular mortality was higher in men than in women (0.7 versus 0.3%). There were no significant changes in cardiovascular mortality over time in either men or in women. Advanced age, male gender, type of surgery, diabetes mellitus, hypertension, ischemic heart disease, heart failure, stroke, and renal failure were identified as important clinical risk factors for cardiovascular death. An resting ECG within 90 days prior to surgery was available in 28,457 cases. An abnormal ECG was associated with increased perioperative cardiovascular mortality. Based on these results, a score was developed to estimate an individual patient's risk of cardiovascular death in relation to a specific surgical procedure, which had excellent discriminative ability (c-index in the range 0.809 to 0.870).

Conclusions: The combination of clinical characteristics and ECG measurements identify non-cardiac surgical patients at risk of perioperative cardiovascular death. The developed multivariable risk models showed excellent ability to discriminate between patients at low, intermediate and high risk of cardiovascular complications, and can readily be applied in routine perioperative management. These risk prediction models can also be used to identify target populations for the development of risk reduction strategies.

Introduction

Patients undergoing major non-cardiac surgery are at significant risk of cardiovascular morbidity and mortality. Perioperative myocardial infarction is the most frequent complication in this respect. Evidence exists that, as in non-surgical settings, coronary plaque rupture leading to thrombus formation and subsequent vessel occlusion, is the predominant mechanism.[1,2] The clinical importance of perioperative cardiovascular complications is well recognized, and numerous investigators have described the relationship between patient characteristics and the risk of adverse cardiovascular outcome.[3-10] The multivariable cardiovascular risk indices developed by Goldman, Detsky and Eagle are most frequently quoted in this respect.[3,7,10] However, most studies evaluating cardiovascular risk in a general surgical population date from the 1970s and 1980s. Since then, there have been potentially significant advances in anaesthesia, surgery and postoperative care. The impact of these developments on the incidence and lethality of cardiovascular complications and the predictive value of established risk factors is yet unknown. Furthermore, the classical investigations of unselected surgical patients are based on relatively small samples (the largest series, from 1987, consists of 2,609 patients) and a few outcome events.[5,9]. Consequently, important risk factors may have been missed, due to a lack of statistical power. More recent studies have focused on patients undergoing specific types of surgery, such as thoracic, orthopedic, or vascular.[8,11,12]. These facts prompted us to develop a cardiovascular risk assessment score based on recent data and applicable to patients undergoing a broad spectrum of non-cardiac surgical procedures. Accordingly, we studied the 108,593 patients who underwent non-cardiac surgery in our center from 1991 to 2000. We examined trends in the incidence of fatal perioperative cardiovascular complications over time, and studied the relationship between clinical and electrocardiographic variables and fatal cardiovascular outcome. Our results may facilitate routine perioperative clinical management, and the design of future studies evaluating potential risk reduction strategies.

Methods

Hospital setting, procedures and patients

The Erasmus Medical Center (MC) is a metropolitan university hospital, serving a population of approximately 3 million, in the south-western area of the Netherlands, which acts as a tertiary referral center for approximately 30 affiliated hospitals. In the Erasmus MC, between January 1, 1991 and December 31, 2000, 122,860 non-cardiac surgical procedures were performed in patients above the age of 15 years. We excluded 14,267 unplanned procedures that were conducted within 30 days after an initial operation, and analyzed the perioperative course of the remaining 108,593 cases.

The number of patients involved in this dataset amounts 75,581. Over the 10-year observation period, 20,885 patients had multiple surgeries in the Erasmus MC. They were included as many times as they had surgeries. The median span between two successive procedures was 297 days (interquartile range 123 to 677 days; note that the minimum span was 31 days). Thus, we chose operation (and not patient) as unit of analysis, mainly for two reasons. Firstly, this is consistent with clinical practice, as the risk of perioperative complications is assessed in relation to a specific procedure. Secondly, this approach guarantees an optimal utilization of the available information. Dedicated statistical techniques were applied to account for potential dependence among observations (see paragraph on statistical analysis).

Material

For each patient undergoing surgery, a number of data-items are routinely (and prospectively) stored in the computerized hospital information system. First, the surgical techniques are classified by the treating physician according to a standardized national coding system, which was developed in co-operation with the National Health Service and medical insurance companies. This system is used for reimbursement and to record and monitor the experience of surgeons and surgical residents. Using this classification, we grouped surgical procedures into 14 categories. 11,969 procedures (11.0 %) were classified into multiple categories.

Second, from written information that is provided by the General Practitioner, the referring physician, or the hospital physicians involved in perioperative care, each patient’s medical history is classified according to the ninth International

Classification of Diseases (ICD-9).[13] The classification, primarily used to develop national health statistics, is performed by dedicated administrative personnel who have completed in-depth training on registration of medical data. We recorded medical conditions that are considered potential determinants of perioperative cardiovascular outcome, including diabetes mellitus (ICD-9 250), hypercholesterolemia (ICD-9 272), hypertension (ICD-9 400), myocardial infarction (ICD-9 410, 411, and 412), angina pectoris (ICD-9 413 and 414), heart failure (ICD-9 428), cerebrovascular accident (ICD-9 430), chronic obstructive pulmonary disease (ICD-9 496), and renal disease (ICD-9 580).

Third, according to hospital protocol, patients with established cardiovascular disease, or at increased risk of coronary disease based on their age and clinical characteristics, had a pre-operative resting 12-lead electrocardiogram (ECG) recorded at an outpatient cardiology clinic. Before October 1, 1994, Hewlett-Packard electrocardiographs were used and the ECG's were computer-interpreted using an automated version of the Pipberger algorithm.[14] From October 1, 1994 onwards, the Portrait Electrocardiograph (Mortara Instrument, Inc.) with integrated interpretation software was used.[15] Because ECG-interpretation software generally has high diagnostic sensitivity but low specificity, the automated interpretation was subsequently evaluated, and if necessary changed, by an experienced cardiology resident. The corrected ECG interpretation was recorded in the hospital information system. An electrocardiographic evaluation within 90 days prior to surgery was available for 28,457 cases (26.2 %).

Endpoint definition

The hospital information system also contains data regarding each patient's perioperative course. The vital status at hospital discharge was verified and documented for each patient. The occurrence of perioperative myocardial infarction was also reported, but the protocol did not mandate serial postoperative electrocardiograms, or blood sampling for determination of cardiac enzymes. Consequently, silent ischemic episodes and indistinct events might have been missed. A similar situation occurred with regard to stroke: Clinically apparent strokes were reported, but systematic neurological evaluation and CT-scanning was not performed. In view of these limitations, we chose cardiovascular death as the primary

endpoint of our analyses. Events were counted until hospital discharge or 30 days after surgery, whichever day came first.

To obtain the cause of death, two investigators (MDK, DP) reviewed all available medical records, surgical reports, laboratory values, ECGs and autopsy reports, and aimed to reach consensus. If consensus could not be reached, the opinion of a third, independent investigator (PN) was final. Cardiovascular death was defined as any death with a cardiovascular complication as the principal or secondary cause, and included deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Non-cardiovascular death was defined as any death with a principal non-cardiovascular cause, including surgery-related bleeding complications, cancer, trauma and infection. Sudden death in a previously stable patient was considered as cardiovascular.

Statistical analysis

Univariable and multivariable logistic regression analyses were applied to calculate crude and adjusted odds ratios (and 95 % confidence intervals) for the relationship between the selected clinical and electrocardiographic cardiovascular risk determinants, and the primary endpoint. We observed important differences in the incidence of the primary endpoint in relation to age, gender and type of surgery. Furthermore, during the 10-year study period, differences were observed in the annual volumes of several surgical procedures. Therefore, with regard to the results of univariable analysis, we decided to report odds ratios that are adjusted for age, gender, type of surgery and calendar year. All variables entered the multivariable stage irrespective the results of univariable analyses. The final multivariable model was then constructed by backward deletion of the least significant characteristics, while applying the Akaike information criterion (i.e. the applied threshold of significance depended on the degrees of freedom associated with the variable at hand; in case of one degree of freedom, then $P \approx 0.157$).[16]

In 1986 Liang and Zeger developed the method of generalized estimation equations (GEE) to determine regression model parameters - and corresponding standard errors - in datasets with correlated data when the outcome measure of interest is discrete (e.g. binary or count data).[17] Since our dataset involves patients with multiple operations, independence of observations could not be excluded beforehand. Therefore, to examine this phenomenon, all regression analyses were

first performed using conventional techniques, and then repeated using GEE, with 'patient' as classification factor. No relevant differences were observed between the parameter estimates as determined according to both methodologies. Hence, we concluded that inter-observation correlation did not play a major role, if any, in our dataset. Still, we decided to present the results that are based on the GEE method.

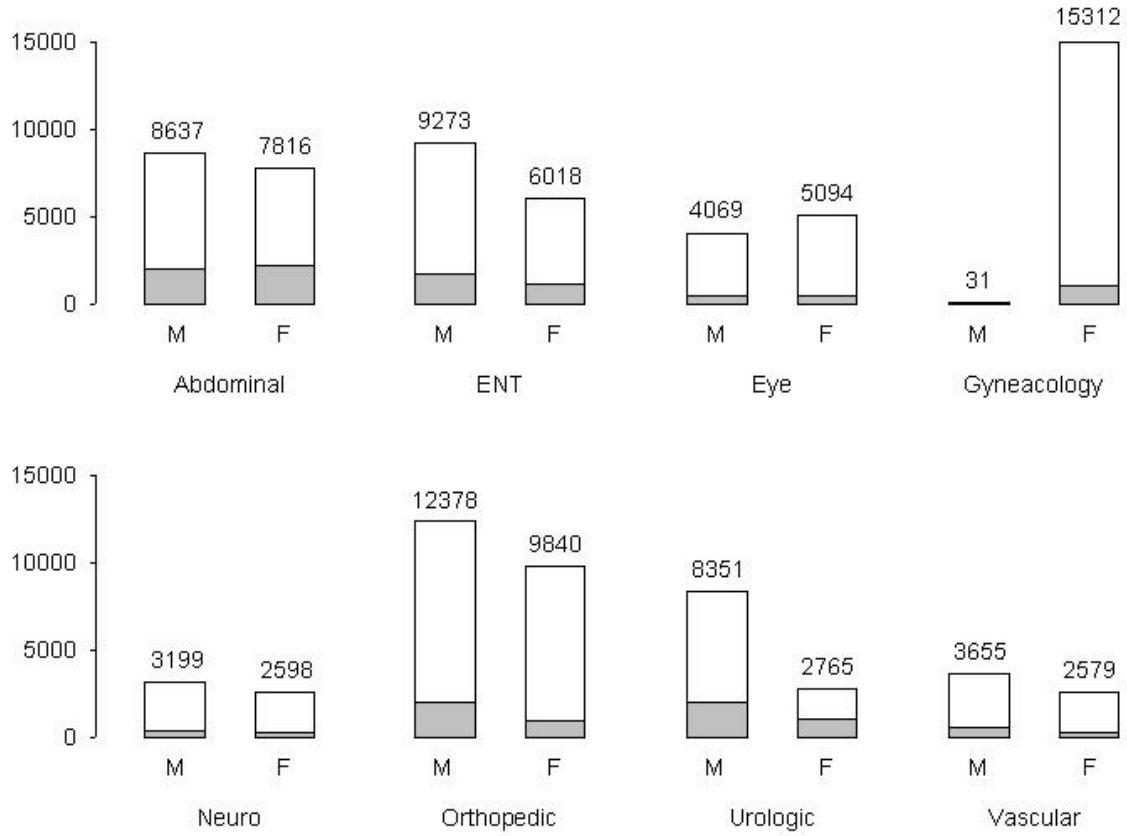
The performance of the risk models was determined by the C-index, which indicates how well a model rank-orders patients with respect to their outcomes. The C-index ranges from 0.5 (no predictive value) to 1.0 (optimal performance).[18] In addition, the Hosmer-Lemeshow statistic for goodness of fit is presented. The predictive accuracy of the models was further evaluated by bootstrapping techniques.[19] One hundred bootstrap samples were drawn from the original dataset (with replacement) and the full modeling process, including the stepwise selection, was redone in every bootstrap sample. The models developed in the bootstrap samples were subsequently tested in the original dataset. This process provides a factor to correct for a possible overestimation ('overoptimism') of the predictive value by the c-index.

Based on the results obtained by these modeling strategies, a score was developed to estimate an individual patient's risk of perioperative cardiovascular death.

Results

52,387 surgical procedures were performed in male patients. Orthopedic surgery (24 %), ENT-surgery (18 %), and abdominal surgery (16 %) were the most frequent (figure 1). Among the 56,206 procedures in women, gynecological surgery was most common (27 %), followed by orthopedic (18 %) and abdominal surgery (14 %). As a result of a reallocation of patients between hospitals in our region, there were significant changes in the annual volumes of ophthalmic and gynecological procedures in the early 1990s (figure 2). Throughout the study period, the number of men and women undergoing orthopedic surgery gradually increased. The number of patients undergoing abdominal surgery decreased slightly over time.

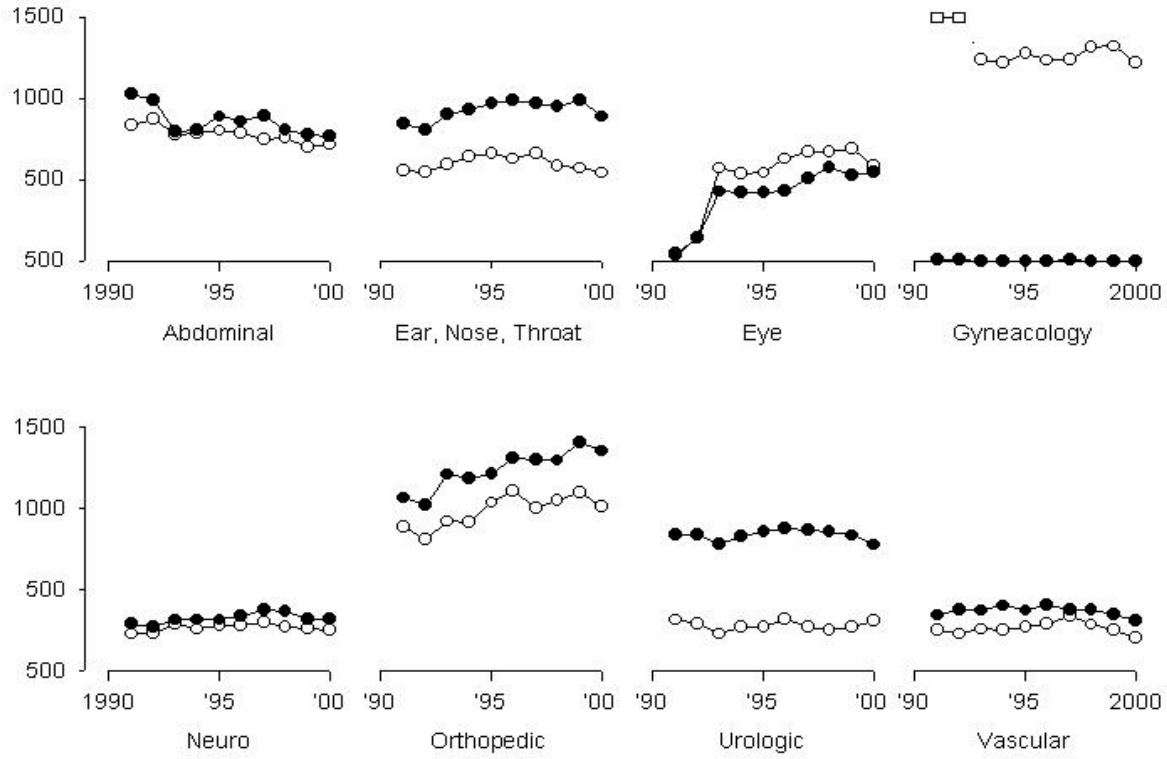
Figure 1. Total number of surgical procedures in men (M) and women (F) that were performed at the Erasmus MC during 1991-2000



The gray proportion of the bars indicate procedures that were classified into multiple categories

A total of 1,877 patients (1.7%) had perioperative death. A cardiovascular complication was the principal cause of death in 405 patients, and the secondary cause in another 138. Thus, 543 patients (0.5% of the population; 29% of deaths) had cardiovascular death. Patients in whom an autopsy report was available (326 patients; 17% of deaths) were more often labeled as having cardiovascular death than patients in whom no such report was available (37 versus 27%; P-value <0.001). Infection was the most common non-cardiovascular cause of death (primary and secondary cause in 231 and 308 patients, respectively; 539 patients in all; 29% of deaths).

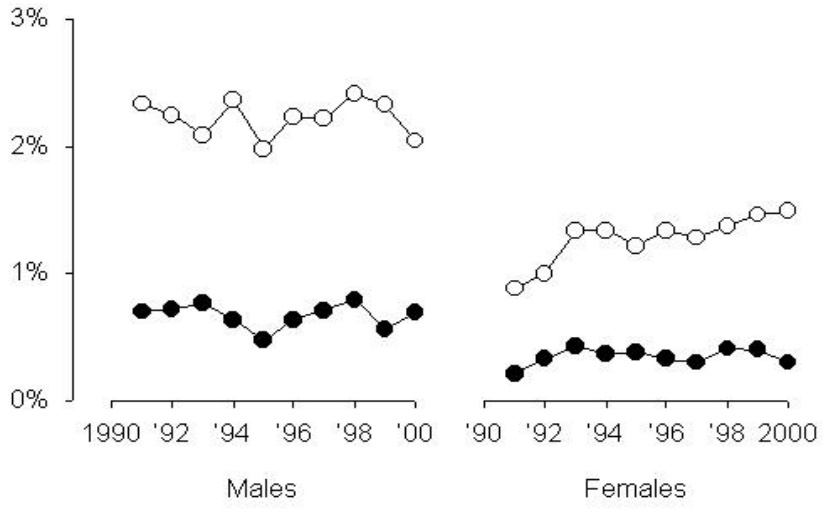
Figure 2. Time trends in the number of surgical procedures in men (closed circles) and women (open circles)



In 1991 and 1992 over 2,500 gynecological procedures were performed, these data are represented by a square

Men were typically 7 years older than women (median age 51 years, interquartile range 34 to 65, and median age 44, interquartile range 32 to 62, respectively). The incidence of all-cause mortality, as well as cardiovascular mortality was higher in men than in women: 2.2 versus 1.3% (P-value <0.001), and 0.7 versus 0.3% (P-value <0.001), respectively. As figure 3 demonstrates, during the study period, no systematic change in all-cause mortality was observed in men. In contrast, all-cause mortality in women increased significantly from 0.9% in 1991 to 1.5% in 2000 (71% increase; P-value <0.001). There were no significant changes in cardiovascular mortality over time in either men or in women. After adjustment for age, calendar year and type of surgery, male gender was associated with a 31% increased risk in perioperative cardiovascular death (odds ratio 1.31, 95% CI 1.1 to 1.6; P-value <0.001).

Figure 3. Time trends in the incidence of perioperative all-cause mortality (open circles) and cardiovascular mortality (closed circles)



Important differences in the incidence of perioperative cardiovascular death were observed in relation to type of surgery (table 1). Patients undergoing vascular surgery, especially those undergoing aortic surgery, had the highest cardiovascular mortality (1.8%), followed by patients undergoing neurosurgery (1.7%), renal transplant (1.1%) and pulmonary surgery (1.1%). Breast, dental, eye and gynecology surgery were associated with cardiovascular mortality rates below 0.1%. A scopic technique was applied in 15,318 patients (14%), who had a lower incidence of cardiovascular death than those undergoing open surgery (0.2 versus 0.6%; crude odds ratio 0.26 and 95% CI 0.2 to 0.4; P-value <0.001). The 774 patients (0.7%) who underwent emergency surgery had a higher incidence of cardiovascular death than patients undergoing non-emergency surgery (6.1 versus 0.5%; crude odds ratio 5.1 and 95% CI 3.7 to 7.1; P-value <0.001).

Table 1. Perioperative vascular and all-cause death in patients undergoing noncardiac surgery for various indications

Type of surgery	Number of procedures	Cardiovascular death			All-cause death
		Primary cause	Secondary cause	Total	N (%)
		N (%)	N (%)	N (%)	
Abdominal	16 453	63 (0.4)	50 (0.3)	113 (0.7)	606 (3.7)
Hepatico, Pancreatico, Billiary	2 752	10 (0.4)	4 (0.1)	14 (0.5)	129 (4.7)
Oesophago-Gastric	11 982	53 (0.4)	44 (0.4)	97 (0.8)	488 (4.1)
Other abdominal	3 714	12 (0.3)	7 (0.2)	19 (0.5)	122 (3.3)
Breast	2 411	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dental	1 225	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.2)
ENT	15 291	114 (0.7)	22 (0.1)	136 (0.9)	411 (2.7)
Endocrine	1 029	1 (0.1)	2 (0.2)	3 (0.3)	6 (0.6)
Eye	9 163	1 (0.0)	0 (0.0)	1 (0.0)	11 (0.1)
Gyneacology	15 343	2 (0.0)	1 (0.0)	3 (0.0)	20 (0.1)
Neuro	5 797	87 (1.5)	14 (0.2)	101 (1.7)	381 (6.6)
Orthopedic	22 218	34 (0.2)	9 (0.0)	43 (0.2)	116 (0.5)
Plastic / Reconstructive	4 157	5 (0.1)	2 (0.0)	7 (0.2)	12 (0.3)
Pulmonary	1 965	14 (0.7)	7 (0.4)	21 (1.1)	86 (4.4)
Renal transplant	711	8 (1.1)	0 (0.0)	8 (1.1)	14 (2.0)
Urologic	11 116	28 (0.3)	10 (0.1)	38 (0.3)	159 (1.4)
Vascular	6 234	90 (1.4)	25 (0.4)	115 (1.8)	277 (4.4)
Aortic - acute	196	21 (10.7)	7 (3.6)	28 (14.3)	57 (29.1)
Aortic - elective	890	29 (3.3)	7 (0.8)	36 (4.0)	72 (8.1)
Carotid endarterectomy	891	4 (0.4)	2 (0.2)	6 (0.7)	18 (2.0)
Peripheral bypass	927	14 (1.5)	2 (0.2)	16 (1.7)	28 (3.0)
Other vascular	3 854	36 (0.9)	13 (0.3)	49 (1.3)	142 (3.7)
Other	9 423	18 (0.2)	13 (0.1)	31 (0.3)	92 (1.0)
Any type	108 593	405 (0.4)	138 (0.1)	543 (0.5)	1 877 (1.7)

In univariable analyses, diabetes mellitus, hypercholesterolemia, hypertension, ischemic heart disease (CAD, i.e. myocardial infarction or angina pectoris), heart failure, stroke, and renal failure were associated with an increased risk of cardiovascular death (table 2). Diabetes, hypertension, established CAD, and heart failure remained significantly associated with adverse outcome after adjustment for multiple risk factors. Renal insufficiency was a strong outcome determinant in univariable analysis, but was not part of the multivariable regression model. It is noteworthy in this respect, that renal insufficiency was significantly correlated with hypertension and heart failure (Pearson correlation coefficient 0.36 and 0.23, respectively). Fifty-one percent of patients with renal failure had hypertension and 21% had heart failure. In contrast, only 3% of patients without renal failure had hypertension, and only 1 % had heart failure. In combination with the mentioned clinical characteristics, age, gender, and type of surgery remained strong determinants of adverse perioperative cardiovascular outcome. Patients between 40 and 50 years of age had a 2.3 times higher risk of cardiovascular death than those below 40, and the risk in octogenarians was over 20 times higher. The C-index for the cardiovascular mortality model based on age, gender, type of surgery, and clinical characteristics (as presented in table 2) was 0.870, reflecting good ability to discriminate between patients who did and did not have a fatal cardiovascular complication. The associated goodness of fit P-value was 0.54, indicating that the model adequately fitted with the data. After correction for overoptimism the C-index was 0.842, still reflecting good performance.

Table 2. Relation between demographic and clinical characteristics, and perioperative death

Characteristic		Number of procedures	Cardiovascular death	Odds ratio (95 percent CI)	
			N (%)	Crude	Multivariably adjusted
Age, years	≥80	5 314	77 (1.5)	24.2 (15.6 - 37.6)	20.9 (13.4 - 32.6)
	70-80	12 619	165 (1.3)	14.2 (9.4 - 21.3)	12.6 (8.4 - 19.1)
	60-70	15 742	146 (0.9)	8.8 (5.8 - 13.3)	8.2 (5.4 - 12.4)
	50-60	15 675	91 (0.6)	5.6 (3.6 - 8.6)	5.3 (3.4 - 8.2)
	40-50	16 987	37 (0.2)	2.4 (1.5 - 4.0)	2.4 (1.4 - 3.9)
	<40	42 256	27 (0.1)	1	1
Gender	Male	52 387	350 (0.7)	1.31 (1.1 - 1.6)	1.22 (1.0 - 1.5)
	Female	56 206	193 (0.3)	1	1
Diabetes mellitus	Yes	2 001	36 (1.8)	2.6 (1.8 - 3.6)	1.71 (1.2 - 2.5)
	No	106 592	507 (0.5)	1	1
Hypercholesterolemia	Yes	472	10 (2.1)	2.1 (1.1 - 4.1)	did not remain in multivariable model
	No	108 121	533 (0.5)	1	
Hypertension	Yes	3 943	75 (1.9)	2.4 (1.8 - 3.0)	1.59 (1.2 - 2.1)
	No	104 650	468 (0.4)	1	1
CAD	Yes	3 588	77 (2.1)	2.0 (1.6 - 2.6)	1.32 (1.0 - 1.7)
	No	105 005	466 (0.4)	1	1
Heart failure	Yes	1 377	50 (3.6)	4.5 (3.3 - 6.0)	3.0 (2.2 - 4.3)
	No	107 216	493 (0.5)	1	1
CVA	Yes	500	11 (2.2)	1.92 (1.0 - 3.5)	did not remain in multivariable model
	No	108 093	532 (0.5)	1	
COPD	Yes	1 125	14 (1.2)	1.28 (0.7 - 2.2)	did not remain in multivariable model
	No	107 468	529 (0.5)	1	
Renal insufficiency	Yes	1 894	31 (1.6)	2.3 (1.6 - 3.3)	did not remain in multivariable model
	No	106 699	512 (0.5)	1	
Type of surgery†	Class IV	12 721	224 (1.8)	6.7 (5.2 - 8.7)	5.5 (4.3 - 7.1)
	Class III	32 102	231 (0.7)	3.3 (2.5 - 4.3)	3.6 (2.8 - 4.7)
	Class II	38 178	84 (0.2)	1	1
	Class I	25 592	4 (0.0)	0.07 (0.0 - 0.2)	0.08 (0.0 - 0.2)
Type of procedure	Scopic	15 318	24 (0.2)	0.26 (0.2 - 0.4)	0.29 (0.2 - 0.4)
	Open	93 275	519 (0.6)	1	1
Emergency surgery	Yes	774	47 (6.1)	5.1 (3.7 - 7.1)	5.4 (3.9 - 7.5)
	No	107 819	496 (0.5)	1	1

Crude odds ratios are adjusted for age, gender, type of surgery (when appropriate) and calendar year only.
Multivariably adjusted odds ratios are only presented for the variables that remained in the multivariable model (see method section for the modeling strategy), and were adjusted for all the components of the multivariable model, and calendar year.
Point estimates of odds ratios below 2.0 are presented with two decimals.
† Class I include breast, dental, eye, gynecology, and urologic surgery; Class II include endocrine, orthopedic, and plastic/reconstructive surgery; Class III include abdominal, ENT, and pulmonary surgery; Class IV include neuro surgery, renal transplant, and vascular surgery

The 28,457 patients who underwent electrocardiographic evaluation within 90 days prior to surgery had higher cardiovascular mortality than those who did not undergo such evaluation (0.7 versus 0.4%; P-value <0.001). This is a reflection of the applied hospital protocol that calls for a resting ECG in patients at suspected increased cardiovascular risk. Several electrocardiographic markers were independently associated with increased cardiovascular mortality, including atrial fibrillation, right bundle branch block (P-value 0.09), left ventricular hypertrophy, premature ventricular complexes, abnormal Q-waves, and ST-segment depression (table 3). Patients with a pacemaker were also at increased risk. The multivariable model that combined clinical data with ECG results had a better discriminating power than the clinical-data-only model (C-indices based on the 28,457 patients with complete ECG data 0.840 versus 0.812; P-value <0.001). The associated goodness of fit P-value was 0.55, and the overoptimism-corrected C-index was 0.809.

Table 3. Relation between electrocardiographic characteristics and perioperative cardiovascular death

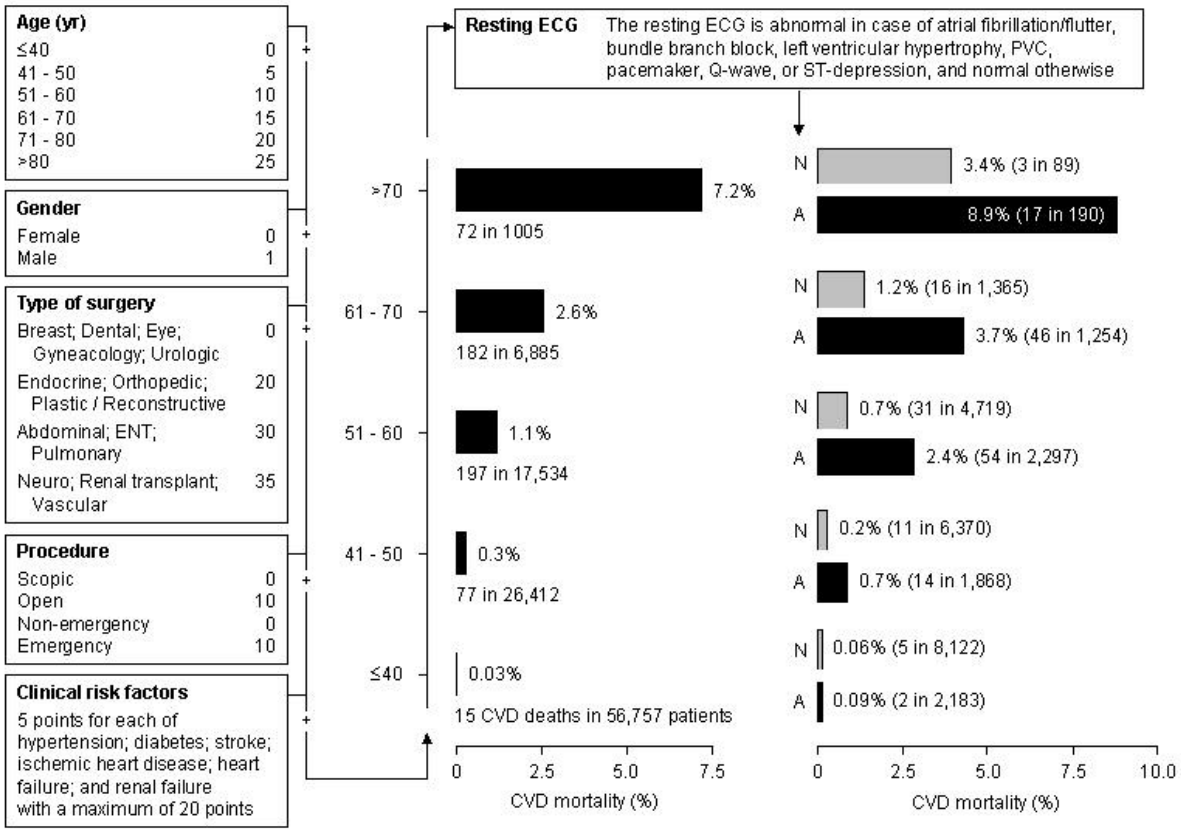
Characteristic		Number of procedures	Cardiovascular death	Odds ratio (95 percent CI)	
			N (%)	Crude	Multivariably adjusted
Atrial fibrillation or flutter	Yes	748	28 (3.7)	3.7 (2.4 - 5.6)	3.1 (2.0 - 4.8)
	No	27 709	171 (0.6)	1	
Left bundle branch block	Yes	301	4 (1.3)	1.09 (0.4 - 3.0)	did not remain in multivariable model
	No	28 156	195 (0.7)	1	
Right bundle branch block	Yes	808	13 (1.6)	1.55 (0.9 - 2.8)	1.66 (0.9 - 3.0)
	No	27 649	186 (0.7)	1	
Left ventricular hypertrophy	Yes	2 836	38 (1.3)	1.58 (1.1 - 2.3)	1.54 (1.1 - 2.2)
	No	25 621	161 (0.6)	1	1
Premature ventricular complexes	Yes	980	19 (1.9)	1.91 (1.2 - 3.1)	1.74 (1.1 - 2.9)
	No	27 477	180 (0.7)	1	
Pacemaker	Yes	151	4 (2.6)	2.5 (0.9 - 7.0)	3.5 (1.2 - 9.9)
	No	28 306	195 (0.7)	1	1
Q-wave	Yes	2 772	56 (2.0)	2.4 (1.8 - 3.3)	2.1 (1.5 - 2.9)
	No	25 685	143 (0.6)	1	1
ST-depression	Yes	884	19 (2.1)	2.4 (1.5 - 3.9)	1.80 (1.1 - 3.0)
	No	27 573	180 (0.7)	1	1
Any of the above	Yes	7 792	133 (1.7)	3.7 (2.7 - 5.0)	
	No	20 665	66 (0.3)	1	

Crude odds ratios are adjusted for age, gender, type of surgery and calendar year only.

Multivariably adjusted odds ratios are only presented for the variables that remained in the multivariable model (see method section for the modelling strategy), and were adjusted for all the components of the multivariable model (which included clinical characteristics, see table 2), and calendar year.
Point estimates of odds ratios below 2.0 are presented with two decimals.

Figure 4 presents a simple risk score for perioperative cardiovascular mortality based on age, gender, type of surgery and clinical characteristics. The 56,757 patients (52% of the population) with a score ≤40 points had a very low cardiovascular death rate (0.03%). In contrast, the 1,005 patients (1 % of the population) with a score >70 points had a very high cardiovascular death rate (7.2%). In the remaining 50,831 patients (47% of the population) with moderate to high cardiovascular mortality rates, the resting ECG (classified as normal versus abnormal) further discriminated between those at higher and lower risk. Still, patients in the highest risk categories with a normal resting ECG had cardiovascular mortality rates that were as high as 1.2 to 3.4%.

Figure 4: A simple scheme to evaluate the risk of perioperative cardiovascular death in noncardiac surgery



Discussion

In accordance with previous studies, our data showed that cardiovascular mortality is a major burden in patients undergoing non-cardiac surgery.[3-12] On average 7 out of 1,000 procedures in men and 3 out of 1,000 procedures in women had a fatal in-hospital outcome as a result of cardiovascular complications. In contrast, anaesthesia related mortality only occurs in approximately 1 out of 250,000 procedures.[20] Interestingly, patients who underwent post-mortem examination were considerably more often classified as cardiovascular death than patients in whom no such examination was performed. This suggests that the incidence and impact of cardiovascular complications after non-cardiac surgery may be underestimated in clinical practice.

Guidelines of the American Heart Association (AHA) / American College of Cardiology (ACC) indicate advanced age as a minor predictor of cardiovascular risk.[21] In our data, however, perioperative cardiovascular mortality progressively increased with age. In fact, along with type of surgery, age was a much stronger outcome determinant than any other clinical characteristic. This finding may reflect the broad spectrum of surgical procedures that were included in our analysis as compared to other investigations,[3-12] and, along with that, a large diversity of patients with respect to age. Indeed, elderly patients often have (asymptomatic) coronary disease, which places them at an increased risk of perioperative cardiovascular complications.

At the other hand, the modest contribution of clinical characteristics, relative to age and type of surgery, might be the result of under-reporting. Details of the medical history were classified by administrative personnel on the basis of written information provided by health-care professionals. These employees are specifically instructed to avoid inappropriate over-diagnosis. As a result, important medical conditions might have been overlooked, and, consequently, the odds ratios for cardiovascular death related to these factors might have been underestimated. Also, we restricted our analyses to patients who underwent surgery. No information was included from patients who were screened, but did not undergo surgery because the risk was perceived as prohibitive. Obviously, exclusion of patients at risk of adverse cardiovascular outcome might have diluted estimates of relative risk.

Resting 12-lead electrocardiography seemed to be of limited value in the sizeable group of patients (±50 % of the population studied) who are at low risk of perioperative cardiovascular mortality according to clinical characteristics and type of surgery. In contrast, the resting ECG provided useful additional prognostic information in patients with an intermediate risk. The resting ECG also contained prognostic information in high-risk patients, but failed to identify patients at sufficiently low risk to allow for surgery without additional cardiovascular evaluation. It should be noticed in this respect, that perioperative cardiac complications often occur in patients with clinically silent myocardial ischaemia,[22,23] which cannot be revealed by tools that evaluate the resting heart function. Instead, exercise or pharmacological stress testing is warranted.[24] However, perioperative resting ECG recordings are useful for detection of myocardial ischaemia (ST- and T-wave changes) and myocardial infarction (new Q-waves).

The identification of patients at risk of perioperative cardiovascular complications has considerably improved over the recent years. Also, effective risk-reduction strategies have been defined for particular patient categories, such as those undergoing major vascular surgery.[25-27] In general, however, the investigations that successfully aimed at cardiovascular risk identification were not succeeded by investigations that aimed at systematic risk reduction. Hence, effective cardioprotective treatment strategies remain undefined for substantial portions of the non-cardiac surgery population. The development and implementation of such strategies for the entire surgical spectrum remains an important challenge for contemporary medicine. In that regard, it is noteworthy that the incidence of fatal perioperative cardiovascular complications at our centre did not decline during the 10-year study period. Although information on large series of unselected surgical patients in comparable high-volume, tertiary referral centres is lacking, several observations in selected patients indicate that the Erasmus MC data are no exception.[11,28,29]

Of particular interest with regard to the development of risk-reduction strategies is the group of patients with an estimated perioperative cardiovascular mortality rate in the range 0.5 % to 3.0 %, comprising approximately 25 % of the study population. Current evidence suggest a potential role for exercise or pharmacological testing to identify the presence of stress-inducible myocardial

ischaemia.[12,21] According to the AHA / ACC guidelines, patients with inducible ischaemia should then undergo coronary angiography followed by coronary revascularisation.[21] Another option might be to proceed with surgery under effective pharmacological protection without preoperative evaluation of the heart function, since excessive myocardial ischaemia will likely be diagnosed in a minority of patients.[12] Promising results are observed in selected patients with beta-blockers and inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (statins),[25-27] and properly sized randomised clinical trials are warranted to further evaluate the efficacy and safety of these agents.

We acknowledge that this investigation has some limitations because of the retrospective nature of the data. Particularly, the prognostic value of established risk factors that were not classified according to the ICD-9 classification, such as smoking and aortic valve stenosis, and the influence of cardiovascular medication, remained undefined. Furthermore, information on cardiovascular medication and interventions were available in the hospital medical records, but not in a systematic database. Consequently, it's impact on perioperative outcome could not be assessed. Nevertheless, the developed multivariable risk models showed excellent ability to discriminate between patients at low, intermediate and high risk of cardiovascular complications, and can readily be applied in routine perioperative management. These risk prediction models can also be used to identify target populations for the development of risk reduction strategies.

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Chapter 8

Small abdominal aortic aneurysm

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N Eng J Med 2002;347:1112-1113

Correspondence

Small Abdominal Aortic Aneurysms

To the Editor: Two randomized trials reported by Lederle et al.[1] and the United Kingdom Small Aneurysm Trial Participants[2] (May 9 issue) revealed that early surgery in patients with small abdominal aortic aneurysms can only be expected to have a benefit if the risk of surgery is considerably smaller than the risk of spontaneous rupture. Operative mortality rates in these studies ranged from 2.7 to 5.5 percent, and the annual risk of a spontaneous rupture was 0.6 percent in one study and ranged from 1.6 to 3.2 percent in the other.

The decision about whether to perform early surgery or to institute surveillance should be made on an individual basis, after an evaluation of the perioperative risk. In a group of 661 patients (mean age, 67 years; 532 of them men) who underwent elective abdominal aortic surgery in our institution between 1991 and 2000, the perioperative mortality was 9.1 percent (mortality from cardiac causes, 4.1 percent). Patients without chronic pulmonary disease or cardiac risk factors — including angina, myocardial infarction, diabetes mellitus, heart failure, stroke, and renal failure — represent a population at low risk for operative death. Patients with

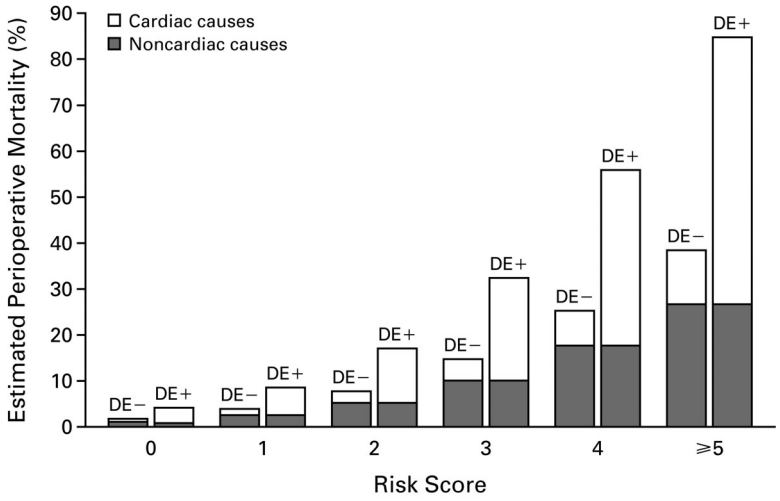

Figure 1. Estimate of the Perioperative Risk of Death from Noncardiac and Cardiac Causes.

The risk score was determined by the number of risk factors present; risk factors included chronic pulmonary disease, angina, myocardial infarction, diabetes mellitus, heart failure, stroke, and renal failure. Patients with a negative result on dobutamine echocardiography (DE−) were considered not to have stress-induced ischemia, and those with a positive result (DE+) were considered to have stress-induced ischemia.

one or more cardiac risk factors were further stratified according to the absence or presence and extent of myocardial ischemia, as determined by dobutamine echocardiography (Fig. 1). Patients without stress-induced ischemia had a low-to-intermediate perioperative risk, despite the presence of clinical risk factors.

In view of these data, we suggest that risk assessment and modification be undertaken for each patient. This process includes the identification of risk factors, an objective evaluation of myocardial ischemia, and the administration of proper perioperative medical therapy (beta-blockers) or coronary revascularization.

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1. Lederle FA, Wilson SE, Johnson GR, et al. Immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med 2002;346:1437-44.
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To the Editor: The articles by Lederle et al. and the United Kingdom Small Aneurysm Trial Participants both suggest that aneurysms can be followed carefully until their diameter reaches 5.5 cm. If perioperative mortality is high, and if patients are more likely to die from other causes than from the aneurysm in the several subsequent years, then the conservative strategy will look even better. The older a patient is, the more likely it is that these two conditions will be met. The mean age in both trials was less than 70 years. Can the authors make any more specific recommendations about how older age should affect the decision to repair electively abdominal aortic aneurysms that are discovered incidentally?

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To the Editor: In their controlled, randomized study, Lederle et al. found that long-term mortality did not differ between the surveillance group and the immediate-surgery group. The authors conclude that these data "support a policy of reserving elective repair for abdominal aortic aneurysms at least 5.5 cm in diameter." Given the fact that an accumulated 70 percent of the surveillance group underwent repair by the end of the study — and more strikingly, that half of this population required surgery by three and a half years — we find this conclusion remarkable.

If the majority of patients will need surgery anyway, why follow them until they do? Why subject patients to the anxiety, expense, and inconvenience of being scanned for a period of years instead of just fixing the problem and being done with it? As long as operative mortality is under 2 percent, surveillance provides no advantage beyond repeated confirmation of the natural history.

Caution must be exercised in applying the results of clinical trials to clinical practice. Women, who are known to have a higher rate of rupture for aneurysms of a given size,[1] made up less than 1 percent of the study population. In cases in which computed tomographic scanning is indicated, the expense of watchful waiting in terms both of dollars and exposure to radiation is high. Mortality among patients who do not comply with surveillance was not studied, and such noncompliance could be disastrous.

This study shows that surveillance is equivalent to immediate surgery with respect to long-term mortality under highly controlled conditions. Whether it is effective clinical practice is another matter entirely.

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1. Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. Ann Surg 1999;230:289-96.

To the Editor: The results of the study by Lederle et al. confirming the conclusions of the United Kingdom Small Aneurysm Trial will undoubtedly have a striking influence on the management of small abdominal aortic aneurysms. However, we wonder about the advisability of generalizing the final recommendation — that small abdominal aortic aneurysms should be observed until they reach at least 5.5 cm in diameter and that repair should be avoided unless they expand rapidly or symptoms develop.

The safety of ultrasonographic surveillance is dependent on meticulous follow-up that is unlikely to be achievable in routine practice outside a controlled trial. It is no surprise that Valentine et al.[1] report, in a program based on watchful waiting involving 101 veterans with small abdominal aortic aneurysms, that 32 percent did not comply with the follow-up, missing at least three consecutive appointments and accounting for a rate of aneurysm rupture of 13 percent in 34 months. The selected patients enrolled in the study by Lederle et al. were not high-risk patients and were therefore presumably most likely to benefit from elective repair. In practice, many good candidates for repair become poor candidates during the period of watchful waiting, as congestive heart failure develops, chronic obstructive pulmonary disease worsens, or other problems occur.[1-3]

Moreover, the fact that 61.6 percent of patients in the surveillance group underwent repair within 4.9 years confirms that the issue of aneurysm repair for such patients with a good life expectancy is a matter of when rather than if. Given the relatively low risk of rupture for small abdominal aortic aneurysms, for early repair to be recommended, the

perioperative outcome has to be outstanding and consistent with the situation reported in the trial.

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The authors reply:

To the Editor: Because more than half of our surveillance group underwent aneurysm repair, Miller et al. and Ballotta and Toniato question our conclusion that elective repair should be reserved for abdominal aortic aneurysms of 5.5 cm or larger. Any operative threshold based on the diameter of the aneurysm (such as 5.5 cm) will eventually be crossed in many patients whose aneurysms are smaller at the outset. Lowering the threshold would result in the same scenario, in which abdominal aortic aneurysms in many patients eventually reach the new threshold; this logic would lead to repeated lowering of the threshold and ultimately to the repair of all abdominal aortic aneurysms. If all small abdominal aortic aneurysms (which are common and have a low risk of rupture) were repaired, the number of operative deaths as a result would probably greatly exceed the number of rupture-related deaths prevented. The 5.5-cm threshold has been shown in two randomized trials to result in a safe reduction of the number of operations performed (by an estimated 20 percent in our study), and we see no advantage to changing it. Surveillance with ultrasonography is adequate and inexpensive and does not require exposure to radiation. The assertion by Ballotta and Toniato that operative mortality will increase when surgery is deferred is not supported by our findings.

The most important consideration in applying our results to clinical practice is that higher operative mortality in other settings or groups of patients may be an indication for raising the threshold for elective repair beyond 5.5 cm, as implied by the letters from Finucane and Kertai et al. Our trial data do not support precise recommendations for patients who differ from the trial patients, although we have reported rupture rates among patients with large abdominal aortic aneurysms and high operative risk elsewhere.[1] Women are not well represented in our study, but there is more evidence for increased operative mortality among women[2-4] than there is for a higher rate of rupture,[5] making it difficult to justify a lower threshold in women.

As noted by Miller et al. and Ballotta and Toniato, compliance with follow-up imaging is extremely important, but the optimal management of aneurysms in noncompliant patients remains unclear. The conclusions of the study by Valentine et al. (cited by Ballotta and Toniato) are based on only three episodes of rupture, and the operative mortality for elective repair in that study was 8 percent — which again makes it difficult to justify a lower threshold for repair. Physicians who wish to individualize patient care should be aware that there is no group of patients for whom elective repair of abdominal aortic aneurysms that are less than 5.5 cm has been shown to be beneficial.

Recently obtained medical records have allowed our outcomes committee to reclassify one death of a patient in the surveillance group in our study as a rupture-related death (so that the risk of such death is now 0.7 percent per year), and five deaths (two in the immediate-repair group and three in the surveillance group) have been classified as indirectly due to aneurysm repair (including the one following the repair of a ventral hernia that was mentioned in the article). There have thus been 19 deaths related to abdominal aortic aneurysm in each group (relative risk in the surveillance group, 1.03; 95 percent confidence interval, 0.54 to 1.94).

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To the Editor: The increasing importance of patients' involvement in decision making makes high-quality evidence and honesty essential. First, as Kertai and colleagues note, in the "real world," operative mortality rates for elective aneurysm repair are likely to be as high as 8 to 9 percent — 1 in 12 patients will die as the result of prophylactic elective surgery.[1] Second, the safety of surveillance for small aneurysms has been demonstrated in the two trials recently reported in the *Journal* and in the care of patients with aneurysms detected through screening studies.[2] The study mentioned by Ballotta and Toniato was very small. Third, there is currently no prospectively validated method of risk assessment for patients undergoing open aneurysm repair, although the revised Goldman Cardiac Risk Index holds promise.[3] In the United Kingdom Small Aneurysm Trial, with its pragmatic approach to preoperative assessment, physiological age appeared to be more important than chronologic age: poor renal and lung function were the most important predictors of postoperative mortality.[4] Fourth, neither the study by Lederle et al. nor ours identified a subgroup of patients, defined according to age or aneurysm diameter, who benefited from early surgery.

Given the rapid advances in endovascular repair and pharmacology, why not wait safely, with the potential for a less

invasive method of management later, rather than take a 1-in-12 chance of death now? Cost-conscious health economies are also likely to support this approach.[5] The focus should now be on advancing endovascular technology, so that a higher proportion of patients with aneurysms of 5.5 cm or more in diameter can undergo endovascular correction with low operative mortality and assured durability.

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Therapy to Prevent Type 1 Diabetes Mellitus

To the Editor: The results of the Diabetes Prevention Trial–Type 1 Diabetes Study (DPT-1) (May 30 issue)[1] show that parenteral insulin therapy does not prevent type 1 diabetes in the relatives of patients with the disease. We made a similar observation in a smaller population of young, nondiabetic first-degree relatives of patients with diabetes. A total of 29 children and adolescents (median age, 10.3 years; interquartile range, 7.5 to 13.8; range, 3.4 to 18.0) were identified through screening of a population of 4000 relatives of patients with type 1 diabetes for diabetes-related autoantibodies. These children and adolescents participated in a double-blind trial (the European Prediabetes Prevention–Subcutaneous Insulin Trial), in which they received either an injectable placebo preparation[2] or ultralente insulin (0.2 U per kilogram of body weight before breakfast [Ultratard, Novo Nordisk]). Subjects were followed for a median of 3.3 years (interquartile range, 1.6 to 4.5). Diabetes developed in 6 of the 14 subjects in the insulin group and 8 of the 15 subjects in the placebo group. The cumulative incidence of diabetes was similar in the two groups and similar to that observed in the DPT-1 (Fig. 1). These results strengthen the conclusions of the DPT-1, because our trial was double-blind and placebo-controlled and used a different insulin regimen. The use of parenteral insulin to prevent type 1 diabetes through the modulation of the anti-islet immune response ("beta-cell rest") did not prove efficacious in two independent controlled trials. Moreover, the concept of beta-cell rest appears to have little basis

Chapter 9

Which test is superior for perioperative cardiac risk stratification in patients undergoing major vascular surgery?

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Which Stress Test is Superior for Perioperative Cardiac Risk Stratification in Patients Undergoing Major Vascular Surgery?

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Objective: *to compare the additional prognostic value of Dobutamine Stress Echocardiography (DSE), Dipyridamole Stress Echocardiography (DiSE) and Perfusion Scintigraphy (DTS) on clinical risk factors in patients undergoing major vascular surgery.*
Design: *retrospective analysis.*
Materials: *2204 consecutive patients who underwent DSE (n = 1093), DiSE (n = 394), or DTS (n = 717) testing before major vascular surgery were studied.*
Methods: *primary endpoint was a composite of cardiac death and non-fatal myocardial infarction (MI). Logistic regression analysis was performed to evaluate the relation between cardiac risk factors, stress test results and the incidence of the composite endpoint.*
Results: *there were 138 patients (6.3%) with cardiac death or MI. Patients with 0, 1–2, and 3 or more risk factors experienced respectively 3.0, 5.7 and 17.4% cardiac events. We found no statistically significant difference in the predictive value of a positive test result for DiSE and DSE (Odds ratio (OR) of 37.1 [95% CI, 8.1–170.1] vs 9.6 [95% CI, 4.9–18.4]; p = 0.12), whereas a positive test result for DTS had significantly lower prognostic value (OR = 1.95 [95% CI, 1.2–3.2]).*
Conclusion: *a result of stress echocardiography effectively stratified patients into low- and high-risk groups for cardiac complications, irrespective of clinical risk profile. In contrast, the prognostic value of DTS results was more likely to be dependent on patients' clinical risk profile.*

Key Words: Prognosis; Major vascular surgery; Risk assessment; Dobutamine stress echocardiography; Dipyridamole stress echocardiography; Dipyridamole perfusion scintigraphy.

Introduction

Patients undergoing major vascular surgery are at increased risk of cardiovascular complications, such as cardiac death and nonfatal myocardial infarction (MI), due to underlying coronary artery disease (CAD).[1] These complications may occur during or directly after surgery. Evaluation of CAD is often difficult since patients have limited exercise capacity. Therefore, multiple non-exercise dependent stress tests have been developed. It has been suggested that the most accurate information on the individual patient's risk can be obtained by a combination of clinical characteristics and results of dipyridamole perfusion scintigraphy (DTS).[2] Recently, the use of pharmacological stress echocardiography either with dipyridamole (DiSE)[3–6] or dobutamine (DSE)[7–13] has been proposed for risk stratification.

Pharmacological stress echocardiography has proved to be a safe and sensitive technique for predicting perioperative cardiac events, with an excellent negative predictive power.[6,9] However, it has not been well established, which of the available tests is best for predicting perioperative cardiac complications. The purpose of this investigation was to compare the ability of dipyridamole and dobutamine stress echocardiography, and dipyridamole stress perfusion scintigraphy to predict perioperative cardiac events in large cohorts of patients undergoing major vascular surgery.

Materials and Methods

Description of the study population

The study population consisted of 2204 consecutive patients undergoing preoperative screening with one

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of the noninvasive tests before their scheduled abdominal aortic surgery or infrainguinal procedure.

Dobutamine stress echocardiography

Dobutamine stress echocardiography was performed according to study protocol in 1093 consecutive patients who participated in the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography study (DECREASE) between 1996 and 1999.[9,14] Two investigators who were aware of the doses of dobutamine and atropine used during tests were blinded to clinical information and performed off-line assessment of echocardiographic images. The left ventricle was divided into 16 segments and wall motion was scored on a 5-point ordinal scale; (1) normal wall motion; (2) mild hypokinesis; (3) severe hypokinesis; (4) akinesis and (5) dyskinesis. For each patient, a wall motion score index was calculated at rest and during peak stress. The results of DSE were considered positive if new wall-motion abnormalities (NWMAs) occurred.

Dipyridamole stress testing

Dipyridamole stress echocardiography
Dipyridamole stress echocardiography was performed according to study protocol in 394 prospectively enrolled patients who participated in the Echo Persantin International Cooperative study (EPIC) between 1994–1998.[6] Patients were screened with DiSE prior to their scheduled vascular surgery.[15] During the procedure, 2-dimensional echocardiographic, 12-lead ECG, and blood pressure monitoring were continuously performed. Regional wall motion and test positivity was assessed for DiSE testing. Aminophylline was given at the end of the test. Assessment of stress echocardiography performance was performed using predefined criteria for stress echocardiography reading.[16]

Dipyridamole thallium perfusion scintigraphy
Dipyridamole thallium-201 scintigraphy was performed in 717 consecutive patients between 1984 and 1991, who were referred to DTS testing before major elective vascular surgery at the following institutes: University of Massachusetts Medical Center ($n = 360$),[17] Massachusetts General Hospital ($n = 246$),[2] Medical Center Hospital of Vermont ($n = 111$).[18] Baseline clinical and test characteristics were prospectively collected for all but one study.[2] The DTS test was performed according to a previously described standardised protocol.[19,20] The test was administered and interpreted by experienced nuclear cardiologists who were blinded to the patients' clinical course. Planar thallium imaging was used at all centres. Initial images were obtained in three standard views (anterior, left anterior oblique, and lateral) immediately after the administration of dipyridamole and thallium, and delayed images were obtained on average 3 h later. A positive test result for DTS was defined as planar myocardial scintigraphic images, revealing images exhibiting defects, which were partially or completely redistributed on delayed (> 3 h) images.

Definition of cardiac endpoint

For the present study, a composite of cardiac death and nonfatal myocardial infarction (MI) occurring within 30 days after surgery was chosen. Cardiac death was defined as death directly attributable to myocardial infarction, congestive heart failure, or ventricular arrhythmia in the absence of any other precipitating factor. Myocardial infarction was diagnosed by either serum creatinine-kinase level of more than 110 U/L with a myoglobin isoenzyme fraction of more than 10%, or by new electrocardiographic Q waves ≥ 1 mm, or faster than 30 ms in duration.

Clinical risk factors

Potential clinical determinants of perioperative cardiac events were selected by review of the current published literature, and included: advanced age (> 70 years), a current or stable angina pectoris (AP), a history of MI, a history of heart failure, and a history of diabetes mellitus (DM). Current stable angina pectoris was characterised according to the Canadian Cardiovascular Society Angina Classification.[21] History of MI was defined as a documented history of a MI or a finding of pathologic Q waves on electrocardiography. Congestive heart failure was defined according to the presence of a history of symptoms or signs of pulmonary congestion, signs of left or right ventricular failure and chest radiographic findings suggestive of heart failure. Diabetes mellitus was defined by a predefined criterion used in each study.

Statistical analysis

Differences in baseline clinical characteristics between the study populations were evaluated by

Kruskal–Wallis tests or Chi-square tests as appropriate. Despite the observed differences, we considered the patients in the separate datasets to be representative of all patients undergoing elective vascular surgery. Thus, the individual datasets were combined. Univariate and multivariate logistic regression analyses were performed to study the prognostic value of the selected clinical characteristics with respect to composite endpoint. Information on heart failure was missing in 35% of patients. In order to include heart failure in the regression analysis missing values were imputed based on the mean value (0.072) of patients either with (value 1) or without (value 0) a history of heart failure. All clinical variables entered the multivariate model irrespective of the results of the univariate analyses. Based on the results of the multivariate analysis a simple clinical risk score was composed. Subsequently, logistic regression analyses were applied to predict the prognostic value of a positive test result. Differences in prognostic value between the tests (DSE, DiSE, DTS) were evaluated by comparing the regression coefficients associated with the test result using the *t*-test. Finally, the additional prognostic value of a positive test result upon the clinical risk score was studied by additional logistic regression analyses. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) are reported. The predictive power of regression models was quantified by the c-index, which is identical to the area under the receiver operating characteristic curve; the c-index ranges from 0.5 (not predictive at all) to 1.0 (optimal performance).

Results

There were important differences in clinical baseline characteristics and test results between the populations (Table 1). Patients in the DSE group were older, and more often had a history of MI than patients undergoing either DiSE or DTS. The majority of patients in the DiSE populations were males, and the prevalence of risk factors was somewhat lower than in the other two populations. Patients undergoing DTS more often had current stable angina pectoris, history of heart failure, diabetes, and a positive test result than patients undergoing DSE or DiSE testing (Table 1). There were also differences in the incidence of adverse cardiac outcome: 43 patients had events (3.9%) among 1093 patients undergoing DSE, 14 (3.6%) in 394 patients with DiSE and 81 (11.5%) in 717 patients undergoing DTS.

Predictive value of clinical risk factors

The relation between clinical variables and the incidence of the composite endpoint is shown in Table 2. Patients with current stable angina, a history of MI or diabetes had more than a 2-fold increased risk of perioperative cardiac events than those without such a history. A history of heart failure was another important clinical determinant of perioperative cardiac complications associated with a 4-fold increased risk in patients with such a history compared to those without. Surprisingly, advanced age was not

Table 1. Clinical characteristics of the patient populations.

Clinical characteristics*	DSE	DiSE	DTS	*p* value
Patients' no.	1093	394	717	
Demographics				
Age ≥ 70 years	557 (51%)	159 (40%)	301 (42%)	<0.001
Men	851 (78%)	356 (90%)	347 (48%)	<0.001
History §				
Current or stable angina pectoris	222 (20%)	51 (13%)	185 (26%)	<0.001
History of myocardial infarction	473 (43%)	86 (22%)	215 (30%)	<0.001
History of congestive heart failure	70 (6%)	–	34 (4.7%)	0.120
History of diabetes mellitus	168 (15%)	37 (9%)	149 (21%)	<0.001
Test result †				
Test positivity	216 (20%)	65 (17%)	198 (28%)	<0.001
Outcome				
Cardiac death or myocardial infarction	43 (3.9%)	14 (3.6%)	81 (11.5%)	0.001

* DSE, dobutamine stress echocardiography; DiSE, dipyridamole stress echocardiography; DTS, dipyridamole thallium perfusion scintigraphy; Ellipse indicates that data is not available.
† Test positivity of DSE and DiSE were considered positive if new wall-motion abnormalities occurred; and for DTS if images exhibiting defects, which partially or completely redistributed on delayed (>3 h) images.
§ For definition of clinical risk factors see "Methods" section.

Table 2. Univariable and multivariable relation between clinical baseline characteristics and perioperative cardiac death and myocardial infarction.

Clinical variables*	Event ($n = 138$) § (%)	No event ($n = 2053$) (%)	Univariable odds ratio (95% CI)	Multivariable odds ratio (95% CI)
Age ≥ 70 years	71 (51)	939 (46)	1.3 (0.9–1.8) †	1.3 (0.9–1.9) †
Current or stable angina pectoris	51 (37)	403 (20)	2.4 (1.7–3.4) ‖	2.0 (1.3–2.9) ‖
History of myocardial infarction	72 (52)	699 (34)	2.1 (1.5–3.0) ‖	1.6 (1.1–2.4) ‡
History of heart failure	17 (12)	87 (4)	4.5 (2.5–8.2) ‖	2.4 (1.4–4.3) ‡
History of diabetes mellitus	40 (29)	310 (15)	2.3 (1.6–3.4) ‖	2.1 (1.4–3.1) ‖

*Numbers may not add to 2204 due to missing data; For definitions of the clinical variables see "Methods" section; CI, confidence interval.
§Event is specified as a composite of cardiac death and nonfatal myocardial infarction.
† $p > 0.05$; ‡ $p < 0.05$; ‖ $p < 0.001$.

Table 3. Univariable and multivariable models to predict perioperative cardiac death or myocardial infarction.*

Variables	No. of Patients	Event, No. (%)	Univariable Odds Ratios (95% CI)	Multivariable Odds Ratios (95% CI)	Multivariable χ^2	p value
Clinical risk score						
Score 0	539	16 (3.0)	1.0	1.0		
Score 1 to 2	1416	81 (5.7)	2.0 (1.1–3.4)	1.8 (1.0–3.0)	4.0	0.045
Score 3	236	41 (17.4)	6.9 (3.8–12.7)	4.6 (2.5–8.6)	23.7	<0.001
Stress echocardiography summary §						
No new wall-motion abnormalities	1206	16 (1.3)	1.0	1.0		
New wall-motion abnormalities	281	41 (14.6)	12.7 (7.0–23.0)	10.1 (5.5–18.5)	56.7	<0.001
Perfusion scintigraphy summary §						
No reversible perfusion defect	519	48 (9.2)	1.0	1.0		
Reversible perfusion defect	198	33 (16.7)	1.9 (1.2–3.2)	1.6 (0.9–2.6)	3.4	0.066

*Numbers may not add to 2204 due to missing data; Event, defined as a composite of cardiac death and nonfatal myocardial infarction; Variables that composed the clinical risk score were advanced age, current or stable angina, a history of myocardial infarction, a history of congestive heart failure and diabetes mellitus.
§In the multivariable analysis dummy variables were introduced in order to account for the fact that patients with stress echocardiography did not undergo perfusion scintigraphy, and patients with perfusion scintigraphy did not undergo stress echocardiography.

significantly associated with adverse perioperative cardiac outcome. The multivariable model showed that current or stable angina, a history of MI, heart failure and diabetes mellitus remained important independent determinants of cardiac outcome (Table 2). The multivariable odds ratios for current or stable angina, a history of MI, and diabetes slightly decreased, whereas the odds ratio for heart failure almost halved compared to its univariable estimate. Based on these results, a simple risk score was developed to aggregate the available clinical information. To compose the clinical risk score one point was assigned to each of the following characteristics: age ≥ 70 years, current or stable angina, history of MI, history of heart failure and diabetes. Despite the fact that advanced age was not a significant risk factor in the present analysis it was included in the risk score because of its confirmed predictive value in previous studies.[8,9] In all, 539 (25%) had a risk score 0, 1416 (64%) had an index of 1 to 2, and 236 (11%) had a risk score of 3 or more points. The incidence of the composite endpoint in these patients was 3.0, 5.7 and 17.4% ($p < 0.001$). Regression analysis revealed a 2-fold increased risk for the composite endpoint associated with a risk score 1 to 2, and an almost 7-fold increased risk associated with a risk score 3 or more points (Table 3). Additional multivariate analyses demonstrated the prognostic value of clinical risk scores.

Predictive value of a positive test result

Patients who had NWMAs during DiSE had a 37-fold (OR = 37.0 [95% CI, 8.1–170.1]) increased risk of adverse cardiac events compared to those without NWMAs during DiSE. The presence of stress-induced ischaemia during DSE also was associated with the risk of perioperative cardiac complications (OR = 9.6 [95% CI, 4.9–18.4]). A comparison of univariate standardised beta coefficients (DiSE, [$\beta = 3.6 \pm 0.8$] vs DSE, [$\beta = 2.3 \pm 0.3$]) showed that there was no statistically significant difference in the predictive value of a positive test result for DiSE and DSE ($p = 0.12$). Therefore, pharmacologic stress

echocardiography was considered as a single test modality irrespective of the pharmacologic agent (dobutamine vs dipyridamole) used for inducing myocardial ischaemia. A regression analysis of a test positivity then revealed that patients with NWMAs during pharmacologic stress echocardiography were at significantly higher risk for cardiac death or MI (OR = 12.7 [95% CI, 7.0–23.0]) than those without NWMAs. The predictive value of a positive test result during DTS (OR = 1.9 [95% CI, 1.2–3.2]) had significantly lower prognostic value compared to pharmacologic stress echocardiography (pharmacologic stress echocardiography, [$\beta = 2.5 \pm 0.3$] vs DTS [$\beta = 0.7 \pm 0.2$]; $p < 0.001$).

In a univariate analysis, important determinants of perioperative cardiac complications were a presence of 1 to 2 and 3 or more risk scores, and positive test results for pharmacologic stress echocardiography and a positive test result for DTS (Table 3). In a multivariate analysis the clinical risk scores were combined with the test results, and only the scores themselves, and the presence of NWMAs remained important determinants of perioperative cardiac outcome. A presence of a positive test result for DTS lost most of its predictive power with respect to the composite endpoint (Table 3).

The logistic regression model with the clinical risk score had satisfactory ability to discriminate between patients who did and did not have a perioperative cardiac complication (c-index 0.66). The multivariable model that combined clinical data with test result had considerably better discriminating power with a c-index of 0.80.

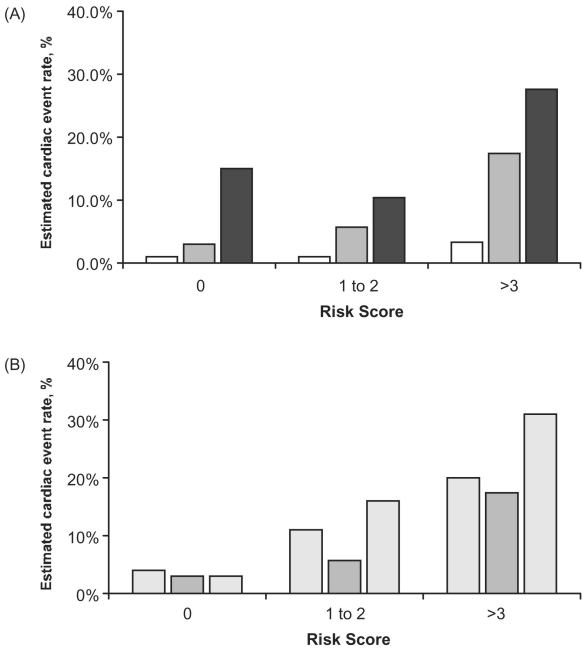

Fig. 1. Estimated risk of perioperative cardiac death or myocardial infarction based on clinical characteristics and results of pharmacologic stress echocardiography or dipyridamole perfusion scintigraphy. Panel A represents the estimated cardiac event rate (a composite of cardiac death and non-fatal myocardial infarction) based on the clinical risk score and the results of pharmacologic stress echocardiography. □ Negative pharmacologic stress echocardiography; ▩ Risk score; ■ Positive pharmacologic stress echocardiography. Panel B represents the estimated cardiac event rate (a composite of cardiac death and non-fatal myocardial infarction) based on the clinical risk score and the results of dipyridamole perfusion scintigraphy. □ Negative dipyridamole perfusion scintigraphy; ▩ Risk score □ Positive dipyridamole perfusion scintigraphy.

Risk classification model

Based on the results described above, a simple scheme was developed to estimate a patient's risk of perioperative cardiac complications (Fig. 1). If the clinical risk score was in the range of 0 or 1 to 2 points and stress echocardiography was negative, the estimated cardiac complication rate was low. The estimated risk of cardiac complications was also low in patients with risk score of 3 or more points without NWMAs (Fig. 1, panel A). Patients with a risk score of 0, 1 to 2 as well as 3 or more points, and with NWMAs were at a considerable risk (Fig. 1, panel A). In contrast, the magnitude of difference between negative and positive test results for DTS showed a different pattern. The prognostic value of DTS seemed to be dependent on the clinical risk profile of patients, but the formal statistical test of heterogeneity failed to show significance. This test had no predictive value in patients with a risk score 0, but its predictive value increased in patients with risk scores 1 to 2, and 3 or more points (Fig. 1, panel B).

Discussion

This study compared the additional prognostic capability of three noninvasive tests upon clinical risk factors used for perioperative cardiac risk assessment in large groups of patients who underwent major vascular surgery. The present analysis of 2204 major vascular surgery patients demonstrated that current or stable angina, a history of myocardial infarction, heart failure and diabetes mellitus are the most important clinical determinants of perioperative cardiac death or MI. Pharmacologic stress echocardiography results were highly predictive of adverse

cardiac outcome irrespective of the pharmacologic stressor used, which also confirms the results of other investigations.[6,7] In contrast, the prognostic value of DTS results was more likely to be dependent on patients' clinical risk profile.

Clinical risk factors for cardiac complications

Preoperative cardiac risk assessment of patients undergoing major vascular surgery is one of the most challenging and controversial areas of clinical medicine. Several large studies demonstrated that perioperative cardiac complications are particularly high in patients undergoing major vascular surgery.[2,6,7] Patients are at particularly high risk when they are $\geq$70 years old, and have a history or symptoms of CAD. In the present study, the selected group of risk factors stratified patients into low-, intermediate- and high-risk groups for cardiac complications. However, clinical variables alone did not provide an adequate power for stratification. Using pharmacologic stress echocardiography patients could be effectively stratified into group with very low estimated cardiac complication rate. The additional value of DTS imaging upon clinical risk factors showed a different pattern. Patient with a negative DTS results did remain at high risk for cardiac complications and there was no difference in the event rate between patients who had and did not have a perioperative adverse cardiac outcome.

Pharmacologic stress echocardiography

Pharmacologic stress echocardiography with dobutamine or dipyridamole is now widely accepted as an alternative stress test for patients unable to exercise. Stress echocardiography with dobutamine has proven to be a useful method for detection of CAD, and as a predictor of perioperative cardiac events in patients undergoing vascular surgery.[7–9] In contrast to other coronary vasodilators, dobutamine directly increases myocardial oxygen demand through positive chronotropic and inotropic effects, and also impairs myocardial oxygen supply by reducing the duration of systole. These factors may induce ischaemia if supply cannot meet the increased demand. The addition of atropine further increases heart rate and improves the sensitivity of the test without increasing side effects. In contrast to dobutamine, dipyridamole induces coronary hyperaemia, which leads to coronary steal[22] and can result in myocardial ischaemia characterised by stress-induced regional dysfunction. In theory, stress echocardiography with dipyridamole is considered less effective in inducing new wall motion abnormalities, especially for milder forms of CAD.

However, in our study there was not statistically significant difference in the predictive value of a positive test result for dipyridamole vs dobutamine stress echocardiography. The present study confirmed the findings of a small-scale study, which directly compared dipyridamole vs dobutamine stress echocardiography.[23] They found that the two tests had excellent negative predictive values for perioperative cardiac events and similar comparable positive predictive values.

Dipyridamole perfusion scintigraphy

The most extensively studied non-invasive approach to the cardiac risk stratification is DTS in combination of clinical risk factors. The presence of dipyridamole induced flow heterogeneity has been shown to be highly sensitive for the detection of coronary stenoses.[17] In practice, it implies that significant coronary stenoses are rarely missed, thus allowing a negative DTS imaging test to have a high predictive value for patients having no cardiac events after surgery.[2,19,20] In the present study, the prognostic value of DTS results was more likely to be dependent on patients' clinical risk profile. In patients at low-risk for cardiac complications test results did not differentiate between those who did and did not have a cardiac complication. In part, this observation suggests that the specificity of scintigraphy is less satisfactory compared to pharmacologic stress echocardiography. Artefacts and possible inclusion of unselected group of patients at high risk for false-positive perfusion scintigrams may have influenced the observed prognostic value of the test. Thus, it seems that DTS should be performed in patients at higher risk for cardiac complications such as patients with 1 to 2, or 3 or more cardiac risk factors.

Our study also revealed that a positive DTS result had significantly lower prognostic value than pharmacologic stress echocardiography. In agreement with our findings, current evidence suggests that the available data from direct comparison of dipyridamole echocardiography testing vs perfusion imaging suggest that perfusion defects are more frequent than transient dyssynergies and have a lower predictive value.[5] There are no studies to date that directly compare DSE and DTS in the same patient population. Hence, comparison of these two noninvasive tests can only be derived from the published reports. A recent meta-analysis comparing DSE and DTS concluded that the prognostic value of the two

noninvasive stress imaging was similar between DSE and DTS but accuracy varied with CAD prevalence.[24]

Study limitations

This study has certain limitations, which should be considered when interpreting the results. Three different noninvasive tests were compared for their ability to predict the incidence of perioperative cardiac events in three separate patient populations studied at different points in time in different hospitals. In order to study their relation to clinical risk factors, test characteristics the three datasets were combined. The differences in the prevalence of selected risk factors between the datasets, and the fact that patients were selected at different points in time in different hospitals may have biased the estimation of the predictive value of each test. However, by merging the datasets major vascular surgery patients in the present study could represent a wider range of patients.

In the present study DTS patients underwent planar perfusion scintigraphy, which reflects the available imaging technique at that time. Since then, single-photon computed tomography (SPECT) has been introduced.[25–27] Baron *et al.*, however, questioned the predictive value of SPECT. They found that it did not provide additional prognostic information over clinical risk factors.[25] Thus, we assume that our results remain applicable.

Due to the retrospective nature of this study information on risk factors such as smoking, hypertension and renal failure were not available in all datasets as well as the use of concomitant cardiac medication in the two of the three datasets was unavailable. Including information on these risk factors and perioperative cardiac medication such as beta-blockers could help to further elucidate the nature of the predictive values of these three noninvasive tests.

Conclusion

This study confirmed the utility of clinical risk factors and additional non-invasive testing in preoperative management of patients undergoing major vascular surgery. The decision between myocardial perfusion imaging and stress echocardiography either with dobutamine or dipyridamole is influenced by numerous factors. Stress echocardiography has many practical advantages over nuclear perfusion imaging-due to its lower costs, wider availability, reduced imaging time, and absence of radiation exposure. The results of the present study suggest that pharmacological stress echocardiography either with dipyridamole or dobutamine appears to have more favourable prognostic performance, irrespective of clinical risk profile. In contrast, the prognostic value of DTS results was more likely to be dependent on patients' clinical risk profile. In order to confirm these findings future randomised clinical trials with large number of patients are necessary. The physician's choice of preoperative cardiac testing, however, should also take into account factors such as local expertise and experience, availability, and costs.

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Chapter 10

A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery

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A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery

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Objective: To evaluate the discriminatory value and compare the predictive performance of six non-invasive tests used for perioperative cardiac risk stratification in patients undergoing major vascular surgery.
Design: Meta-analysis of published reports.
Methods: Eight studies on ambulatory electrocardiography, seven on exercise electrocardiography, eight on radionuclide ventriculography, 23 on myocardial perfusion scintigraphy, eight on dobutamine stress echocardiography, and four on dipyridamole stress echocardiography were selected, using a systematic review of published reports on preoperative non-invasive tests from the Medline database (January 1975 and April 2001). Random effects models were used to calculate weighted sensitivity and specificity from the published results. Summary receiver operating characteristic (SROC) curve analysis was used to evaluate and compare the prognostic accuracy of each test. The relative diagnostic odds ratio was used to study the differences in diagnostic performance of the tests.
Results: In all, 8119 patients participated in the studies selected. Dobutamine stress echocardiography had the highest weighted sensitivity of 85% (95% confidence interval (CI) 74% to 97%) and a reasonable specificity of 70% (95% CI 62% to 79%) for predicting perioperative cardiac death and non-fatal myocardial infarction. On SROC analysis, there was a trend for dobutamine stress echocardiography to perform better than the other tests, but this only reached significance against myocardial perfusion scintigraphy (relative diagnostic odds ratio 5.5, 95% CI 2.0 to 14.9).
Conclusions: On meta-analysis of six non-invasive tests, dobutamine stress echocardiography showed a positive trend towards better diagnostic performance than the other tests, but this was only significant in the comparison with myocardial perfusion scintigraphy. However, dobutamine stress echocardiography may be the favoured test in situations where there is valvar or left ventricular dysfunction.

Patients undergoing major vascular surgery are at increased risk for cardiovascular complications such as cardiac death and non-fatal myocardial infarction because of underlying coronary artery disease.[1] These complications may occur during or directly after surgery. The aim of preoperative evaluation is to identify patients with significant coronary artery disease who are thus at increased risk of cardiac complications. Appropriate patient management would then include strategies to reduce this risk.

The identification of clinical risk factors and the role of non-invasive diagnostic testing to predict perioperative cardiac risk have been evaluated over recent decades. These have included multifactorial clinical scoring systems[2–4] based on non-invasive tests such as ambulatory electrocardiography,[5–12] exercise electrocardiography,[13–19] radionuclide ventriculography,[20–27] and myocardial perfusion scintigraphy.[10 28–49] It has been suggested that the most accurate information about the individual patient risk profile can be obtained by adding clinical characteristics to those obtained by myocardial perfusion scintigraphy.[33] Recently, the use of pharmacological stress echocardiography with either dipyridamole[50–53] or dobutamine[54–61] has also been proposed for risk stratification. Pharmacological stress echocardiography has proven to be a safe and sensitive technique for predicting perioperative cardiac events, with an excellent negative predictive power.

It is still uncertain, however, which of these tests shows the best prognostic accuracy. Limited data are available directly comparing the performance of these tests. In addition, variability in the pretest probability of coronary artery disease, the mixture of surgical procedures, and differences in criteria for positivity have made it difficult to compare the performance of the tests directly.

Our aim in this study was to evaluate the comparative performance of these six diagnostic tests under conditions which adjusted for variations in preoperative risk and diagnostic thresholds, using a meta-analytic design.

METHODS

Data extraction

An electronic search of published reports was undertaken to identify studies published between January 1975 and April 2001 in English language journals. A computer generated Medline search was applied, using the terms ''cardiac evaluation'', ''cardiac risk'', ''perioperative myocardial ischaemia'', ''perioperative cardiac morbidity'', ''myocardial infarction'', ''perioperative outcome predictors'', and ''major vascular surgery'', in conjunction with one of the following non-invasive tests used for detection of myocardial ischaemia: ''exercise electrocardiography'', ''continuous ambulatory electrocardiography monitoring'', ''radionuclide ventriculography'', ''dobutamine and dipyridamole stress echocardiography'', and ''myocardial perfusion scintigraphy''. Additional references were obtained from the bibliographies of review articles and original papers.

Studies were included if perioperative (30 day) data on cardiac death and non-fatal myocardial infarction or the composite were reported, and if the absolute numbers of true positive, false negative, true negative, and false positive observations were available (including positivity thresholds), or were derivable from the data presented. If several studies were done on overlapping patient populations then one report was selected which had the largest sample size. If several tests were studied simultaneously, data from each were extracted separately. Studies in which preoperative coronary revascularisation occurred as a result of a positive test result were only included if patients who underwent such procedures could be excluded or analysed separately.

Pertinent data from the selected studies were extracted independently by two of us (MDK and EB), using standardised spreadsheets. Discrepancies were resolved by consensus. Information extracted included reference data (first author, journal, institution), publication year, number of patients, mean age, proportion of male patients, type of vascular surgery, percentage of patients with a history of coronary artery disease (defined as either past or current angina pectoris, history of myocardial infarction, or heart failure) and diabetes mellitus, type of radionuclide used, and the type of exercise performed or the type of pharmacological stress agent used. Criteria for positivity were recorded. This information is shown in table 1.

Data analysis

One hundred and thirty one studies published between January 1975 and April 2001 were screened. Fifty eight met the inclusion criteria (table 2). Data on some explanatory variables were not specified in the studies included. In seven studies[14 15 18 22 37–39] the mean age was absent; in six[14 15 24 36 37 42] the sex distribution was absent; in three[10 13 14] the proportion of patients with a history of coronary artery disease was not specified; and in 20[7 10 13–16 20–23 25–31 35 37 40] the proportion of patients with diabetes was not given. Estimates for these variables were used, based on a best subset regression analysis, so that the maximum number of selected studies could be included. Weighted mean values for the missing data using sensitivity analysis or excluding studies from the analysis did not alter the results. Therefore, all selected studies were included for analyses.

Differences in baseline clinical characteristics between the study populations were evaluated using χ^2 statistics. To account for a possible source of heterogeneity in diagnostic threshold between studies, pooled results weighted by the sample size of each study were calculated using a random effect model, based on a single treatment effect and standard error for each of a set of studies.[62] Results are presented as percentage sensitivity and specificity with 95% confidence intervals (CI).

Table 1 Test positivity criteria used for each non-invasive preoperative test

Non-invasive test	Positivity criterion
Ambulatory ECG	ST segment depression of ⩾1 mm or ST elevation ⩾2 mm after J point (measured at 60 ms) lasting at least one minute
Exercise ECG	Development of exercise induced horizontal or downsloping ST depression of 1 mm or more
Radionuclide ventriculography	Ejection fraction ⩽35%
Myocardial perfusion scintigraphy	One or more fixed or reversible thallium-201 myocardial defects
Dipyridamole stress echocardiography	New or worsening ventricular wall motion abnormalities
Dobutamine stress echocardiography	New or worsening ventricular wall motion abnormalities

Summary receiver operating characteristic (SROC) curves were generated to describe diagnostic performance over a range of threshold values for each non-invasive test (see the appendix). Univariable and multivariable regression analyses were undertaken to study the influence of clinical and study characteristics on test performance, including the number of patients tested and operated on, the mean age of the patients, the proportion of men, the proportion of patients with a history of coronary artery disease, the proportion of patients with diabetes mellitus, and the year of publication.

Comparisons using SROC analysis were also undertaken to enable us to study diagnostic performance between separate tests. In each case we included all significant explanatory variables, along with the variable indicating the test comparison. We developed models with identical explanatory variables across all comparisons. The differences in diagnostic performance between separate tests are represented by the relative diagnostic odds ratios with 95% CI. The relative diagnostic odds ratio indicates the diagnostic performance of a test, with a value larger than 1 indicating better discriminatory power, a value equal to 1 indicating no difference, and values below 1 indicating reduced discriminatory ability. In order to adjust for the fact that multiple comparisons were made, a probability value of $p \leqslant 0.01$ was considered significant. All statistical analyses were done using ''meta'' and ''metareg'' commands for STATA 6.0 for Windows (STATA Corporation, Texas, USA).

RESULTS

Clinical and study characteristics

A summary of the clinical characteristics of the studies included in the meta-analysis is given in table 3. Mean age was similar between the studies. The majority of patients in the studies were male, with no significant difference between the studies ($p = 0.380$). Coronary artery disease was more common in patients who underwent radionuclide ventriculography, ambulatory ECG, and myocardial perfusion scintigraphy ($p = 0.03$) compared with the other tests. The prevalence of diabetes was less than that of coronary artery disease, with no significant difference between the studies ($p = 0.06$). Vascular surgery was not cancelled because of a positive test result after ambulatory ECG, radionuclide ventriculography, or dobutamine stress echocardiography. Preoperative revascularisation was undertaken following a positive test result in 16 patients who underwent exercise ECG, in 70 who underwent myocardial perfusion scintigraphy, and in 12 who underwent dipyridamole stress echocardiography. Patients undergoing preoperative coronary revascularisation were excluded or analysed separately in these studies. No operations were cancelled as a result of any exercise ECG abnormalities, but in 36 cases the operation was cancelled after a positive test result during myocardial perfusion scintigraphy.

Weighted pooled results

The diagnostic test performance for individual studies is outlined in table 3. In pooled data weighted by the number of patients with and without disease in each study, dobutamine stress echocardiography showed the highest sensitivity (true positive ratio) of 85% (95% CI 74% to 97%) with a specificity (1 − false positive ratio) of 70% (95% CI 62% to 79%) compared with the other tests (table 3).

Summary receiver operation characteristic analysis for each diagnostic test

In a univariable analysis for ambulatory ECG, none of the selected clinical risk factors was a significant predictor of the

Table 2 Clinical characteristics of the studies included in the meta-analysis

Reference	Mean age (years)	Male (%)	CAD (%)	DM (%)	Isotope used	Test used	Positivity criterion	Preop revascularisation (%)	Op cancelled (%)	TP	FN	TN	FP
Ambulatory electrocardiography													
Ouyang[5]	64	71	71	29	NA	Preop monitoring	ST depression >1 mm	0	0	2	0	9	13
Raby[6]	66	70	40	21	NA	Preop monitoring	ST depression >1 mm	0	0	3	1	143	29
Pasternack[7]	70	79	41	–	NA	Preop monitoring	ST depression >1 mm	0	0	9	0	73	118
Mangano[8]	69	100	51	25	NA	Preop monitoring	ST depression >1 mm/ST elevation >2 mm	0	0	1	5	109	25
Fleischer[9]	66	61	57	34	NA	Preop monitoring	ST depression >1 mm/ST elevation >2 mm	0	0	1	2	49	15
McPhail[10]	67	86	–	–	NA	Preop monitoring	ST depression >1 mm	0	0	5	4	62	29
Kirwin[11]	73	55	66	47	NA	Preop monitoring	ST depression >1 mm	0	0	1	14	73	8
Fleischer[12]	69	50	72	43	NA	Preop monitoring	ST depression >1 mm/ST elevation >2 mm	0	0	2	2	64	18
Exerciseelectrocardiography													
Cutler[13]	62	77	–	–	NA	Treadmill/arm ergometry	ST depression >1 mm	8	0	8	1	79	32
Gardine[14]	–	–	–	–	NA	Treadmill	ST depression >1 mm	0	0	1	0	10	6
von Knorring[15]	–	–	52	–	NA	Treadmill	ST depression >1 mm	0	0	2	1	78	24
Hanson[16]	62	73	20	–	NA	Arm ergometry	ST depression >1 mm	0	0	1	0	32	41
Leppo[17]	67	62	51	18	NA	Treadmill/arm ergometry	ST depression >1.5 mm	0	0	3	4	44	9
Kaaja[18]	–	67	29	22	NA	Bicycle	ST depression >1 mm	0	0	2	0	44	2
Urbinati[19]	62	74	15	46	NA	Bicycle	ST depression >1 mm	0	0	2	0	93	48
Radionuclide ventriculography													
Fiser[20]	61	100	25	–	Tc99m	NA	EF <30%	0	0	2	0	18	0
Pasternack[21]	70	96	34	–	Tc99m	NA	EF <35%	0	0	4	4	41	1
Mosley[22]	–	90	63	–	Tc99m	NA	EF <35%	0	0	3	1	36	1
Pasternack[23]	66	80	36	–	Tc99m	NA	EF <35%	1	0	6	8	84	1
Kazmers[24]	68	–	42	7	Tc99m	NA	EF <35%	0	0	1	4	46	9
Franco[25]	68	55	61	–	Tc99m	NA	EF <35%	0	0	3	12	58	12
McCann[26]	68	87	49	–	Tc99m	NA	EF <35%	0	0	1	2	83	18
Fletcher[27]	68	79	50	–	Tc99m	NA	EF <35%	0	0	3	0	62	7
Myocardial perfusion scintigraphy													
Boucher[28]	63	96	100	–	T201	Planar	Fixed or reversible perfusion defect	11	0	3	0	20	25
Cutler[29]	65	69	34	–	T201	Planar	Fixed or reversible perfusion defect	5	8	9	0	62	30
Fletcher[30]	64	72	27	–	T201	Planar	Fixed or reversible perfusion defect	7	0	2	0	57	3
Sachs[31]	60	83	30	–	T201	Planar	Reversible perfusion defect	0	0	2	0	32	12
Lane[32]	65	65	63	100	T201	Planar	Fixed or reversible perfusion defect	0	0	9	0	20	72
Eagle[33]	66	71	29	18	T201	Planar	Reversible perfusion defect	0	0	13	2	116	69
Younis[34]	65	72	42	31	T201	Planar	Fixed or reversible perfusion defect	4	15	8	0	51	48
McEnroe[35]	69	58	28	–	T201	Planar	Fixed or reversible perfusion defect	8	0	4	2	44	37
Strawn[36]	66	–	62	15	T201	Planar	Reversible perfusion defect	13	9	1	3	18	31
Waters[37]	–	–	100	–	T201	Planar	Fixed or reversible perfusion defect	4	4	3	0	11	12
Mangano[38]	–	98	45	25	T201	Planar/SPECT	Fixed or reversible perfusion defect	0	0	2	1	19	38
Hendel[39]	–	65	35	23	T201	Planar	Reversible perfusion defect	0	0	23	5	155	144
Madsen[40]	65	65	22	–	T201	Planar	Fixed or reversible perfusion defect	0	0	5	0	20	40
McPhail[10]	67	86	–	–	Tc99m	Planar	Fixed or reversible perfusion defect	0	0	6	3	67	24
Bry[41]	66	69	30	34	T201	Planar	Fixed or reversible perfusion defect	4	0	17	0	97	114
Baron[42]	63	–	36	9	T201	SPECT	Fixed or reversible perfusion defect	0	0	26	16	187	228
Ombrellaro[43]	68	62	38	23	T201/Tc99m	Planar	Fixed or reversible perfusion defect	7	0	2	2	125	33
Erickson[45]	67	88	26	15	T201	Planar	Fixed or reversible perfusion defect	3	0	6	1	55	80
Vanzetto[46]	65	94	36	13	T201	SPECT	Fixed or reversible perfusion defect	0	0	11	1	50	72
Klonaris[47]	67	87	36	32	T201	Planar	Fixed or reversible perfusion defect	0	0	7	1	43	116

Table 2 Continued

Reference	Mean age (years)	Male (%)	CAD (%)	DM (%)	Isotope used	Test used	Positivity criterion	Preop revascularisation (%)	Op cancelled (%)	TP	FN	TN	FP
Huang[48]	68	89	12	27	T201	SPECT	Fixed or reversible perfusion defect	0	0	5	0	24	75
de Virgilio[49]	65	96	26	33	T201	Planar	Fixed or reversible perfusion defect	4	0	2	0	27	30
de Virgilio[50]	65	78	29	74	T201/Tc99m	SPECT	Fixed or reversible perfusion defect	0	0	3	1	35	41
Dipyridamole stress echocardiography													
Tischler[51]	68	61	34	29	NA	NA	New or worsening RWMA during test	0	0	4	0	100	5
Pasquet[52]	67	84	19	17	NA	NA	New or worsening RWMA during test	9	0	2	3	99	25
Rossi[53]	66	80	39	76	NA	NA	New or worsening RWMA during test	0	0	4	3	74	22
Sicari[54]	66	88	20	11	NA	NA	New or worsening RWMA during test	0	0	15	2	419	73
Dobutamine stress echocardiography													
Lalka[55]	64	78	30	18	NA	NA	New or worsening RWMA during test	0	0	8	1	21	30
Davila-Roman[56]	67	73	63	19	NA	NA	New or worsening RWMA during test	14	0	2	0	68	8
Langan[57]	69	84	31	10	NA	NA	New or worsening RWMA during test	5	6	3	0	31	40
Poldermans[58]	68	89	31	12	NA	NA	New or worsening RWMA during test	0	0	5	0	96	30
Eichelberger[59]	68	60	37	29	NA	NA	New or worsening RWMA during test	0	0	2	0	48	25
Poldermans[60]	67	85	31	11	NA	NA	New or worsening RWMA during test	0	0	17	0	228	55
Shafritz[61]	66	64	33	17	NA	NA	New or worsening RWMA during test	0	0	1	0	30	11
Boersma[62]	69	78	4 3	15	NA	NA	New or worsening RWMA during test	0	0	29	14	863	187

CAD, coronary artery disease; DM, diabetes mellitus; EF, ejection fraction; FN, false negative; FP, false positive; NA, not applicable; Op, operation; Preop, preoperative; RW positive; -, missing values.

performance of the test. In fig 1, the SROC curve describes the test characteristics of ambulatory ECG monitoring in the studies included. When the selected clinical risk factors and study characteristics were tested in univariable analyses, none of the characteristics changed the SROC curve substantially. This was also observed when the performance of exercise ECG and dobutamine stress echocardiography was tested in separate univariable analyses—again analyses of exercise ECG and dobutamine stress echocardiography showed that none of the clinical and study characteristics changed the SROC curves (fig 1). Unlike the above described non-invasive tests, separate univariable SROC analyses for radionuclide ventriculography and myocardial perfusion scintigraphy showed that among the clinical risk factors and study characteristics only publication year changed the SROC curves significantly. The performance of the tests diminished with a later year of publication (fig 1). Remarkably, the estimates of sensitivity (true positive rates) and 1 − specificity (false positive rates) for dipyridamole stress echocardiography were inversely correlated when individual studies were plotted (fig 1). In this case only pooled sensitivity and specificity could be calculated. Thus the SROC analysis was not done and an SROC curve for dipyridamole stress echocardiography was not constructed.

Comparison of diagnostic tests

Table 4 shows the results of the comparison of SROC analyses with (table 4B) and without (table 4A) adjustment for publication year. In the present study only publication year was a significant predictor of test performance for some of the tests analysed (radionuclide ventriculography and myocardial perfusion scintigraphy). In order to compare differences in diagnostic performance between the studies, the variable ''publication year'' was also included in all comparisons.

Ambulatory ECG performed no better than exercise ECG or myocardial perfusion imaging. Although there was a trend for ambulatory ECG to have a lower predictive performance than radionuclide ventriculography ($p = 0.04$) or dobutamine stress echocardiography ($p = 0.03$), this did not reach significance in univariable analysis and after correcting for publication year. Indeed, after adjustment for publication year an inverse relation was observed between radionuclide ventriculography and ambulatory ECG, though this was not significant. Exercise ECG showed a trend for a better discriminative power than ambulatory ECG and myocardial perfusion scintigraphy, and a reduced discriminative ability compared with radionuclide ventriculography and dobutamine stress echocardiography. However, these differences were non-significant (table 4). Myocardial perfusion scintigraphy showed lower discriminatory ability than ambulatory ECG, exercise ECG, or radionuclide ventriculography, though the differences were also non-significant. However, myocardial perfusion scintigraphy had a substantially lower discriminatory power than dobutamine stress echocardiography ($p = 0.001$), and this difference remained significant after adjusting for publication year ($p = 0.002$). Finally, dobutamine stress echocardiography showed a positive trend towards a better diagnostic performance than all the other tests, but this only reached significance in comparison with myocardial perfusion scintigraphy.

DISCUSSION

Our report is a meta-analysis of contemporary papers on six non-invasive tests used for preoperative risk stratification in patients selected for vascular surgery. We used an innovative meta-analytic method to estimate the diagnostic accuracy of these tests from multiple studies. The accuracy of the tests is presented and compared using a summary ROC curve, and

Table 3 Summary of clinical characteristics and sensitivity and specificity of the studies included in the meta-analysis

Type of test	No. of studies	No. of patients	Mean age (years)	Proportion of men (%)	History of CAD (%)	Proportion of DM (%)	Sensitivity (%; 95% CI)	Specificity (%; 95% CI)
Radionuclide ventriculography	8	532	67.0	83	45	25	50 (32 to 69)	91 (87 to 96)
Ambulatory electrocardiography	8	893	68.0	72	55	32	52 (21 to 84)	70 (57 to 83)
Exercise electrocardiography	7	685	64.5	72	36	28	74 (60 to 88)	69 (60 to 78)
Dipyridamole stress echocardiography	4	850	66.8	78	28	33	74 (53 to 94)	86 (80 to 93)
Myocardial perfusion scintigraphy	23	3119	65.5	78	40	30	83 (77 to 89)	49 (41 to 57)
Dobutamine stress echocardiography	8	1877	67.3	76	37	16	85 (74 to 97)	70 (62 to 79)

Tests are sorted according to ascending sensitivities.
CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus.

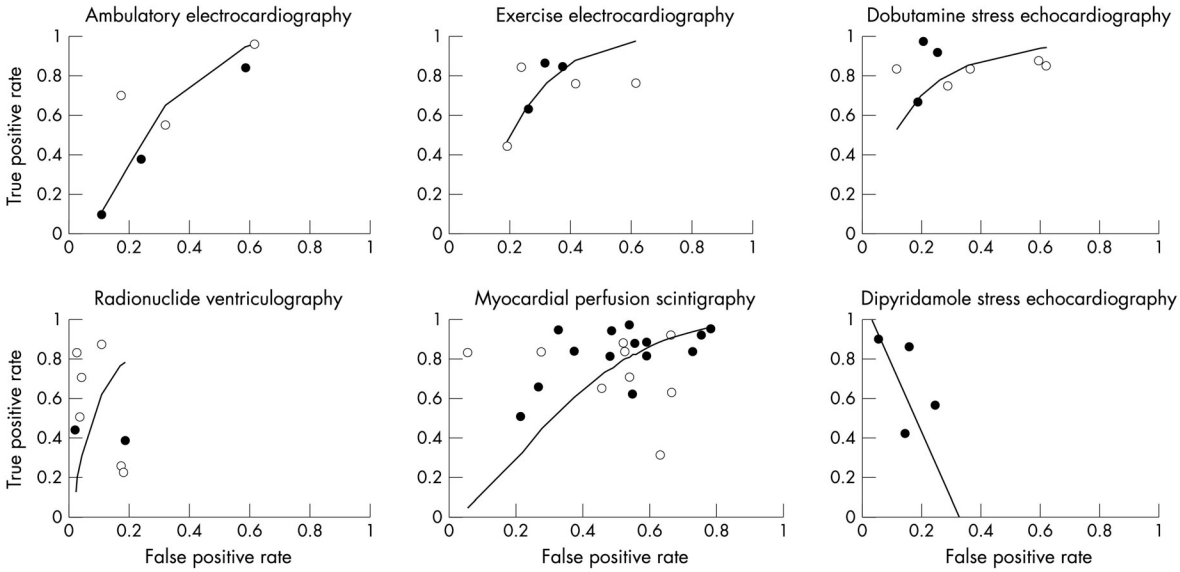

Figure 1 Graphs showing summary receiver operating characteristic (SROC) curves for ambulatory ECG, exercise ECG, dobutamine stress echocardiography, radionuclide ventriculography, and myocardial perfusion scintigraphy. The horizontal axis represents the false positive rate (1 − specificity) and the vertical axis the true positive rate (sensitivity). The graph for dipyridamole stress echocardiography represents a plot of the estimates of the true positive rate for dipyridamole stress echocardiography against the estimates of false positive rate, with a solid line representing the regression line. In all graphs, solid circles represent studies with more than 100 patients and open circles represent studies with less than 100 patients.

Table 4 Results of the comparison of summary receiver operating characteristic analyses between diagnostic tests

	Reference test				
	Ambulatory electrocardiography	Exercise electrocardiography	Radionuclide ventriculography	Myocardial perfusion scintigraphy	Dobutamine stress echocardiography
(A) Not adjusted for publication year					
Ambulatory electrocardiography		0.6 (0.2 to 1.8)	0.2 (0.0 to 1.0)	1.6 (0.5 to 5.0)	0.3 (0.1 to 1.0)
Exercise electrocardiography	1.6 (0.5 to 24.5)		0.5 (0.0 to 6.1)	2.7 (0.3 to 8.2)	0.6 (0.2 to 1.8)
Radionuclide ventriculography	5.5 (1.1 to 24.5)	2.2 (0.2 to 30.0)		5.5 (0.8 to 36.6)	0.9 (0.1 to 18.2)
Myocardial perfusion scintigraphy	0.6 (0.2 to 1.8)	0.4 (0.1 to 30.0)	0.2 (0.0 to 1.2)		0.3 (0.1 to 0.6)†
Dobutamine stress echocardiography	3.0 (1.2 to 7.4)	1.6 (0.5 to 4.5)	1.1 (0.1 to 20.1)	4.1 (1.6 to 10.0)†	
(B) Adjusted for publication year					
Ambulatory electrocardiography		0.7 (0.4 to 3.0)	1.3 (0.2 to 8.2)	1.5 (0.5 to 4.1)	0.4 (0.1 to 2.5)
Exercise electrocardiography	1.5 (0.3 to 6.7)		0.4 (0.0 to 4.1)	1.5 (0.4 to 5.5)	0.7 (0.1 to 6.7)
Radionuclide ventriculography	0.7 (0.1 to 4.5)	2.7 (0.2 to 30.0)		2.2 (0.3 to 13.5)	0.08 (0.0 to 5.5)
Myocardial perfusion scintigraphy	0.7 (0.3 to 2.0)	0.7 (0.2 to 2.5)	0.5 (0.1 to 3.0)		0.2 (0.1 to 0.5)†
Dobutamine stress echocardiography	2.5 (0.4 to 16.4)	1.5 (0.2 to 14.9)	12.2 (0.2 to 897.8)	5.5 (2.0 to 14.9)†	

The figures indicate relative diagnostic odds ratios for comparison between the reference test in the column *v* the test in the row; the relative diagnostic odds ratio indicates the diagnostic performance of a test, with a value larger than 1 indicating better discriminatory power, a value equal to 1 no difference, and values below 1 corresponding to reduced discriminatory ability. Figures in parenthesis are the 95% confidence intervals.
†$p<0.01$.

the performance of individual tests was corrected for selected patient and study characteristics. Our results show that pharmacological stress tests have a higher overall sensitivity and specificity than the other tests. In particular, dobutamine stress echocardiography showed a positive trend for better diagnostic performance than the other tests, but this was only significant in comparison with myocardial perfusion scintigraphy. Ambulatory ECG, exercise ECG, and radionuclide ventriculography yielded a lower sensitivity and reasonable specificity, but no significant difference in predictive performance.

Ambulatory ECG monitoring showed low sensitivity and higher specificity in the present study, but no significant difference in predictive performance. The use of ambulatory ECG monitoring for perioperative cardiac risk assessment was first described by Raby and colleagues.[6] They reported a sensitivity of 75% and a specificity of 83% for predicting cardiac death and non-fatal myocardial infarction. In later studies the predictive value of the test was corroborated, but the sensitivity was less than reported here.[9 10] Variation in end point composition, surgical procedures, and the timing of events could explain the observed differences in sensitivity and specificity between studies. The advantages of the test are that it is cheap and widely available. However, the presence of resting ECG changes (bundle branch block, left ventricular hypertrophy, digitalis use) may preclude reliable ST segment analysis in 40% of patients.[63] Hence, the combination of low sensitivity and resting ECG changes limits the application of the technique.

In our study the pooled data showed reasonable sensitivity and specificity for exercise ECG compared with the other tests. However, SROC analyses showed that it did not perform better than the other non-invasive tests. This observation may be explained by type II error—that is, differences could be missed owing to lack of power. Conventional exercise ECG is considered the most physiological form of stress.[64] However, the test may not always be feasible because of exercise intolerance in such patients.

The value of radionuclide ventriculography for predicting perioperative cardiac complications has been assessed in many studies.[20–27] A preoperatively assessed low ejection fraction (<35%) showed a relatively poor sensitivity but a high specificity in our meta-analysis. The SROC analysis showed that resting left ventricular dysfunction, as determined by radionuclide ventriculography, did not have a significantly better predictive performance than the other tests. The observed limitation of the predictive performance of this test may be explained by the failure to detect severe underlying coronary artery disease, changes in predictive value over time, and improved anaesthetic and surgical perioperative care. Thus, radionuclide ventriculography may not be a suitable test for preoperative risk stratification. However, a low ejection fraction may be a useful predictor of long term survival.[64]

In patients unable to perform adequate exercise (and in most vascular surgery patients unable to exercise), a non-exercising test is mandatory. In this regard, myocardial perfusion scintigraphy—often combined with clinical risk assessment—is the most extensively studied non-invasive approach to cardiac risk stratification. In the present study a high sensitivity but a low specificity was observed for perioperative hard cardiac events, with a lower diagnostic accuracy than with dobutamine stress echocardiography. The earliest studies (between 1985 and 1987) showed that patients with fixed or reversible scintigraphic myocardial perfusion defects were at increased cardiac risk.[28 29] However, these results were later questioned by other investigators.[38 42] The poor prognostic value observed in these studies may reflect small sample sizes.

Comparison of myocardial perfusion scintigraphy with stress echocardiography in our study showed that dobutamine stress echocardiography performed significantly better. There are several possible explanations for these findings. First, myocardial perfusion scintigraphy is more widely used in consecutive patients presenting for vascular surgery than in selected patients with clinical risk factors; second, unblinded test results are available to clinicians, thus influencing perioperative care; third, repeat imaging 3–4 hours after thallium infusion may not allow sufficient time for thallium redistribution; and finally, thallium uptake may be uniformly restricted in patients with severe and diffuse coronary artery disease. Nevertheless myocardial perfusion scintigraphy is a valuable test for cardiac risk assessment, especially in patients with contraindications to stress echocardiography, with a reported complication rate of 3.9% in the studies included in the present meta-analysis. However, myocardial perfusion scintigraphy should be avoided in patients with significant bronchospasm, critical carotid disease, or on regular theophylline treatment.[64]

Dipyridamole stress echocardiography has been proposed for cardiac risk stratification in patients undergoing major vascular surgery.[50–53] The low false positive rates and extremely high negative predictive values can make this test a useful predictor in low risk scenarios. Indeed, in the present meta-analysis dipyridamole stress echocardiography had a higher specificity than myocardial perfusion scintigraphy or dobutamine stress echocardiography. However, there have been limited numbers of studies published to date, and in these studies the true positive and false positive rates for dipyridamole stress echocardiography showed a negative correlation when they were plotted graphically. Hence only weighted pooled sensitivity and specificity could be calculated and the performance of the test could not be studied in further detail. The high specificity of dipyridamole stress echocardiography in clinical practice may indicate that the test can identify patients at less severe ischaemic responses. These patients may not need to undergo further testing and can proceed to major vascular surgery directly. However, in clinical practice it is more valuable to have a sensitive test that can identify patients at increased risk of perioperative cardiac events. Further conclusions about dipyridamole stress echocardiography are limited by the reported differences in sensitivity and specificity between the few studies reported to date.

Dobutamine stress echocardiography showed a similar high sensitivity, but a significantly higher specificity, compared with myocardial perfusion scintigraphy. Comparison using SROC analysis showed a trend towards better performance than the other tests, but this was only significant versus myocardial perfusion scintigraphy. As with dipyridamole, dobutamine stress echocardiography has been proposed for cardiac risk stratification owing to its high negative predictive value.[54–61] Moreover, in the present study this test showed significantly higher sensitivity than dipyridamole stress echocardiography. The role of dobutamine stress echocardiography in cardiac risk stratification has been studied extensively in recent reports.[59 61 65] The results of these studies suggest that the investigation can be done safely and with reasonable patient tolerance and may provide additional information about valvar dysfunction, in contrast to myocardial perfusion scintigraphy. The test has certain limitations—for example, it should not be used in patients with serious arrhythmias, severe hypertension, or hypotension. However, in a recent report of the use of dobutamine stress echocardiography in 6595 patients it was found that the incidence of cardiac arrhythmias and hypotension was 8% and 3%, respectively, and these complications were well tolerated and rarely required treatment.[66]

Study limitations

The study has several limitations. Meta-analyses are subject to publication bias—that is, studies with a significant result are more likely to be submitted. Heterogeneity of study design is another aspect that may influence the interpretation of the results. The predictive value of a given test can be influenced by at least two important factors: patient selection and the blinding of test results. A test done in consecutive patients may have a lower diagnostic accuracy than the same test done in a selected group of patients. This is commonly referred to as selection bias and it occurs when consecutive cohorts of patients with a high prior probability of coronary artery disease, and therefore of adverse cardiac outcome after surgery, are more likely to get the test. The predictive value of a given test may also be influenced by the availability of the test result to the treating physicians. In this case patients with positive test results may undergo less invasive operations or receive better perioperative care, such as cardioprotective drugs, invasive haemodynamic monitoring, and admission to an intensive care unit. Studies in which patients are enrolled consecutively and treating physicians are blinded to test results are more likely to provide a relatively unbiased estimate for a given test.

Conclusions

Our meta-analysis shows that ambulatory ECG monitoring has a relatively low sensitivity and a low specificity, with no incremental value over the other tests. Furthermore, resting ECG changes frequently preclude reliable assessment of the ambulatory ECG and this test is therefore not recommended for perioperative risk assessment. Radionuclide ventriculography had the highest specificity but a relatively low sensitivity, with a limited predictive performance for perioperative events. This test should not therefore be considered as a tool for preoperative cardiac risk assessment. The test of choice in most ambulatory patients is an exercise ECG done according to the American College of Cardiology/American Heart Association guideline.[64] However, most vascular surgical candidates have important abnormalities on their resting ECG and are unable to perform adequate exercise. In such patients stress echocardiography or myocardial perfusion scintigraphy should be considered. In the current study dobutamine stress echocardiography showed a similar sensitivity to myocardial perfusion scintigraphy but a higher specificity and a better overall predictive performance. Moreover, dobutamine stress echocardiography is the favoured test if there is an additional question of valvar or left ventricular dysfunction. Dipyridamole stress echocardiography had a lower sensitivity and a higher specificity than myocardial perfusion scintigraphy. However, further conclusions about dipyridamole stress echocardiography are limited by the reported differences between studies and the limited number of studies reported to date.

Meta-analysis of six non-invasive tests showed a positive trend for dobutamine stress echocardiography to have a better diagnostic performance than the other tests, but this only reached significant difference in comparison with myocardial perfusion scintigraphy.

To see the appendix, visit the Heart website—www.heartjnl.com/supplemental

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In appendix

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A meta-analysis comparing the prognostic accuracy of six diagnostic tests for prediction perioperative cardiac risk in patients undergoing major vascular surgery

Appendix

Summary receiver characteristics curves

Conventional receiver operating characteristic curves (ROC) graphically represent the true positive and false positive rates for a diagnostic test when the threshold for a positive test result is varied.[67] The area under the curve summarises the overall diagnostic performance of the test, with larger areas corresponding to a more discriminating test. Most reports of the performance of a diagnostic test provide only single estimates of the true positive (TP) and false positive (FP) rates for one fixed threshold value. A possible source of heterogeneity in a meta-analysis of a diagnostic test is the variability of threshold values across studies. Variability in TP and FP rates derived from published reports may represent different operating points on one common underlying ROC curve. Hence, pooling TP and FP rates from different sources would underestimate the diagnostic performance.[68]

Summary ROC (SROC) analysis assumes that part of the reported variability in test performance reflects the difference in the cut off points or positivity criteria used, and aims to adjust for these differences. SROC analysis also allows adjustment for important clinical covariates and for comparison between different types of tests.[69] In this case, a variable corresponding to the type of non-invasive testing used is entered into the regression equation. The differences in diagnostic performance of the tests are represented by the regression coefficients and can be interpreted after antilogarithm transformation as relative diagnostic odds ratios. They indicate the diagnostic performance of a test, with a value larger than 1 indicating better discriminatory power, whereas a value equal to 1 indicates no difference, and values below 1 indicate reduced discriminatory ability.[70]

First, the estimates of sensitivity (true positive rate) against the estimates of 1specificity (false positive rate) were plotted. If there was a positive relation between true positive rates and false positive rates (that is, both true positive and false positive rates increase), then this association was identified using the non-parametric Spearmen correlation test.[71] If the true positive rates and false positive rates were positively correlated, then summary ROC analysis was undertaken. In case of a negative correlation only summary point estimates that is, weighted

sensitivity and specificity of the test were given.

Construction of a summary receiver characteristics curve

The construction of a SROC curve requires that the number of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) observations in each study be available.[69]

Computational steps involved in the construction of summary ROC curve

Computation of the difference (D) and the sum (S) of the logit transforms of TP and FP rates

$$D = \ln((TP+1/2)/(FN+1/2)) \ln((FP+1/2)/(TN+1/2))$$

$$S = \ln((TP+1/2)/(FN+1/2))+\ln((FP+1/2)/(TN+1/2))$$

where TP, FN, TN, and FP are corrected by one half to ensure that D and S would not be undefined if TP, FN, TN, or FP equals zero.

Computation of the asymptotic variance (VAR) of D

$$VAR(D) = ((1/TP+1.2)+(1/FN+1/2)+(1/TN+1/2)+(1/FP+1/2)$$

Weighted least square regression analysis, using weights proportional to the inverse of VAR (D)

In our study, the following equation was used to evaluate the prognostic accuracy of individual tests:

$$D = \alpha + \beta_s * S + \varepsilon$$

where D is the dependent variable from equation 3, α, β_s, are regression coefficients, S is the independent variable for equation 4, and ε is the error term.

The following equation was used for between-test comparisons to compare the prognostic accuracy of two tests:

$$D = \alpha + \beta_s * S + \beta_t * T + \varepsilon$$

where D is the dependent variable from equation 3, α, β_s, β_t are regression coefficients, S is the independent variable for equation 4, and T is a dummy variable indicating the type of test for between-test comparison (with T=0 for one test and T=1 for the other).

The regression lines were converted to the ROC space using the following formula:

$$TPRp = [1+e^{(intercept)/(1-slope)}*(1-FPR/FPR)^{(1+slope)/(1-slope)}]^{-1}$$

where TRPp is the predicted value of the TP rate for a given FP rate (FPR), the intercepts represents intercept of the regression line in the (S, D) space, and slope is the slope of this line.

Chapter 11

Is there any reason to withhold beta-blockers from high-risk patients with coronary artery disease?

Kertai MD, Bax JJ, Klein J, Poldermans D

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Is There Any Reason To Withhold β Blockers from High-risk Patients with Coronary Artery Disease during Surgery?

IN this issue of the Journal, London *et al.*[1] summarize the physiologic foundations and clinical controversies of perioperative β blockers in patients undergoing noncardiac surgery. The presented data provide solid evidence for their efficacy and support a more widespread use for the reduction of perioperative mortality in patients with known or suspected coronary artery disease (CAD), particularly those with diabetes, left ventricular hypertrophy, and renal insufficiency. However, despite their beneficial effects, oddly enough it seems that some physicians are more afraid of the side effects of β blockers than the harmful effects of myocardial ischemia; β blockers are currently underused in the perioperative setting.

How often are β blockers underused? In a recent study, Schmidt *et al.*[2] showed that in 158 patients undergoing major noncardiac surgery, of the 67 who were eligible to receive perioperative β blockers only 25 (37%) received β-blocker therapy. Similar results were shown in a survey of Canadian anesthesiologists.[3] This study revealed that 93% of anesthesiologists agreed that β-blockers were beneficial in patients with known CAD, but only 57% reported β-blocker use in these patients, and only 34% of these regular users continued taking β-blockers beyond the early postoperative period.[3]

What may be the reason for withholding β blockers? The several potential factors preventing more widespread use of β blockers during the perioperative period include (1) β blockers may not be effective enough in reducing perioperative cardiac events, (2) limited experience with respect to timing and dosing of perioperative β blockers, (3) contraindications to β blockers, and (4) availability of effective alternative cardioprotective treatment strategies. These factors are discussed below.

1. β blockers are effective in reducing perioperative cardiac events. A rupture of a coronary atherosclerotic plaque is implicated in about half of perioperative myocardial infarctions, resulting in platelet aggregation and thrombus formation. However, the location of perioperative myocardial infarction is not always related to the location of the culprit coronary lesion. In two separate studies,[4,5] histopathologic analyses of coronary arteries and myocardium revealed that predicting the site of infarction based on severity of underlying stenosis would have been unsuccessful in a majority of the patients. This may indicate the presence of CAD in numerous locations throughout the coronary tree and the possibility that perioperative myocardial infarction may result from plaque rupture and thrombosis at the site of a hemodynamically (in)-significant atherosclerotic plaque. In addition to acute plaque rupture and thrombosis, prolonged myocardial ischemia due to a supply–demand mismatch has been suggested as another mechanism for major cardiac complications. Patients undergoing noncardiac surgery with known CAD or those at risk may have an incidence of perioperative myocardial ischemia exceeding 40% with an associated 9- to 16-fold increased risk for cardiac death and myocardial infarction.[6,7] During prolonged myocardial ischemia, elevated levels of cardiac troponins can be detected verifying structural myocardial damage. Elevated levels of cardiac troponins are confirmed to have prognostic information for perioperative and long-term cardiac complications.[8,9] In a recent study, we demonstrated that asymptomatic perioperative myocardial damage, indicated by cardiac troponin elevations without angina pectoris or new electrocardiographic changes, resulted in a more than 2-fold increase in risk of all-cause mortality during a median follow-up of 4 yr (personal communication, Don Poldermans, M.D., Professor, Department of Vascular Surgery, Erasmus Medical Center, Rotterdam, The Netherlands, August 2003).

β blockers may play a substantial role in the prevention of perioperative cardiac complications. Apart from their direct hemodynamic effect, such as reduction in heart rate and contractility, β blockers may also indirectly influence the determinants of shear stress and reduce inflammation through decreases in sympathetic tone.[10] Reduction in heart rate and pulse pressure by β blockers are also considered important in stabilizing the

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vulnerable plaques. As a result of these properties of β blockers, the intensity of myocardial ischemia is reduced and the extent of myocardial infarction can be decreased. Several studies have demonstrated the clinical efficacy of perioperative β-blocker use to decrease cardiac complications in patients with risk factors or those with known CAD who are undergoing noncardiac surgery. Mangano *et al.*[11] randomly assigned 200 patients to receive atenolol or placebo before the induction of anesthesia, immediately after surgery, and daily throughout their hospital stay. There was no difference in the incidence of perioperative myocardial infarction or cardiac-related death. During long-term follow-up, the mortality was 10% in patients who had been previously given atenolol and 21% in the controls. A more recent study of Poldermans *et al.*[12] randomized patients to bisoprolol an average of 30 days preoperatively with dose adjustment to achieve a resting heart rate of 60 beats per minute or less, and patients continued to receive β blockers for an average of 2 yr. The results of these studies, combined with previous investigations, show a protective effect of β blockers for perioperative myocardial ischemia and support the hypothesis that perioperative β-blocker use can substantially reduce cardiac risk among high-risk patients undergoing noncardiac surgery.

2. Timing, hemodynamic targets, and duration of perioperative β-blocker use. Currently, there is no consensus about the optimal timing of institution of perioperative β blockers, duration of therapy after surgery, or hemodynamic targets. On the basis of our own experience, treatment with perioperative β blockers should start as soon as the eligibility of a high-risk patient for surgery is confirmed. If possible, this should occur days or weeks before surgery with dose adjustment to achieve a resting heart rate of 60 beats per minute or less.[12] London *et al.*[1] clearly state that provision of perioperative β blockade may allow better assessment of tolerance to therapy and perhaps might take advantage of "cellular-level" effects of β blockade, but these advantages are strictly speculative. Adjusting treatment to resting heart rate alone may not be an adequate measure of β blockade, which could be most accurately assessed by response to exercise or adrenergic challenge. In that respect, in patients at intermediate- or high-risk who are already receiving β blockers, additional noninvasive testing as part of the routine preoperative risk assessment with dobutamine stress echocardiography could be useful in facilitating additional titration of β blockers in relation to the heart rate at which myocardial ischemia is induced. A few studies are available to derive recommendations for the duration of β-blocker use. Mangano *et al.*[11] demonstrated that patients receiving perioperative β blockers experienced fewer cardiac events throughout the 2-year study period than those in the placebo group. Poldermans *et al.*[13] showed that a selective β1 blocker bisoprolol reduced cardiac death and myocardial infarction in high-risk patients for as long as 2 yr after successful major vascular surgery.

3. Adverse effects of perioperative β blockers. Contraindications such as the presence of severe left ventricular dysfunction, exacerbation of reactive airway disease, insulin-dependent diabetes, or worsening of symptoms of peripheral vascular disease may be important reasons to withhold β blockers. Despite these "classic" contraindications, several investigators have demonstrated that perioperative and long-term administration of β blockers was well tolerated with no substantial increase of adverse effects, despite that many of these patients were known to have CAD, pulmonary disease, diabetes mellitus, and intermittent claudication.[11–16] The use of cardio-selective β blockers, such as bisoprolol or metoprolol, given their lower potential for adverse effects at routine clinical doses, may further encourage physicians to use these agents in patients with relative contraindication to β blockers. The potential absolute contraindication to β blockers, such as major atrioventricular nodal conduction disease in the absence of a pacemaker, severe asthma, or a strong reactive airway disease, may preclude patients from tolerating β blockers. In such situations, α2 agonists or less invasive anesthetic and surgical techniques should be considered.

4. Alternative cardioprotective treatment strategies. Prophylactic coronary revascularization prior to surgery could be an attractive alternative approach for the management of CAD in patients who have been identified as having increased risk for cardiac complications. This may not only improve perioperative outcome, but it would also result in better long-term survival after surgery. No prospective, randomized trials have addressed the effectiveness of coronary bypass grafting (CABG) for reducing the incidence of perioperative cardiac complications.[17,18] The findings of retrospective studies suggest that, when indicated, CABG might reduce the risk of cardiac complications. However, one should consider that the combined risks of CABG and noncardiac surgery might exceed the risk of noncardiac surgery alone. A possible less invasive alternative to preoperative CABG would be percutaneous transluminal coronary angioplasty with coronary stenting, provided that a delay of surgery of at least 6 weeks is acceptable. In two recent studies it was shown that patients treated with percutaneous transluminal coronary angioplasty and coronary stenting were at high risk for perioperative mortality, stent thrombosis, or bleeding complications.[19,20] The frequency of these events was higher among patients undergoing surgery within 6 weeks of stent placement. Until randomized trials become available, it is recommended to follow the American College of Cardiology/American Heart Association guidelines and to perform CABG or percutaneous transluminal coronary angioplasty if they are indicated independently of the need for noncardiac surgery.

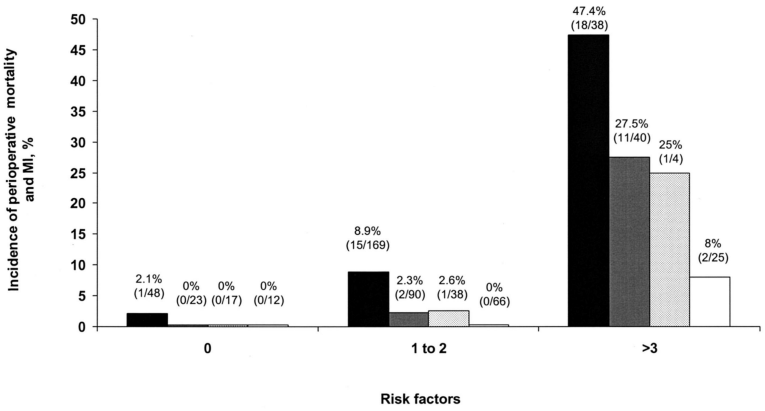

Fig. 1. Incidence of perioperative mortality and myocardial infarction (MI) in 570 patients undergoing abdominal aortic aneurysm surgery. *Filled bars* = no medication use; *gray bars* = β blocker use only; *dotted bars* = statin use only; *open bars* = combination of β-blocker and statin use. Results are based on the number of clinical risk factors (age > 70 yr, current angina, previous MI, heart failure, previous cerebrovascular event, diabetes mellitus, renal insufficiency and pulmonary disease) and on statin and β-blocker use.

Recently, data have been reported about the cardioprotective effect of lipid-lowering medications, such as hepatic hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) (fig. 1). Poldermans *et al.*[21] demonstrated that statin use was associated with a more than 4-fold reduction of perioperative mortality in patients undergoing vascular surgery.

Recommendations: The findings of these studies and the work of London *et al.*[1] reveal that despite that perioperative β blockers have proved beneficial in high-risk patients, they are still underused and enhancing β-blocker use should be a priority. Practice guidelines of the American College of Cardiology/American Heart Association and the American College of Physicians may provide one possible approach for improving the use of perioperative β blockers in patients with known CAD or those at risk who are undergoing major noncardiac surgery. According to these guidelines and previous clinical studies, β blockers should be prescribed to all patients with one or more risk factors correlated with higher risk of cardiac complications. Cardioselective β blockers such as bisoprolol or metoprolol should be started days to weeks before a planned surgical procedure, aiming at a resting heart rate of 60 beats per minute. During surgery, additional intravenous β-blocker therapy can be administrated, whereas after surgery in patients with multiple risk factors for CAD, β blockers should be continued to reduce long-term cardiac complications.

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Chapter 12

Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery

Poldermans D, Bax JJ, Kertai MD, Krenning B, Westerhout CM, Schinkel AFL, Thomson IR, Lansberg PJ, Fleisher LA, Klein J, van Urk H, Roelandt JRTC, Boersma E

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Statins Are Associated With a Reduced Incidence of Perioperative Mortality in Patients Undergoing Major Noncardiac Vascular Surgery

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Background—Patients undergoing major vascular surgery are at increased risk of perioperative mortality due to underlying coronary artery disease. Inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A (statins) may reduce perioperative mortality through the improvement of lipid profile, but also through the stabilization of coronary plaques on the vascular wall.

Methods and Results—To evaluate the association between statin use and perioperative mortality, we performed a case-controlled study among the 2816 patients who underwent major vascular surgery from 1991 to 2000 at the Erasmus Medical Center. Case subjects were all 160 (5.8%) patients who died during the hospital stay after surgery. From the remaining patients, 2 controls were selected for each case and were stratified according to calendar year and type of surgery. For cases and controls, information was obtained regarding statin use before surgery, the presence of cardiac risk factors, and the use of other cardiovascular medication. A vascular complication during the perioperative phase was the primary cause of death in 104 (65%) case subjects. Statin therapy was significantly less common in cases than in controls (8% versus 25%; $P<0.001$). The adjusted odds ratio for perioperative mortality among statin users as compared with nonusers was 0.22 (95% confidence interval 0.10 to 0.47). Similar results were obtained in subgroups of patients according to the use of cardiovascular therapy and the presence of cardiac risk factors.

Conclusion—This case-controlled study provides evidence that statin use reduces perioperative mortality in patients undergoing major vascular surgery. **(*Circulation*. 2003;107:1848-1851.)**

Key Words: statins ■ mortality ■ vasculature ■ surgery

Patients undergoing major vascular surgery experience a 30-day operative mortality of 5% to 6%, which arises principally from cardiac events.[1] Myocardial infarction is the most frequent fatal complication. Although the understanding of the pathophysiology is not entirely clear, there is evidence that coronary plaque rupture, which leads to thrombus formation and subsequent vessel occlusion, is the dominant causative mechanism behind such complications, similar to myocardial infarctions occurring in the nonoperative setting.[2] Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (statins) may have a beneficial influence because of a direct effect on the vascular function, which results in coronary plaque stabilization.[3] The current study aimed to examine the association between statin therapy and perioperative mortality in patients undergoing major vascular surgery.

Methods

Study Design

We undertook a retrospective case-controlled study among the population of 2816 patients above the age of 15 years who underwent major vascular surgery between January 1, 1991, and December 31, 2000, in the Erasmus Medical Center, Rotterdam, the Netherlands. The computerized hospital information system was used to identify cases and controls. This system holds demographic data of all admitted patients and information on the perioperative course.

Selection of Cases and Controls

Case subjects were all 160 patients (5.8%) from this population who died because of any cause during surgery or during the hospital stay after surgery, excluding those patients who died after 30 days of continuous hospital stay. From the remaining patients, 2 controls were selected for each case. One control was operated on immediately before the case and one after the case, and they were stratified according to type of surgery.

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TABLE 1. Baseline Characteristics of 160 Patients Who Died During Hospital Stay After Major Vascular Surgery and 320 Controls

Characteristic	Cases (n=160)	Controls (n=320)	*P* Value
Age, y	72 (66 to 77)	69 (62 to 5)	<0.001
Male gender, n (%)	126 (79)	267 (83)	0.21
History of hypertension, n (%)	81 (51)	144 (45)	0.24
History of hypercholesterolemia, n (%)	65 (41)	149 (47)	0.22
Total cholesterol, mmol/L	6.1 (4.9 to 7.2)	5.7 (4.8 to 6.6)	0.05
Diabetes mellitus, n (%)	25 (16)	45 (14)	0.65
History of renal insufficiency, n (%)	34 (21)	37 (12)	0.005
History of angina pectoris, n (%)	55 (34)	76 (24)	0.01
History of myocardial infarction, n (%)	84 (53)	109 (34)	<0.001
History of heart failure, n (%)	44 (28)	35 (11)	<0.001
History of stroke, n (%)	35 (22)	29 (9)	<0.001
Type of surgery, n (%)			1.0
Acute abdominal aortic repair	60 (38)	120 (38)	
Elective abdominal aortic repair	76 (48)	152 (48)	
Carotid endarterectomy	7 (4)	14 (4)	
Lower extremity revascularization	17 (11)	34 (11)	

Data Collection

For all cases and controls, the computerized hospital database, patient medical records, nurses reports, surgical reports, and discharge letters were manually screened to identify cardiac risk factors, and information on the duration of statin therapy, and β-blocker use, and aspirin use before surgery. The most recent measurements of total cholesterol and low-density lipoprotein (LDL) cholesterol within 3 months of surgery were recorded. Patients were labeled as having raised cholesterol if the total cholesterol exceeded 5.5 mmol/L or the LDL-cholesterol exceeded 3.5 mmol/L.

Statistical Analysis

Unconditional logistic regression analyses were applied to evaluate the relation between statin use and perioperative mortality. Stratified analyses were performed according to a number of clinically important baseline characteristics. To reveal a possible heterogeneity in odds ratios between subgroups of patients, interaction terms between the stratification characteristic and statin use were included in the models. Interaction was considered statistically significant at the classic 0.05 probability level. We adjusted for the stratification factors calendar year and type of surgery, and for a number of potential confounding factors, including age, gender, history of cardiovascular or cerebrovascular disease, and cardiovascular therapy. Individual factors were omitted from the regression models when stratification made adjustment inappropriate. We only report the adjusted odds ratios and corresponding 95% confidence intervals.

Results

Baseline clinical characteristics of cases and controls are presented in Table 1. A vascular complication during the perioperative phase was the primary cause of death in 104 (65%) case subjects; 88 (56%) had a fatal myocardial infarction, and 14 (9%) had a fatal stroke. The most common nonvascular causes of death were bleeding complications (21 cases [13%]) and sepsis (30 cases [19%]).

Statin use was significantly less common in cases than in controls (12 cases [8%] and 81 controls [25%]; $P<0.001$). The risk of perioperative mortality among statin users was reduced 4.5 times compared with nonusers (adjusted odds ratio 0.22 and 95% confidence interval 0.10 to 0.47). This variation in statin use was accompanied by a difference in the level of total cholesterol before surgery, which was higher in cases than in controls (the median values and interquartile ranges were 6.1 [4.9 to 7.2] and 5.7 [4.8 to 6.6] mmol/L, respectively), although statistical significance was not reached ($P=0.052$). A similar difference was observed among statin users in cases and controls (6.3 [5.5 to 6.8] and 5.7 [4.9 to 6.7] mmol/L; $P=0.15$). In addition, among statin users, the duration of statin therapy was apparently shorter in cases (median and interquartile range 4 [1 to 14] months) than in controls (11 [4 to 22] months), although statistical significance was not reached ($P=0.054$). Among 21 patients with a fatal bleeding complication, there was no relation to statin use (19 non-statin users [13%] versus 2 statin users [17%]; $P=0.67$).

There was no evidence of a heterogeneity in the mortality reduction among statin users as compared with nonusers between subgroups of patients according to clinically important baseline characteristics or type of surgery, with the exception of age; perioperative mortality reduction by statins was stronger in patients below the age of 70 years as compared with the elderly (Table 2).

Aspirin was more frequently used in cases than in controls (51 cases [32%] and 73 controls [23%]; $P=0.003$). However, it should be taken into account that, according to the Erasmus Medical Center surgical protocol, aspirin was discontinued 10 days before elective major vascular surgery. Additionally, aspirin use was associated with a high prevalence of cardiovascular disease, including myocardial infarction and stroke. After adjustment for these differences, aspirin use was no longer associated with an increased risk of perioperative mortality. Importantly, there was no interaction between the use of statins and (previous) aspirin use with regard to perioperative mortality (Table 2).

TABLE 2. Odds Ratios for Perioperative Mortality After Major Vascular Surgery in Relation to Statin Therapy in Subgroups of Patients

	Cases		Controls			
Characteristic	N	Statin Use, n (%)	N	Statin Use, n (%)	Odds Ratio (95% CI)*	Interaction†
Age						0.03
<70 years	64	3 (5)	172	57 (33)	0.09 (0.02 to 0.36)	
≥70 years	96	9 (9)	148	24 (16)	0.27 (0.09 to 0.76)	
Gender						0.27
Male	126	7 (6)	267	69 (26)	0.15 (0.06 to 0.39)	
Female	34	5 (15)	53	12 (27)	0.35 (0.07 to 1.7)	
Diabetes mellitus						0.23
No	135	11 (8)*	275	67 (24)	0.24 (0.11 to 0.56)	
Yes	25	1 (4)	45	14 (31)	0.26 (0.03 to 2.8)	
Myocardial infarction						0.66
No	76	4 (5)	210	41 (20)	0.19 (0.06 to 0.64)	
Yes	84	8 (10)	109	40 (37)	0.25 (0.09–0.71)	
Heart failure						0.06
No	116	11 (9)	285	96 (24)	0.32 (0.14 to 0.72)	
Yes	44	1 (2)	35	12 (34)	0.02 (0.00 to 0.29)	
No. of risk factors‡						
0 or 1	41	2 (5)	177	43 (24)	0.15 (0.03 to 0.65)	0.83
2	41	3 (7)	79	21 (27)	0.19 (0.05 to 0.80)	
3 or more	78	7 (9)	64	17 (27)	0.24 (0.09 to 0.68)	
β-blocker use						
No	129	7 (5)	206	43 (21)	0.18 (0.07 to 0.46)	0.33
Yes	31	5 (16)	114	38 (33)	0.30 (0.07 to 1.4)	
Aspirin use						0.41
No	109	8 (7)	247	54 (22)	0.28 (0.13 to 0.62)	
Yes	51	4 (8)	73	27 (37)	0.15 (0.05 to 0.45)	

CI indicates confidence interval.

*Odds ratios were adjusted for age, gender, hypertension, diabetes mellitus, renal failure, angina pectoris, myocardial infarction, heart failure, stroke, β-blocker use, and aspirin use, as appropriate.

†*P* value of the interaction term between the stratification characteristic and statin use in the multivariable logistic regression model.

‡Age >70 years, myocardial infarction, angina pectoris, heart failure, renal failure, and stroke.

β-blocker therapy was less common in cases than in controls (31 cases [19%] and 114 controls [36%]; $P<0.001$), and the risk of perioperative mortality among β-blocker users was 2.3 times reduced compared with nonusers (adjusted odds ratio 0.43 and 95% confidence interval 0.26 to 0.72). There was no significant interaction between the use of statins and β-blockers with regard to perioperative mortality, which implies that both agents have an additional effect (Table 2). These findings were similar in several strata according to the number of cardiac risk factors.

Discussion

In this case-controlled study we found that statin use reduced perioperative mortality in patients undergoing major vascular surgery. As compared with nonusers, patients on statin therapy had a more than 4-fold reduced risk. This result was consistent in subgroups of patients according to the type of surgery, cardiac risk factors, and cardiovascular therapy, including aspirin and β-blockers.

Patients with peripheral vascular disease often have extensive coronary artery disease, characterized by the presence of asymptomatic but vulnerable atherosclerotic plaques, which may rupture because of the stress of surgery.[1] The progression of these plaques during surgery is not predictable by the current imaging techniques.[4,5] Therefore, a systemic medical therapy for plaque stability is an attractive option. Statins may provide such systemic effect because of the antiinflammatory action and the reversal of endothelial dysfunction.[3] All these factors may induce a shift from pro-thrombosis and vasospasm to more stable thrombo-resistant conditions and vasodilation, thereby reducing perioperative myocardial ischemia.

Aspirin has shown benefits in patients with established coronary artery disease. In the present study, no such benefit was observed. In fact, aspirin use was associated with an increased mortality risk. However, it should be noted that aspirin was discontinued at least 10 days before elective surgery, and aspirin users had a higher prevalence of cardiac

risk factors. Importantly for our study, there was no interaction between the beneficial effects of statins and aspirin use (Table 2).

Besides the beneficial effect of statins, our data confirmed the cardioprotective effect of β-blockers. Furthermore, the effect of statins on perioperative mortality was similar in β-blocker users and nonusers. Indeed, β-blockers may particularly influence the myocardial supply/demand mismatch, whereas statins may mainly affect the coronary plaque stabilization. Nevertheless, it should be realized that interactions between these drugs might exist that are simply missed because of lack of statistical power. A difference was observed in mortality reduction among younger patients and those with a history of heart failure. A large prospective randomized study showed no difference in the effect of statins in these subgroups on late cardiovascular events in patients with or at risk for coronary artery disease, and showed a beneficial effect in patients with peripheral vascular disease with low or normal cholesterol levels.[6] Therefore, future investigations should be considered to evaluate this issues in more detail.

Among statin users, the duration of therapy was apparently shorter in cases than in controls. This observation is in accordance with evidence from large prospective studies, in which the beneficial effects of statins on cardiovascular events usually appear after long-term treatment.[7] Nonetheless, the possibility of a beneficial effect after a short period of statin treatment should not be excluded.[8]

Our study has several limitations that are common with any study relying on retrospective data collection. Most importantly, information on statin use might have been missed, and probably differently so in cases and controls because of observer bias. Our estimate of the beneficial effect of statin therapy may therefore be overoptimistic. Thus, although our results indicate a strong reduction of perioperative mortality by statins, this early evidence needs confirmation through a series of large-scale, randomized clinical trials.

Conclusion

Preoperative statin therapy is associated with a reduction of perioperative mortality. Although the possible mechanisms of the effect of statins remain unclear, further investigation of early treatment with statins in this population is strongly recommended.

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Chapter 13

A combination of statins and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery

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Abstract

Objective: To investigate the combined beneficial effect of statin and beta-blocker use on perioperative mortality and myocardial infarction (MI) in patients undergoing abdominal aortic aneurysm surgery (AAA).

Background: Patients undergoing elective AAA-surgery identified by clinical risk factors and dobutamine stress echocardiography as being at high-risk often have considerable cardiac complication rate despite the use of beta-blockers.

Methods: We studied 570 patients (mean age 69±9 years, 486 males) who underwent AAA-surgery between 1991-2001 at the Erasmus MC. Patients were evaluated for clinical risk factors (age≥70 years, histories of MI, angina, diabetes mellitus, stroke, renal failure, heart failure and pulmonary disease), dobutamine stress echocardiography, statin and beta-blocker use. The main outcome was a composite of perioperative mortality and MI within 30 days of surgery.

Results: Perioperative mortality or MI occurred in 51 (8.9%) patients. The incidence of the composite endpoint was significantly lower in statin users compared to nonusers (3.7% vs. 11.0%; crude odds ratio [OR]: 0.31, 95% confidence interval [CI]: 0.13-0.74; p=0.01). After correcting for other covariates, the association between statin use and reduced incidence of the composite endpoint remained unchanged (OR: 0.24, 95% CI: 0.10-0.70; p=0.01). Beta-blocker use was also associated with a significant reduction in the composite endpoint (OR: 0.24, 95% CI: 0.11-0.54). Patients using a combination of statins and beta-blockers appeared to be at lower risk for the composite endpoint across multiple cardiac risk strata; particularly patients with 3 or more risk factors experienced significantly lower perioperative events.

Conclusions: A combination of statin and beta-blocker use in patients with AAA-surgery is associated with a reduced incidence of perioperative mortality and nonfatal MI particularly in patients at the highest risk.

Introduction

Despite recent advances in perioperative care the 30-day mortality of elective abdominal aortic aneurysm (AAA) surgery still varies between 2.7% and 5.5% in selected series, up to 9% in population based studies (1, 2). In fact, cardiac related morbidity and mortality are one of the most frequently observed perioperative complications (3, 4). Thirty-six percent of patients undergoing AAA-surgery have severe coronary artery disease (CAD), whereas only 6% have normal coronary arteries (5, 6). Clinical risk assessment tools (7-9) have been successful risk stratifying patients, and thereby identifying those at particular benefit from beta-blockers (10, 11). However, not all patients are equally protected by beta-blocker therapy. Patients identified by clinical risk factors and dobutamine stress echocardiography as being at high-risk often have a considerable cardiac complication rate despite the use of beta-blockers (12). Thus, additional treatment options are necessary to improve perioperative prognosis in high-risk patients undergoing major vascular surgery.

Almost half of fatal postoperative myocardial infarction (MI) cases can be associated with coronary plaque rupture (13). The distribution of postoperative MIs, however, is not necessarily the same as hemodynamically critical coronary artery lesions (14). This may indicate the presence of CAD in numerous locations throughout the coronary tree, and the possibility that perioperative MI may result from plaque rupture and thrombosis at the site of a haemodynamically insignificant but unstable atherosclerotic plaque(s) (13). Lipid lowering therapy with HMG-Co-A reductase inhibitors (statins) has been shown to be beneficial in the primary and secondary prevention of cardiovascular disease, and the role of statins for the reduction of mortality and morbidity from CAD in patients at increased risk or with known CAD has also been established (15-17). In addition to being potent LDL-lowering agents, statins may also attenuate plaque inflammation and influence plaque stability (18). These so called pleiotropic effects of statins can improve endothelial function and coagulation, and hence stabilize unstable atherosclerotic plaque(s) (19-21). We have previously shown that patients who underwent major vascular surgery and were statin users had a reduced risk of perioperative mortality as compared to nonusers (22). However, little is known about the combined effect of statin and beta-blocker use for the prevention of perioperative cardiac complications in different risk group categories. Thus the aim of the current study was to investigate

the relationship between the combined therapy of statin and beta-blocker use and perioperative complications across different cardiac risk categories in patients undergoing elective AAA-surgery.

Methods

Patients and study design

The Erasmus Medical Center (MC) is an academic hospital in Rotterdam, the Netherlands, which acts as a tertiary referral center for approximately 30 affiliated hospitals. Between January 1991 and December 2001, a total of 75,581 patients over 18 years of age underwent 108,613 noncardiac surgical procedures at the Erasmus MC. Each surgical technique performed was classified by treating physicians according to a standardized national coding system that was developed in co-operation with the National Health Service and medical insurance companies. The type of surgery, demographic data, medical history, and information on the perioperative course of each patient was then systematically uploaded to an electronic database maintained by the Medical Information Department; via this database 570 patients were identified who underwent elective open infrarenal abdominal aortic surgery.

Data collection and definition of risk factors

Along with clinical information, we also reviewed medical files and discharge letters for additional information on clinical risk factors, chronic cardiac medication use, intraoperative and perioperative hospital course, and cause and type of perioperative complications. Potential clinical determinants of perioperative mortality and MI were advanced age (>70 years), gender, current stable or prior angina pectoris, prior MI on the basis of medical history or a finding of pathologic Q waves on the electrocardiography, compensated congestive heart failure or a history of heart failure, renal dysfunction (serum creatinine >2 mg/dL [180 μmol/L]), current oral or insulin treatment for diabetes mellitus, a history of prior cerebrovascular accident including transient ischemic attack, hypertension, chronic pulmonary disease (forced expiratory volume in 1 s $\leq$75% of normal adjusted for age and gender) and smoking (23, 24). The average of two fasting levels of total cholesterol, LDL and HDL cholesterol levels were also included if they were measured three months prior to abdominal aortic surgery. Patients were defined as having elevated cholesterol levels

if total serum cholesterol level exceeded 212.7 mg/dL (5.5 mmol/L) or the LDL cholesterol level was higher than 135.3 mg/dL (3.5 mmol/L). In addition, data from the preoperative dobutamine stress echocardiography (DSE) were also collected if available. DSE was performed as previously described (3), and a positive test result for dobutamine stress echocardiography was considered if new wall-motion abnormalities occurred. In addition, the year of operation was also included given the influence of advances in perioperative care and surgical techniques.

Chronic medication use

According to routine procedure at Erasmus MC, patients visited the outpatient clinic at least three months prior to the planned major vascular surgery, and all patients were also screened for medication use in conjunction their medical history. During the study period additional cardiac medications including beta-blockers or statins were prescribed at the discretion of the attending physicians. Patients continued taking their cardiac medication also on the day of surgery, and oral medication use was resumed on day 1 after surgery. Based on institutional guidelines aspirin use was discontinued at least 10 days before elective AAA-surgery. Two investigators (JK, DP), blinded to the patients' perioperative outcome, reviewed medical records for medication use including aspirin, ACE-inhibitor, beta-blocker and statin use. Chronic medication use was ascertained if medication use was documented at least one to three months prior to hospital admission for surgery.

Definition of perioperative events

As part of the routine postoperative management all patients were screened for cardiac enzyme elevations (creatine-kinase [CK], creatine-kinase MB [CK-MB], cardiac troponin T), and 12-lead electrocardiogram was made after major vascular surgery. Perioperative events were defined as a composite of all-cause mortality and MI occurring before discharge or within 30 days after surgery, whichever came first. The cause of perioperative death was retrieved from hospital records or autopsy results. MI was diagnosed according to our institutional laboratory protocol as a serum CK level of more than 190 U/L, and a CK-MB activity above 24 IU/L, or the CK-MB activity fraction exceeding 6% of total CK, or from 1996 as cardiac troponin T $\geq$0.1 ng/mL, and by new Q waves $\geq$1mm or >30 ms.

Statistical analysis

Continuous variables were described as mean value ± SD, and categorical variables as percent frequencies. Differences between patient subgroups were evaluated by using the t-test or chi-square test, as appropriate. The number of perioperative events in the study was relatively limited. Therefore, to avoid overfitting and to enable assessment of the relation between clinical risk factors and the composite of all-cause mortality and nonfatal MI, we used the Revised Cardiac Risk Index developed by Lee et al (9). Since the decision to prescribe statin or beta-blocker therapy was not randomized, adjustments were made for baseline characteristics that may have influenced the decision to use either medication. Separate propensity scores were constructed using multiple logistic regression analyses. Baseline clinical characteristics that had an independent association with the decision to prescribe statins or beta-blockers (P=0.25) were included in the multivariable propensity score. Univariable logistic regression analyses were performed to study the relation between statin, beta-blockers, baseline clinical characteristics and the composite endpoint.

Multivariable logistic regression analysis was also performed to study the association of statins and beta-blockers with the composite endpoint, with adjustments for baseline clinical characteristics and the two propensity scores. The discriminatory power of the multivariable regression model was quantified by the c-index, which is identical to the area under the receiver operating characteristic curve; the c-index ranges from 0.5 (not predictive at all) to 1.0 (optimal performance). The performance of the multivariate regression model was further assessed with Hosmer-Lemeshow goodness-of-fit test (25). Finally, to reveal a possible heterogeneity between statin or beta-blocker use and baseline clinical characteristics interaction terms were included in the models. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) are reported. All analyses were performed using SPSS statistical software (SPSS Inc., Chicago, Illinois, version 11.0).

Results

Patient characteristics

Patient characteristics according to statin use are described in Table 1. Statin users were more often younger, women, and had a higher body mass index than nonusers. Furthermore, statin users had a higher prevalence of cardiovascular disease; a higher prevalence of renal dysfunction, more often underwent prior coronary revascularization, and had a lower prevalence of chronic pulmonary disease. There were no significant differences in total cholesterol, LDL- and HDL-cholesterol levels between statin users compared to nonusers. Statin users more frequently used concomitant cardiac medications compared to statin nonusers. Of the 570 patients, 340 also underwent DSE one to three months prior to surgery. Patients who were statin users more often had a positive dobutamine stress echocardiography compared to nonusers. In 162 patients who were statin users the most frequently prescribed statins were simvastatin (71.6%), atorvastatin (14.8%), pravastatin (8.6%), cerivastatin (3.7%) and fluvastatin (1.2%), respectively. Perioperative mortality or MI occurred in 51 (8.9%) patients. Among these, there were 24 (47%) cardiovascular complications: 18 cardiac deaths, 4 nonfatal MIs and stroke in 2 patients. The most common non-vascular causes of death were septic complications (10 patients), respiratory insufficiency (9 patients) and intestinal necrosis (8 patients). Autopsy was performed in 28 (55%) patients. In patients who died and underwent postmortem examination the cause of death was more often classified as cardiac death (50%) than in patients who died but did not undergo autopsy (21%).

Table 1. Characteristics of the population

Characteristics	Patients who used statins*, N=162, (%)	Patients who did not use statins, N=408, (%)	P-value†
Demographics			
Age, years	65.1±8.9	70.5±8.6	<0.001
Age≥70 years	61 (38)	258 (63)	<0.001
Male sex	126 (78)	360 (88)	0.002
Clinical variables			
Body mass index, kg/m^2	25.8±3.5	24.7±2.8	0.002
Current smoker	49 (32)	130 (34)	0.7
Blood pressure, mm Hg			
Systolic	146.7±20.3	146.2±19.6	0.8
Diastolic	85.2±10.4	86.0±11.0	0.5
Cholesterol, mmol/L (mg/dL)			
Total	5.6±1.2 (216±46.4)	5.7±1.1 (220.4±42.5)	0.9
LDL	3.8±1.1 (146.9±42.5)	3.8±0.6 (146.9±23.2)	0.8
HDL	1.1±0.5 (42.5±19.3)	1.1±0.3 (42.5±11.6)	0.8
Medical history			
Current stable or history of angina pectoris	47 (29)	67 (16)	0.001
Previous myocardial infarction	61 (38)	78 (19)	<0.001
Congestive heart failure	8 (5)	11 (3)	0.2
Diabetes mellitus	14 (9)	22 (5)	0.2
Prior cerebrovascular accident	21 (13)	64 (16)	0.4
Renal insufficiency	16 (10)	15 (4)	0.007
Pulmonary disease	27 (17)	124 (30)	0.001
Hypertension	77 (47)	200 (49)	0.8
‡Prior coronary revascularization	24 (15)	23 (6)	0.001

Table 1. Characteristics of the population [cont]

Characteristics	Patients who used statins*, N=162, (%)	Patients who did not use statins, N=408, (%)	P-value†
Chronic cardiac medication			
ACE inhibitors	69 (43)	113 (28)	0.001
Aspirin	57 (36)	72 (18)	<0.001
Beta-blockers	103 (64)	153 (38)	<0.001
Dobutamine stress echocardiography			0.03
New wall motion abnormalities	32 (20)	49 (12)	
No new wall motion abnormalities	75 (46)	184 (45)	
No test performed	55 (34)	175 (43)	

*All data are presented as number (percentage) unless otherwise indicated; LDL, low-density lipoprotein; HDL, high-density lipoprotein; For definition of risk factors see “Methods” section; †Chi-square test

‡It is a combination of prior coronary bypass graft surgery and percutaneous transluminal coronary angioplasty (only one procedure performed in each group)

Univariable analyses

A history of chronic pulmonary disease was the most important determinant of the composite endpoint (Table 2). Patients with a history of chronic pulmonary disease had an almost 5-fold increased risk of perioperative adverse events compared to patients without such history. Other significant univariable predictors of the composite endpoint were prior cerebrovascular accident, renal dysfunction, advanced age ($\geq$70 years) and previous MI. A positive DSE result was also a significant univariable predictor of perioperative events. Patients with a new wall-motion abnormality during DSE had a significantly higher rate of perioperative mortality or nonfatal MI than patients without stress induced myocardial ischemia (17.3% versus 7.3%; P<0.001). Although there was a positive trend for improved perioperative outcome in patients who underwent previous coronary revascularization this association was not statistically significant (Table 2). There was no significant association between the year of operation and the composite endpoint (crude OR, 1.0, 95% CI, 0.9-1.1). In further univariable analyses, patients using statins or beta-blockers were at a significantly lower risk of perioperative adverse events compared to patients not using either of these medications. Compared with nonusers, patients who were using statins had a three-fold reduced risk- and patients using beta-blockers had a two-fold lower risk of the composite endpoint. There was a trend for aspirin and ACE inhibitors to reduce the incidence of perioperative events, however this association was not statistically significant.

Table 2. Univariable relation between clinical characteristics and perioperative mortality or myocardial infarction (N=570)

Variables*	No. of Patients	Perioperative Mortality or Myocardial infarction, No. (%)	Odds Ratio (95% Confidence Interval)	X^2 Test	P-value
	Demographics				
Age, y					
≥70	319	38 (11.9)	2.5 (1.3-4.7)	7.4	0.007
<70	251	13 (5.2)	1		
Gender					
Men	486	42 (8.6)	0.78 (0.36-1.68)	0.4	0.5
Women	84	9 (10.7)	1		
	Medical history				
Current stable or history of angina pectoris					
Yes	114	14 (12.3)	1.6 (0.8-3.0)	8.1	0.2
No	456	37 (8.1)	1		
Previous myocardial infarction					
Yes	139	20 (14.4)	2.2 (1.2-3.9)	6.4	0.01
No	431	31 (7.2)	1		
Congestive heart failure					
Yes	19	4 (21.1)	2.9 (0.9-9.0)	3.3	0.07
No	551	47 (8.5)	1		

Table 2. Univariable relation between clinical characteristics and perioperative mortality or myocardial infarction (N=570), [cont]

Variables*	No. of Patients	Perioperative Mortality or Myocardial infarction, No. (%)	Odds Ratio (95% Confidence Interval)	X^2 Test	P-value
Diabetes mellitus					
Yes	36	6 (16.7)	2.2 (0.9-5.5)	2.7	0.1
No	534	45 (8.4)	1		
Prior cerebrovascular accident					
Yes	85	20 (23.5)	4.5 (2.4-8.4)	22.7	<0.001
No	485	31 (6.4)	1		
Renal insufficiency					
Yes	31	8 (25.8)	4.0 (1.7-9.5)	10.0	0.002
No	539	43 (7.9)	1		
Pulmonary disease					
Yes	151	30 (19.8)	4.7 (2.6-8.5)	26.1	<0.001
No	419	21 (5.0)	1		
Prior coronary revascularization†					
Yes	47	3 (6.4)	0.7 (0.2-2.3)	0.4	0.5
No	523	47 (9.0)	1		
Dobutamine stress echocardiography					
New wall motion abnormalities	81	14 (17.3)	2.5 (1.2-5.2)	5.5	0.02
No new wall motion abnormalities	259	19 (7.3)	0.9 (0.5-1.8)	0.04	0.8
No dobutamine stress echocardiography	230	18 (7.8)	1		

Table 2. Univariable relation between clinical characteristics and perioperative mortality or myocardial infarction (N=570), [cont]

Variables*	No. of Patients	Perioperative Mortality or Myocardial infarction, No. (%)	Odds Ratio (95% Confidence Interval)	X^2 Test	P-value
		Chronic cardiac medication			
Statins					
Yes	162	6 (3.7)	0.31 (0.13-0.74)	7.0	0.01
No	408	45 (11.0)	1		
Beta-blockers					
Yes	256	15 (5.8)	0.48 (0.26-0.90)	5.2	0.02
No	314	36 (11.4)	1		
Aspirin					
Yes	129	9 (6.9)	0.73 (0.34-1.55)	0.7	0.4
No	431	40 (9.2)	1		
ACE inhibitors					
Yes	182	15 (8.2)	0.88 (0.47-1.67)	0.1	0.7
No	380	35 (9.2)	1		

*For definition of risk factors see “Methods” section; †It is a combination of prior coronary bypass graft surgery and percutaneous transluminal coronary angioplasty (only one procedure performed in each group)

Propensity to prescribe statins or beta-blockers

The propensity score for statin use showed that patients were more likely to be prescribed statins if they were younger, had a history of CAD or renal dysfunction, or had elevated total cholesterol levels (Table 3). The propensity score for beta-blocker use showed that beta-blockers were more often used if patients were younger, or had a history of CAD, but were used less often in those with chronic pulmonary disease (Table 3).

Effect of statin use according to the Revised Cardiac Risk Index

Among the 246 patients with a risk score of one, there was one perioperative event observed in the 17.5% of patients using statins and four events (2%) in the remaining 203 patients (p=0.8). In the 242 patients with a risk score of two, 36% were using statins. One perioperative event (1.1%) occurred in this group, whereas 24 (15.5%) events were observed in patients not using statins (p<0.001). Finally, in the 82 patients with a risk score of 3 or more, 39% were statin users, and of those 12.5% had perioperative mortality or MI, while the event rate was 34% in those not using statins (p=0.02). There was no evidence of a differential effect of statin use in these subgroups of patients (P-value for interaction=0.96).

Additional beneficial effect of statin use according to beta-blocker use

Among 103 patients receiving a combination of beta-blockers and statins only two (1.9%) perioperative events occurred compared to 13 (8.5%) perioperative events in 153 patients using only beta-blockers (OR, 0.21, 95% CI, 0.05-0.96). In the 314 patients who were beta-blocker nonusers, 18.7% were using statins. Four (6.8%) perioperative events occurred in this group, whereas approximately 50% more events occurred in patients who were nonusers (OR, 0.51, 95% CI, 0.17-1.50). Test for heterogeneity revealed no evidence for a differential effect of statin use in these patient categories (P-value for interaction=0.36).

Table 3. Odds ratios for propensity scores associated with prescription of statin or beta-blocker use

*Characteristics**	*Statin use*			**ß-blocker use**		
	Regression coefficient	**Odds Ratio (95% CI)**	**P-value**	**Regression coefficient**	**Odds Ratio (95% CI)**	*P-value*
Age	-0.07	0.93 (0.91-0.96)	<0.001	-0.07	0.98 (0.96-1.01)	0.1
Male sex	-0.79	0.45 (0.26-0.78)	0.005	-0.40	0.67 (0.41-1.11)	0.12
Current stable or history of angina pectoris	0.91	2.50 (1.52-4.10)	<0.001	0.99	2.70 (1.73-4.22)	<0.001
Previous myocardial infarction	1.14	3.12 (1.96-4.96)	<0.001	1.16	3.18 (2.09-4.83)	<0.001
Congestive heart failure	0.08	1.08 (0.35-3.38)	0.88	0.23	1.25 (0.46-3.46)	0.66
Diabetes mellitus	0.62	1.86 (0.86-3.90)	0.11	…	…	…
Prior cerebrovascular accident	…	…	…	0.52	1.68 (1.03-2.76)	0.04
Renal dysfunction	1.03	2.80 (1.25-6.24)	0.01	0.54	1.73 (0.80-3.77)	0.17
Chronic pulmonary disease	-0.78	0.46 (0.27-0.78)	0.004	-0.49	0.61 (0.41-0.96)	0.02
Elevated total cholesterol	1.14	3.12 (2.04-4.78)	<0.001	…	…	…

*Characteristics that had an independent relationship with the decision to prescribe statins or ß-blockers at p=0.25, and were included the multivariable logistic regression model to form the propensity score; CI, confidence interval; Ellipses indicate variables that did not reach a p=025 level to be included in the multivariable logistic regression models

Multivariable analyses

Patients with advanced age (≥70 years) and with a history of pulmonary disease remained at an elevated risk for perioperative mortality and nonfatal MI after an adjustment for the Revised Cardiac Risk Index (Table 4). One point increase in the Revised Cardiac Risk index was also significantly associated with adverse perioperative outcomes. Finally, the association between statins, beta-blockers and the composite endpoint remained statistically significant. Both, statin and beta-blocker use were associated with 4-fold reduction in perioperative mortality and nonfatal myocardial infarction. In a separate model, a trend for aspirin and ACE-inhibitors to reduce the likelihood for perioperative mortality and MI was revealed but these associations were not statistically significant. The combination of the Revised Cardiac Risk Index, statin and beta-blocker use with the corresponding propensity scores had excellent discriminatory power and good fit (c-index, 0.86; overall goodness-of-fit Hosmer-Lemeshow test; X^2 =2.9, p=0.93).

Table 4. Multivariable relation between clinical characteristics, statin and beta-blocker use and perioperative mortality or myocardial infarction

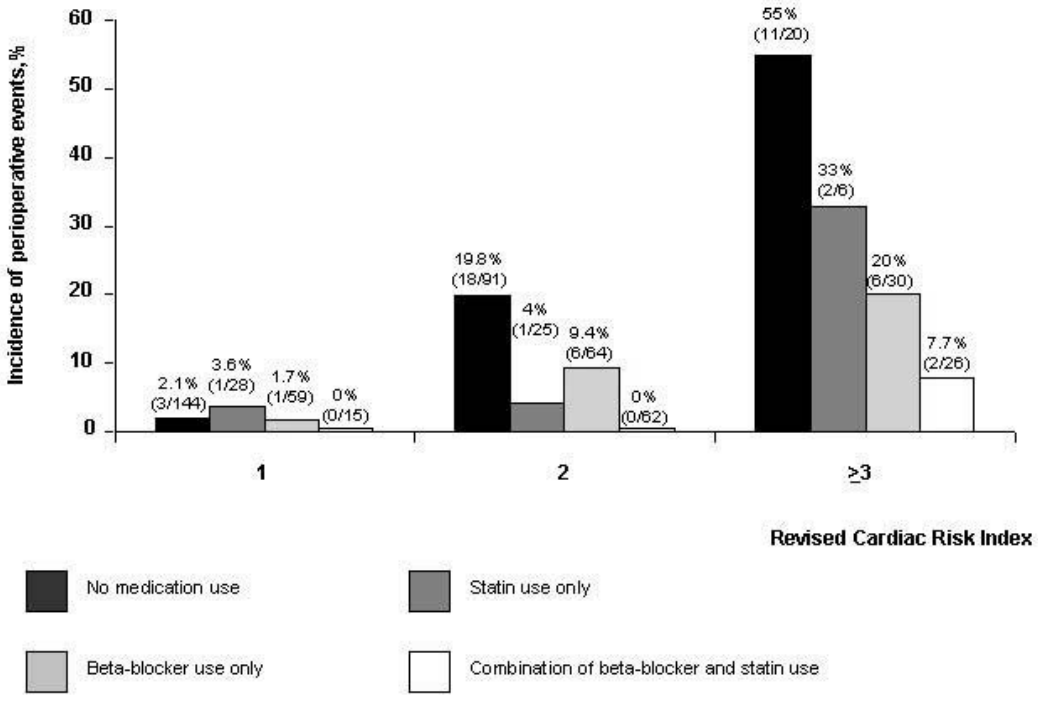
Variables	Odds Ratios (95% Confidence Interval)	X^2 Test	P-value
Age > 70 years	3.0 (1.23-7.30)	5.8	0.02
Chronic pulmonary disease	5.57 (2.60-12.0)	19.3	<0.001
Revised Cardiac Risk Index*			
One point increase	3.52 (2.10-6.03)	21.1	<0.001
Beta-blocker use	0.24 (0.11-0.54)	11.7	0.001
Propensity score for beta-blocker use	3.51 (0.13-92.78)	0.6	0.5
Statin use	0.24 (0.10-0.70)	6.8	0.01
Propensity score for statin use	5.17 (0.34-79.10)	1.4	0.2

*To compose the Revised Cardiac Risk Index 1 point is assigned to each of the following characteristics: high-risk type of surgery, known ischemic heart disease (history of myocardial infarction, positive dobutamine stress echocardiography, history of angina pectoris), history of heart failure, history of cerebrovascular disease, diabetes mellitus, and preoperative serum creatinine level > 2.0 mg/dL.

Combined effect of statins and beta-blockers according to the Revised Cardiac Risk Index

Based on the number of clinical risk scores, a combination of statin and beta-blocker use the incidence of the composite endpoint was calculated (Figure 1). Patients with a risk score of 1 had a low event rate, with those receiving combine therapy tending to experience the lowest event rates (p=ns). Although not statistically significant, a similar relationship was observed in patients with a risk score of 2. However, in patients at highest risk (risk score of 3 or more) a significant descending gradation of risk was revealed with those on combined therapy experiencing only 7.7% perioperative event rates.

Figure 1. Incidence of perioperative mortality and myocardial infarction.



Results are based on the number of clinical risk factors by the Revised Cardiac Risk Index (ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes, preoperative serum creatinine > 2mg/dL), statin and beta-blocker use.

Discussion

The current study showed that clinical risk factors and DSE data aggregated in the Revised Cardiac Risk index were significant predictors of perioperative mortality and nonfatal MI. In addition patients who were statin users had a four-fold reduced risk of perioperative events. Although, statin users had a different clinical risk profile than nonusers, this association remained after adjustment for these differences. Furthermore, our findings also suggest the benefit of combined therapy with statins and beta-blockers especially in patients at the highest risk as defined by the Revised Cardiac Risk Index.

Clinical predictors of adverse perioperative outcome for patients with abdominal aortic surgery have been well documented and clearly identify a history of CAD, renal dysfunction and pulmonary comorbidity as having prognostic significance in these patients (23, 24, 26). Still, cardiac complications such as cardiac death and nonfatal MI are the most frequently observed perioperative adverse events in these patients. Among patients in whom postmortem examination was performed in the present study, the cause of death was more often classified as cardiac than in patients who died but did not undergo autopsy (50% vs. 21%). This suggests that the incidence and impact of cardiac complications after abdominal aortic surgery could be underestimated in clinical practice. There is growing evidence, which points to an association between the presence of an abdominal aortic aneurysm, and atherosclerosis (27, 28), which may well explain the observed high proportion of adverse events due to cardiovascular causes. While favorable actions of statins on atherosclerosis and vascular properties have mainly been attributed to cholesterol lowering (19-21, 29-32), statins may also attenuate coronary artery plaque inflammation, influence plaque stability in addition to antithrombogenic, antiproliferative and leukocyte-adhesion inhibiting effects (19-21, 33). All these properties of statins may stabilize unstable coronary plaques, and thereby reducing myocardial ischemia and subsequent myocardial damage.

Consistent with previous studies, an association between beta-blocker use and reduced perioperative events was observed (10, 11). Despite that beta-blocker users were more often statin users, there was no evidence of differential beneficial effect of statin use on beta-blocker therapy. Thus, statin use appears to be independently associated with a reduced incidence of perioperative mortality and MI even in the presence of beta-blockers. Beta-blockers apart form their direct

hemodynamic effect such as reduction in heart rate and contractility may also indirectly influence the determinants of shear stress and reduce inflammation through decreases in sympathetic tone (34). These properties of beta-blockers may reinforce the effect of statins on vulnerable plaques.

To date, there are few studies that have evaluated the effect of statin use on the reduction of perioperative and short-term cardiovascular complications in patients undergoing vascular surgery (35, 36). In a preliminary study by Durazzo et al., a marked reduction of adverse cardiovascular events among vascular surgery patients who were randomly assigned to atorvastatin compared with placebo was reported (35). The study showed that short-term (within six months) treatment with atorvastatin significantly reduced the incidence of cardiovascular events after vascular surgery (atorvastatin vs. placebo, 8.3% vs. 26.0%). Landesberg et al (36) also found that patients who underwent major vascular surgery and were using lipid-lowering therapy had a tendency for better event-free survival rates. In our previous case-control study, we found that statin users had a nearly five-fold reduction of in-hospital mortality as compared to nonusers (22). The current study builds upon these earlier findings by highlighting the combined beneficial effect of statin and beta-blocker use for the reduction not only of perioperative mortality but also nonfatal MI in a large cohort of patients undergoing elective AAA-surgery. Secondly, the Revised Cardiac Risk Index was also applied to adjust for important clinical risk factors. Finally, we used propensity scores and multivariable modeling to adjust for potential confounders. Beta-blockers may offer protection in patients at low- to intermediate risk but their effect appears to be marginal in patients at the highest risk (12). In this context, statins appear to have additional beneficial effect for the prevention of perioperative mortality and nonfatal MI.

This study has certain limitations, which should be considered when interpreting the results. Statin users had more often a history of CAD and renal dysfunction, and as a result of that, were more often prescribed other cardiac medications or underwent previous coronary revascularization prior to the elective AAA-surgery. It is possible, therefore that statin users would have also been more likely to receive better medical attention during the perioperative period. Moreover, the incidence of perioperative mortality was relatively higher than reported from other studies (2.7% to 5.5%) (23). This may question the generalizability of our findings. However, it is important to note that patients in this study were operated in a tertiary

referral center, and studies that reported lower mortality rates usually implied strict inclusion criteria and selected patients at low risk for perioperative complications (23). Finally, given the retrospective nature of our study it was not possible to ascertain unless it was clearly stated in the medical records whether treatment with statins was discontinued throughout the perioperative period or discontinued during hospitalization. This could be particularly relevant since current American Heart Association Clinical Advisory Statement on statin safety suggests the discontinuation of statin treatment during major surgery or critical illness (37). Conversely a recent study has suggested that discontinuation of statins may be associated with adverse outcomes in hospitalized patients (38).

Conclusions

This study revealed that a combination of statin and beta-blocker use in patients undergoing AAA-surgery is associated not only with a reduced incidence of perioperative mortality but also nonfatal MI, particularly in patients at the highest risk for perioperative complications. This early evidence of the beneficial effect of statin use particularly in combination with beta-blocker use should be confirmed in future large-scale clinical trials.

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Chapter 14

Optimizing long-term cardiac management after major vascular surgery. *Role of beta-blocker therapy, clinical characteristics, and dobutamine stress echocardiography to optimize long-term cardiac management after major vascular surgery*

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ORIGINAL INVESTIGATION

Optimizing Long-term Cardiac Management After Major Vascular Surgery

Role of β-Blocker Therapy, Clinical Characteristics, and Dobutamine Stress Echocardiography to Optimize Long-term Cardiac Management After Major Vascular Surgery

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Background: Survivors of major vascular surgery are at increased risk of late cardiac complications.

Objective: To examine the cardioprotective effect of β-blockers.

Methods: A follow-up study was conducted in 1286 patients who survived surgery for at least 30 days. Patients were screened for cardiac risk factors and dobutamine stress echocardiography (DSE) results; 1034 patients (80%) underwent preoperative DSE, and 370 (29%) received β-blockers. The main outcome measure was late cardiac death or myocardial infarction.

Results: Seventy-four patients (5.8%) had late cardiac events. Cardiac event rates in patients with 0, 1 to 2, and 3 or more risk factors were 1.6%, 4.7%, and 19.2%, respectively. In patients without risk factors, β-blockers were associated with improved event-free survival (2.8% vs 0%), and DSE had no additional prognostic value. In patients with 1 to 2 risk factors, the presence of ischemia during DSE increased cardiac events from 3.9% to 9.8%. However, if patients with ischemia were treated with β-blockers, the risk decreased to 7.2%. In patients with 3 or more risk factors, DSE and β-blockers stratified patients into intermediate- and high-risk groups. In patients without ischemia, β-blockers reduced the cardiac event rate from 15.1% to 9.5%, whereas the cardioprotective effect was limited in patients with 3 or more risk factors and positive DSE findings.

Conclusions: Long-term β-blocker use is associated with a reduction in the cardiac event rate, except for patients with 3 or more risk factors and positive findings on DSE.

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AFTER MAJOR vascular surgery, patients are at increased risk of cardiac complications during short- and long-term follow-up. Although the incidence of perioperative cardiac death and myocardial infarction (MI) after elective surgery has decreased gradually during the past decades, 30-day operative mortality (5%-6%) and 5-year mortality (45%), both of which arise principally from cardiac causes,[1] remain high. The frequency of late postoperative cardiac morbidity reflects the high prevalence of underlying coronary artery disease (CAD) in this population. To date, the optimal approach to the diagnosis and long-term management of CAD, which is often stable or asymptomatic in these patients, is unclear.

Dobutamine stress echocardiography (DSE) is a useful tool for the diagnosis of CAD, and it is valuable in the assessment of perioperative and late cardiac risk in patients scheduled for major vascular surgery.[2,3] Of the long-term prognostic features of DSE, the most important are poor left ventricular function at rest and the extent of stress-induced ischemia.[4] Preoperative identification of high-risk patients using DSE may initiate strategies to reduce the incidence of late cardiac events in patients who have successfully undergone major vascular surgery. Interventions such as perioperative and long-term use of a β-blocker medication and myocardial revascularization may be applied.

In the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) study, we[2] showed that perioperative β-blocker use was associated with a reduced incidence of perioperative cardiac complications in a large cohort of vascular surgery patients. The present study builds on these results by examining the relation of clinical characteristics, DSE results, β-blocker use, and the incidence of long-term cardiac events in the survivors of the same cohort.

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A complete listing of the DECREASE Study Group members was published previously (N Engl J Med. *1999;341:1789-1794).*
The authors have no relevant financial interest in this article.

METHODS

STUDY PROTOCOL

Between January 1, 1996, and December 31, 1999, we prospectively screened all patients undergoing elective abdominal aortic or infrainguinal arterial reconstruction at 8 participating medical centers. The hospital ethics committee at each center approved the study protocol, and all of the patients gave written informed consent. A total of 1351 consecutive patients were screened for the following cardiac risk factors: age older than 70 years, current or previous angina pectoris, previous MI, compensated or previous congestive heart failure (CHF), current treatment for diabetes mellitus, previous cerebrovascular events, and renal failure (serum creatinine level >2.0 mg/dL [>180 μmol/L]). Any patient with 1 or more risk factors or a reduced exercise capacity underwent DSE. Overall, DSE prior to surgery was performed in 1097 patients (81%). Stress-induced ischemia was present in 199 patients (18%). Initially, β-blockers were administered to 360 patients (27%). Two hundred forty-eight patients (18%) underwent abdominal aortic aneurysm repair, 640 (47%) underwent aortofemoral reconstruction, and 463 (34%) underwent infrainguinal procedures. A total of 1299 patients (96%) survived after surgery for at least 30 days; 1286 successfully completed follow-up.

LONG-TERM ADMINISTRATION OF β-BLOCKERS

Of the 360 patients who were taking a β-blocker medication at the time of surgery, 301 were treated with long-term β-blockers and 59 were randomized to receive β-blockers within the framework of the DECREASE study.[5] Follow-up data were successfully obtained for 346 patients (8 patients died during the postoperative period and 6 were loss to follow-up). During long-term follow-up, β-blockers were administered to an additional 24 patients as a result of CAD-related symptoms. Thus, the total number of patients using β-blockers during long-term follow-up was 370. Continuous administration of β-blockers required that the resting heart rate was 50 to 70/min and that systolic blood pressure was 100 mm Hg or greater. Patients were reassessed at each visit, and the β-blocker dose was adjusted according to heart rate and systolic blood pressure. All of the patients visited the outpatient clinic every 3 months, and at each visit a questionnaire was filled with reference to the use, type, and dose of β-blockers.

DOBUTAMINE STRESS ECHOCARDIOGRAPHY

Dobutamine stress echocardiography was performed as previously described.[6] The left ventricle was divided into 16 segments, and wall motion was scored on a 5-point ordinal scale (1 indicates normal wall motion; 2, mild hypokinesis; 3, severe hypokinesis; 4, akinesis; and 5, dyskinesis). For each patient, a wall-motion score index was calculated at rest and during peak stress based on the standard 16-segment model. The results of DSE were considered positive if new wall-motion abnormalities occurred (ie, if wall motion in any segments worsened by ≥1 grades during the test, except for akinesia becoming dyskinesia).

FOLLOW-UP STUDY

In December 1999, a follow-up study was performed of all patients who survived after surgery for at least 30 days. Study end points were defined as a composite of cardiac death and MI. Hospital records and death certificates were used to ascertain the cause of death, which was considered cardiac if death was directly attributable to MI, CHF, or ventricular arrhythmia in the absence of any other precipitating factor or if death was sudden and unexpected. Myocardial infarction was defined by a serum creatine kinase level greater than 110 U/L, with a myoglobin isoenzyme fraction greater than 10%, and a finding of new Q waves lasting more than 30 milliseconds on the 12-lead electrocardiogram. The occurrence of death (any cause), stroke, and new or progressive angina pectoris was also noted.

STATISTICAL ANALYSIS

Descriptive statistics such as the frequency and percentage of categorical variables are provided, as are the mean and SD of continuous variables. The Kaplan-Meier method was applied to evaluate the prognostic importance of the extent of stress-induced ischemia and β-blocker use with respect to cardiac event–free survival. Differences among survival curves were compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression models were applied to evaluate the relations among a few baseline clinical characteristics, DSE results, β-blocker therapy, and the composite end points. All of the variables were entered into the multivariable stage, irrespective of the significance level in univariable analysis. Multivariable models were constructed by backward deletion of the least significant characteristics. In the final model, variables that reached $P<.15$ were retained. The additional and additive prognostic values of DSE results and β-blocker therapy were analyzed using further regression analyses. We specifically evaluated the interaction between β-blocker therapy and DSE results. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported. All analyses were performed using statistical software (SPSS; SPSS Inc, Chicago, Ill).

RESULTS

PATIENT CHARACTERISTICS

Characteristics of the 1286 patients who survived for at least 30 days after surgery and completed follow-up are described in **Table 1**. Patients receiving β-blockers during long-term follow-up had a clinical risk profile that was worse than that of patients not taking such medications: patients taking β-blockers had higher rates of angina pectoris (34% vs 10%), previous MI (58% vs 26%), and CHF (7% vs 4%). There was no relationship between the type of surgery and the use of β-blocker medication.

FOLLOW-UP

Follow-up data were successfully obtained in 1286 patients (95%) at a median of 23 months (25th-75th percentile, 14-33 months). Seventy-four patients (5.8%) experienced cardiac death (n=58) or nonfatal MI (n=16) during follow-up. Among 14 patients who experienced a nonfatal perioperative MI, 3 late cardiac deaths occurred during follow-up. Twenty-seven patients had a stroke, and there were 39 noncardiac deaths (3.0%). The cause of noncardiac death was cancer in 16 patients, respiratory insufficiency in 10, sepsis secondary to infected prosthetic grafts in 7, and other causes in 9. In addition, 12 patients (0.9%) had late coronary revascularization because of progression of angina pectoris. Of these 12 patients, 3 (25%) underwent the revascularization within 30 days of major vascular surgery. The distribution of all revascularization in patients with 0, 1 to 2, and 3 or more risk factors was 0.3%, 1.1%, and 1.7%, respectively.

UNIVARIABLE ANALYSES

In univariable analyses, a history of CHF was most important determinant of adverse cardiac outcome among selected clinical variables (**Table 2**). Patients with a CHF history (4.7% of total study population) had an almost 5-fold increased risk of late cardiac death or MI compared with those without such a history. Other important univariable determinants of late cardiac complications were a history of MI, current or previous angina pectoris, advanced age, and renal failure. There was no relationship between the type of surgery and long-term cardiac complications.

In univariable analysis, patients using β-blockers were at slightly higher risk of late cardiac complications, but this association was not significant (HR, 1.1; 95% CI, 0.7-1.8; $P=.56$). Among the 252 patients who did not undergo DSE, no late cardiac complications occurred in the 24 patients using β-blockers, whereas there were 3 events (1.3%) in the remaining patients. In the 840 patients without stress-induced ischemia during DSE, 197 were using β-blockers. Nine late cardiac complications (4.6%) occurred in this group vs 32 (5.0%) in those not using β-blockers. Finally, in the 194 patients with stress-induced ischemia, 148 used β-blockers; 15 using β-blockers (10.1%) had late cardiac events vs 15 (32.6%) not using β-blockers.

A positive test result during DSE was a significant predictor of late cardiac complications (**Table 3**). Patients without stress-induced ischemia had a significantly lower rate of late cardiac death or MI than patients with stress-induced ischemia during DSE (4.9% vs 15.5%; $P<.001$). In addition, the extent of stress-induced ischemia also provided important prognostic information, as the event rate ranged from 11.5% in those with stress-induced ischemia in 1 to 2 segments to 18.7% in patients with stress-induced ischemia in 3 or more segments. Event-free survival curves for patients without testing, for those with negative stress test results, and for those with mild (1-2 segments) or extensive (≥3 segments) ischemia during stress are presented in **Figure 1**.

Table 1. Characteristics of the 1286 Patients Who Survived for at Least 30 Days After Major Vascular Surgery

Characteristic	Patients, No. (%) β-Blockers (n = 370)	Patients, No. (%) No β-Blockers (n = 916)	*P* Value*
Age >70 y	153 (41)	390 (43)	.68
Male sex	283 (77)	714 (78)	.57
Current or stable angina pectoris	127 (34)	89 (10)	<.001
Previous myocardial infarction	216 (58)	234 (26)	<.001
Congestive heart failure	27 (7)	33 (4)	<.01
Diabetes mellitus	58 (16)	118 (13)	.23
Previous cerebrovascular accident	40 (11)	66 (7)	.04
Renal failure	19 (5)	29 (3)	.11
Type of surgery			
Infrainguinal reconstruction	126 (34)	314 (34)	.82
Abdominal aortic aneurysm repair	65 (18)	148 (16)	
Aortofemoral reconstruction	179 (48)	454 (50)	

*Fisher exact test, 2-sided.

Table 2. Univariable Relation Between Clinical Baseline Characteristics and Long-term Cardiac Death or Myocardial Infarction

Variable	Patients, No. (n = 1286)*	Events, No. (%) (n = 74)†	Hazard Ratio (95% Confidence Interval)	χ^2 Test	*P* Value
Age >70 y					
Yes	543	47 (8.7)	2.4 (1.5-3.8)	13.0	<.001
No	743	27 (3.6)	1.0		
Current or stable angina pectoris					
Yes	216	29 (13.4)	2.6 (1.7-4.2)	16.3	<.001
No	1050	45 (4.3)	1.0		
Previous myocardial infarction					
Yes	450	48 (11.0)	3.3 (2.1-5.4)	23.7	<.001
No	822	25 (3.0)	1.0		
Congestive heart failure					
Yes	60	13 (22.0)	4.7 (2.6-8.6)	26.0	<.001
No	1201	61 (5.1)	1.0		
Diabetes mellitus					
Yes	176	15 (8.5)	1.7 (0.9-3.0)	3.0	.08
No	1093	59 (5.4)	1.0		
Previous cerebrovascular accident					
Yes	106	9 (8.5)	1.5 (0.8-3.1)	1.4	.23
No	1155	65 (5.6)	1.0		
Renal failure					
Yes	48	8 (16.7)	3.6 (1.7-7.4)	11.6	.001
No	1222	66 (5.4)	1.0		
Type of surgery					
Infrainguinal reconstruction	440	31 (7.0)	1.4 (0.9-2.4)	2.3	.13
Abdominal aortic aneurysm repair	213	13 (6.1)	1.4 (0.7-2.6)	1.0	.31
Aortofemoral reconstruction	633	30 (4.7)	1.0		

*Numbers may not sum to 1286 owing to missing data.
†A composite of cardiac death and myocardial infarction. Numbers may not sum to 74 owing to missing data.

Table 3. Univariable Relation Between Dobutamine Stress Echocardiography Results and Long-term Cardiac Death or Myocardial Infarction

Variable	Patients, No. (n = 1034)	Events, No. (%), (n = 71)*	Hazard Ratio (95% Confidence Interval)	χ^2 Test	*P* Value
Dobutamine stress echocardiography					
No new wall-motion abnormalities	840	41 (4.9)	1.0		
New wall-motion abnormalities	194	30 (15.5)	3.8 (2.4-6.2)	31.1	<.001
Segments with new wall-motion abnormalities, No.					
0	840	41 (4.9)	1.0		
1-2	87	10 (11.5)	2.7 (1.3-5.3)	7.7	.005
≥3	107	20 (18.7)	5.0 (2.8-8.5)	33.8	<.001

*A composite of cardiac death and myocardial infarction.

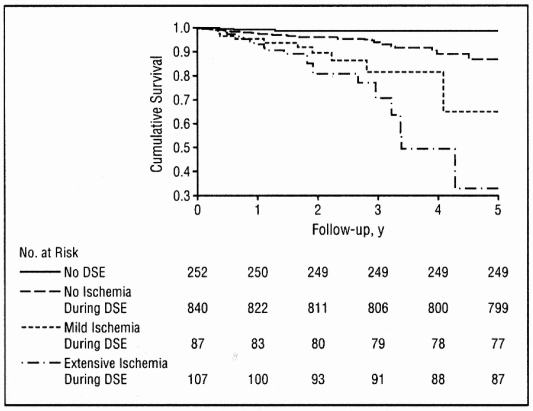

Figure 1. Kaplan-Meier survival curves for the prediction of late cardiac complications for patients without dobutamine stress echocardiography (DSE), for those with a negative test result, and for those with mild or extensive stress-induced ischemia.

MULTIVARIABLE ANALYSES

In multivariable analysis, advanced age, a history of MI, a history of CHF, and angina pectoris remained significant predictors of late cardiac complications (**Table 4**). After correcting for differences in clinical characteristics, patients who used β-blockers were at lower risk of cardiac death or MI than patients who did not use β-blockers, but this association was not significant (adjusted HR, 0.7; 95% CI, 0.4-1.2; *P*=.18).

When clinical data were combined with DSE results, advanced age, previous MI, and CHF retained their predictive power with respect to late cardiac death and MI, but angina pectoris lost most of its predictive value (Table 4). The presence or absence of stress-induced ischemia during DSE was the most important determinant of late cardiac outcome. In association with clinical data and DSE results, β-blocker use was associated with a significantly reduced risk of late cardiac complications (adjusted HR, 0.3; 95% CI, 0.2-0.6; *P*<.001). We also repeated the same analysis with respect to a composite end point of all-cause mortality and MI. In this analysis, the association among clinical data, DSE results, and β-blocker use showed that β-blockers still retained their significant protective effect (adjusted HR, 0.5; 95% CI, 0.3-0.8; *P*=.009).

Table 4. Multivariable Model to Predict Perioperative Cardiac Death or Myocardial Infarction

Variable	Hazard Ratio (95% CI)	χ^2 Test	*P* Value
Clinical Characteristics Only			
Age >70 y			
Yes	2.2 (1.4-3.5)	10.3	.001
No	1.0		
Current or stable angina pectoris			
Yes	1.8 (1.1-2.9)	5.0	.03
No	1.0		
Previous myocardial infarction			
Yes	2.4 (1.4-4.0)	11.1	.001
No	1.0		
Congestive heart failure			
Yes	2.8 (1.5-5.3)	10.0	.002
No	1.0		
Combination of Clinical Characteristics and Results of DSE			
Age >70 y			
Yes	2.6 (1.5-4.3)	13.2	<.001
No	1.0		
Previous myocardial infarction			
Yes	2.2 (1.3-3.8)	8.9	.001
No	1.0		
Congestive heart failure			
Yes	3.1 (1.6-5.8)	12.4	<.001
No	1.0		
New wall-motion abnormalities			
Yes	3.3 (2.0-5.5)	22.4	<.001
No	1.0		

Abbreviations: CI, confidence interval; DSE, dobutamine stress echocardiography.

RISK CLASSIFICATION MODEL

Based on the number of cardiac risk factors, DSE results, and β-blocker use, a previously developed simple scheme was applied to estimate the risk of late cardiac complications (**Figure 2**). A clinical risk score was determined based on patient age and clinical history. In patients without risk factors, β-blocker use was associated with improved event-free survival, 2.8% (4/145) vs 0% (0/34), and DSE had no additional prognostic value. In patients with 1 to 2 risk factors, the presence of ischemia during DSE increased cardiac events from 3.9% (22/565) to 9.8% (12/122). However, if patients with ischemia were treated with β-blockers, the risk decreased to 7.2% (7/97). In patients with 3 or more risk factors, DSE results and β-blocker use stratified pa-

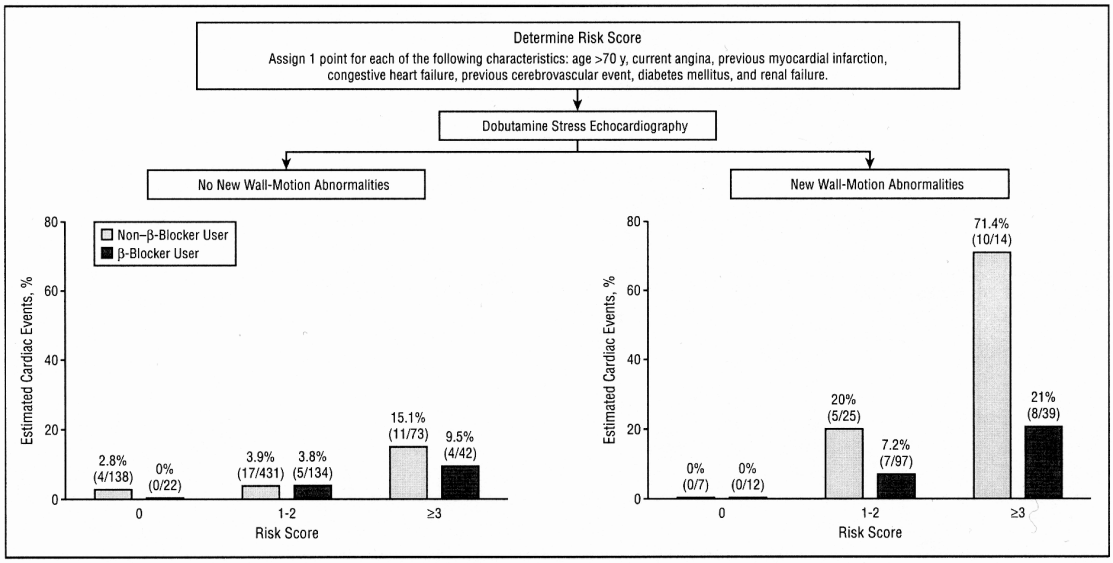

Figure 2. Risk of cardiac death and myocardial infarction during long-term follow-up as observed in subpopulations.

tients into intermediate- and high-risk groups. In patients without ischemia, β-blocker therapy reduced the cardiac event rate from 15.1% (11/73) to 9.5% (4/42). However, patients with 3 or more risk factors and ischemia were at considerable risk despite β-blocker use (20.5% [8/39]).

COMMENT

The present analysis of 1286 patients who underwent major vascular surgery demonstrates that advanced age, current or stable angina pectoris, previous MI, and CHF were the most important clinical determinants of late cardiac death and nonfatal MI. In addition to clinical data, DSE results were predictive of long-term adverse cardiac outcomes. In univariable analyses, there was no significant association between β-blocker use and late cardiac complications. In multivariable analyses, after correcting for clinical and test characteristics, patients with stress-induced ischemia receiving β-blockers had significantly lower risk compared with those not receiving β-blockers. The cardioprotective effect of β-blocker therapy depended on the presence of cardiac risk factors and the extent of stress-induced myocardial ischemia during DSE.

Univariable analyses showed that patients with advanced age, angina pectoris, CHF, and renal failure were more likely to have late cardiac complications than were those without such a history. In contrast, diabetes mellitus and previous cerebrovascular accident were not independent predictors of long-term cardiac complications. In multivariable analyses, advanced age, angina pectoris, and CHF remained significant predictors of cardiac death and nonfatal MI, but renal failure, diabetes mellitus, and previous cerebrovascular accident did not. These findings may reflect a changing patient population or improved long-term management, although it may also be a matter of a relatively low number of events. Despite these observations, these factors may be predictive of long-term complications. Therefore, diabetes mellitus, renal failure, and previous cerebrovascular accident were still used for the clinical risk index.

Consistent with the results of other studies,[4,7] the present DSE results were powerful predictors of long-term cardiac complications. Patients who had stress-induced myocardial ischemia were at substantial risk of late cardiac complications compared with patients who had a negative test result. In addition, the extent of stress-induced ischemia was also an independent predictor of late cardiac events. In univariable analyses, patients using β-blockers were not at significantly lower risk than those not receiving β-blockers, but after adjustment for cardiac risk factors and test characteristics, patients who took β-blockers had a 70% lower risk than nonusers. These observations may reflect the fact that patients who were at higher risk of CAD, confirmed by the presence and extent of stress-induced myocardial ischemia, benefited the most from long-term β-blocker use.

The ability of β-blockers to reduce the perioperative incidence of cardiac complications has been widely studied and confirmed by several investigators.[8-14] However, there are only 2 randomized trials evaluating the long-term cardioprotective effect of β-blockers in this group of patients. Mangano et al[8] studied 200 patients with clinical predictors of cardiac risk who underwent noncardiac surgical procedures. Patients were randomized to receive atenolol or placebo during the perioperative period. Atenolol was administered intravenously or orally beginning 2 days before and continuing for 7 days after surgery. Patients were monitored perioperatively for cardiac events and then were followed for 2 years after surgery. There was no difference in the incidence of perioperative MI or death from cardiac causes. During 2-year follow-up, patients previously treated with atenolol had significantly lower rates of all-cause mortality (9% vs 21%) and cardiac death (4% vs 12%) than those given placebo. The failure of atenolol therapy to significantly alter the perioperative outcome may be related to the low incidence of serious perioperative cardiac events in the study

population (3%). The study included patients with known CAD and those with only coronary risk factors, and patients underwent various surgical procedures. Recently, a study by Poldermans et al[15] demonstrated the cardioprotective effect of long-term administration of bisoprolol in a small-scale randomized trial: long-term bisoprolol use produced a significant, 3-fold reduction in late cardiac death and MI compared with placebo. The present study extends these findings by including a large cohort of patients who underwent successful vascular surgery and patients who continued to receive β-blockers throughout follow-up.

CLINICAL IMPLICATIONS

The optimal treatment strategy to prevent cardiac complications in high-risk patients after successful vascular surgery is controversial. In patients without cardiac risk factors or with negative DSE findings, who were at low risk of cardiac complications, β-blocker therapy had only a marginal additional protective effect. However, considering the unpredictable progression of CAD in these patients, long-term β-blocker therapy might be considered. Patients with multiple cardiac risk factors with or without mild stress-induced myocardial ischemia should receive continuous β-blocker medication to be at lower risk of long-term cardiac complications. In contrast, β-blocker therapy had a limited long-term protective effect in patients with extensive stress-induced myocardial ischemia. Coronary angiography and subsequent coronary revascularization should be considered in these patients.

Only 50% of those patients who underwent late coronary revascularization had stress-induced myocardial ischemia compared with patients without positive test results. The late revascularization was not predicted in the remaining group of patients, which can be considered as a result of the progression of CAD. Accordingly, we suggest that after successful vascular surgery, patients should undergo repetitive late cardiac testing with DSE to reevaluate the risk of late cardiac complications. Patients with multiple cardiac risk factors or a positive test result should be followed carefully, and symptoms of myocardial ischemia should be aggressively treated.

STUDY LIMITATIONS

This study has certain limitations that should be considered when interpreting the results. The risk stratification and modification scheme using a clinical risk score, DSE results, and β-blocker therapy was developed after events had occurred. In addition, only patients participating in the DECREASE study were randomized to receive perioperative and long-term β-blockers or standard care. Patients and physicians were not masked to the treatment, as continuous β-blocker use should be adjusted to the resting heart rate at outpatient visits. Therefore, the results of this study could be affected by the fact that patients treated with β-blockers received more medical attention during follow-up than did those without β-blocker use.

In conclusion, this study revealed the utility of cardiac risk factors and additional DSE testing in the long-term management of patients who underwent successful major vascular surgery. The results of the present study demonstrate that stress-induced ischemia during DSE has additional prognostic value, irrespective of the clinical risk profile. Patients receiving β-blockers had significantly lower risk than patients not receiving them. However, the cardioprotective effect of β-blockers was more likely to depend on the presence or absence of cardiac risk factors and stress-induced myocardial ischemia during DSE testing.

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Chapter 15

Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery

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Association between Long-term Statin Use and Mortality after Successful Abdominal Aortic Aneurysm Surgery

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PURPOSE: To assess the potential long-term beneficial effects of statin use after successful abdominal aortic surgery.

METHODS: Between 1991 and 2001, 570 patients underwent abdominal aortic aneurysm repair at the Erasmus Medical Center. Of the 519 patients (91%) who survived surgery beyond 30 days, 510 (98%) were followed for a median of 4.7 years (interquartile range, 2.7 to 7.3 years). These patients were evaluated for use of statins and beta-blockers, and for clinical risk factors (e.g., advanced age; prior myocardial infarction; diabetes mellitus; renal dysfunction; chronic pulmonary disease; history of heart failure, stroke, or angina), and their association with all-cause and cardiovascular mortality.

RESULTS: A total of 205 patients (40%) died during follow-up; 140 due to cardiovascular causes. The incidence of all-cause (18% [27/154] vs. 50% [178/356], $P < 0.001$) and cardiovascular (11% [17/154] vs. 34% [122/356], $P < 0.001$) mortality was significantly lower in statin users than in nonstatin users. After adjusting for clinical risk factors and beta-blocker use, the association between statin use and reduced all-cause (hazard ratio [HR] = 0.4; 95% confidence interval [CI]: 0.3 to 0.6; $P < 0.001$) and cardiovascular (HR = 0.3; 95% CI: 0.2 to 0.6; $P < 0.001$) mortality persisted. Beta-blocker use was also associated with a significant reduction in all-cause (HR = 0.6; 95% CI: 0.5 to 0.9; $P = 0.003$) and cardiovascular (HR = 0.7; 95% CI: 0.4 to 0.9; $P = 0.03$) mortality. There was no evidence of an association between statin use and all-cause and cardiovascular mortality according to beta-blocker use or clinical risk factors.

CONCLUSION: Long-term statin use is associated with reduced all-cause and cardiovascular mortality irrespective of clinical risk factors and beta-blocker use. **Am J Med. 2004;116: 96–103.** ©2004 by Excerpta Medica Inc.

After successful abdominal aortic aneurysm surgery, patients still remain at increased risk of morbidity and mortality during long-term follow-up, particularly of cardiac-related death and nonfatal myocardial infarction. Krupski et al (1) reported an incidence of 6.3% for cardiac death and myocardial infarction during a 2-year follow-up, and the United Kingdom Small Aneurysm Trial reported an incidence of 28% for death due to cardiovascular causes during a mean follow-up of 8 years (2). This high incidence of cardiac complications may reflect the more frequent prevalence of underlying coronary artery disease. Thirty-six percent of patients undergoing an abdominal aortic aneurysm repair have severe coronary artery disease and only 6% have normal coronary arteries (3).

Perioperative use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, has been shown to reduce all-cause mortality in patients undergoing major vascular surgery (4). Atorvastatin was recently shown to reduce the incidence of cardiovascular events after vascular surgery by 68% as compared with placebo (5). There is growing evidence that long-term use reduces the need for peripheral revascularization (6), as well as the likelihood of new or worsening claudication (7). Statins have also been associated with superior leg functioning in patients with lower-extremity peripheral arterial disease (8). However, the relation with the incidence of long-term cardiovascular events after abdominal aortic aneurysm surgery is not known.

We previously showed that patients who underwent major vascular surgery and used statins had a greater than fourfold reduced risk of perioperative mortality as compared with nonusers (4). The present study extends these results by examining the effects of statin use on the incidence of all-cause and long-term cardiovascular mortality in patients who had undergone successful abdominal aortic aneurysm surgery.

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METHODS

Study Design

The Medical Ethics Committee of the Erasmus Medical Center was informed about the study protocol, and per institutional practice no official approval was requested. We reviewed the medical records of all patients who had

Table 1. Baseline Characteristics of the 510 Patients

Characteristic	Statins (n = 154)	No Statins (n = 356)	*P* Value*
	Number (%), Mean ± SD, or Median (Interquartile Range)		
Age (years)	65.1 ± 8.8	70.3 ± 8.8	<0.001
<60	28 (18)	32 (9)	
60–69	70 (46)	70 (46)	
≥70	56 (36)	218 (61)	
Male sex	121 (79)	315 (89)	0.01
Clinical variables			
Body mass index (kg/m^2)	25.8 ± 3.6	24.7 ± 2.8	0.001
Current smoker	48 (31)	118 (33)	0.2
Stopped during follow-up	26 (54)	61 (52)	0.8
Blood pressure (mm Hg)			
Systolic	147 ± 21	146 ± 19	0.6
Diastolic	85 ± 11	86 ± 10	0.5
FEV_1 (L)	2.6 ± 0.8	2.0 ± 0.7	<0.001
Serum creatinine (mg/dL)†	0.97 (0.79–1.20)	0.96 (0.85–1.13)	0.8
Cholesterol (mg/dL)‡			
Total	220.4 ± 46.4	216.5 ± 42.5	0.8
LDL	150.8 ± 38.7	147.0 ± 23.2	0.9
HDL	42.5 ± 19.3	42.5 ± 11.6	0.6
Medical history			
Current or stable angina pectoris	46 (30)	53 (15)	<0.001
Previous myocardial infarction	59 (38)	71 (20)	<0.001
Heart failure	6 (4)	11 (3)	0.6
Diabetes mellitus	13 (8)	17 (5)	0.2
Prior cerebrovascular accident	18 (12)	50 (14)	0.6
Renal dysfunction	23 (15)	27 (8)	0.01
Chronic pulmonary disease	24 (16)	94 (26)	0.01
Hypertension	71 (46)	172 (48)	0.7
Other cardiac medication			
ACE inhibitors	65 (43)	100 (29)	0.003
Aspirin	55 (36)	64 (18)	<0.001
Beta-blockers	110 (71)	155 (44)	<0.001

* Fisher exact test (two-sided), independent *t* test, or Mann-Whitney test.
† To convert from mg/dL to mmol/L, multiply by 88.4.
‡ To convert from mg/dL to mmol/L, multiply by 0.02586.
ACE = angiotensin-converting enzyme; FEV_1 = forced expiratory volume in 1 second; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

undergone elective abdominal aortic aneurysm repair at the Erasmus Medical Center between January 1991 and December 2001. The hospital database was used to identify patients with the admission diagnosis of abdominal aortic aneurysm. A total of 570 patients had documented abdominal aortic aneurysm and underwent elective open surgical repair, of whom 519 (91%) survived surgery for at least 30 days. Medical files, nurses' reports, surgical records, postoperative charts, discharge letters, and records of the outpatient clinic visits were manually reviewed for information on clinical risk factors and chronic cardiac medication use. Clinical risk factors included age, sex, current or prior stable angina (9), previous myocardial infarction, heart failure, chronic pulmonary disease, renal dysfunction (serum creatinine level ≥1.5 mg/dL [133 μmol/L]), diabetes mellitus, stroke, hypertension, and smoking. Myocardial infarction was defined as a documented history of a myocardial infarction or a finding of pathologic Q waves on an electrocardiogram. Heart failure was defined as a history of symptoms or signs of pulmonary congestion, signs of left or right ventricular failure, or chest radiographic findings suggestive of heart failure. Hypertension was defined as regular use of antihypertensive medication, blood pressure >140/90 mm Hg on three separate measurements, or both. Patients were characterized as having diabetes mellitus if they were treated with insulin or oral hypoglycemic agents; had a history of diabetes mellitus and a pre-

Table 2. Causes of Death

Cause	Patients Who Died (n = 205) Number (%)
Cardiovascular	
Total	140 (68)
Myocardial infarction	46 (22)
Heart failure	28 (14)
Stroke	18 (9)
Sudden death	22 (11)
Other	26 (13)
Cancer	
Total	32 (15)
Lung	8 (4)
Other	22 (11)
Other	31 (15)
Unknown	4 (2)

operative plasma glucose level ≥200 mg/dL (11.1 mmol/L); or had a fasting plasma glucose level ≥126 mg/dL (7.0 mmol/L). Pulmonary comorbidity was considered to be present if forced expiratory volume in 1 second (FEV_1) was ≤75% of normal, adjusted for age and sex.

Prior to surgery, patients were screened for cardiovascular risk factors, including hypercholesterolemia. The results of the two fasting lipoprotein levels were averaged to produce baseline values. Patients were then treated according to Dutch National Guidelines for Treating Patient with Elevated Cholesterol Levels (10). Patients taking statins were screened regularly after surgery and statin therapy was adjusted according to these guidelines. The start of statin use was evaluated in those who were discharged without statin therapy.

Long-term Statin Use

The Erasmus Medical Center requires patients to visit the outpatient clinic at 4 weeks after successful major vascular surgery, and every 6 months thereafter. When a patient fails to attend a follow-up visit, the patient's general practitioner is contacted by telephone. At each visit, a physical examination was performed and recent medical history and medication use were noted. Patients who took statins were also screened for recent myopathy, and serum creatinine kinase and aminotransferase levels. After reviewing medical charts and outpatient clinic files for statin users and nonusers, letters were sent to general practitioners requesting information on the history of lipid-lowering treatment, when treatment was started, and whether patients continued to fill their prescriptions regularly. Of the 162 patients who were using statins at the time of surgery, follow-up data were obtained in 154 patients (6 patients died during the postoperative period and 2 were lost to follow-up) who continued using statins through the follow-up period. During follow-up, statins were prescribed in another 34 patients (10%); these patients were censored at the time of statin prescription in the time-to-event analyses.

Follow-up

In February 2003, a follow-up was performed of all patients who survived abdominal aortic aneurysm surgery for at least 30 days. Adverse cardiac and noncardiac events were noted. Information about vital status was as-

Table 3. Odd Ratios for Propensity Scores Associated with Statin or Beta-blocker Use

	Statin Use			Beta-blocker Use		
Characteristic*	Regression Coefficient	Odds Ratio (95% Confidence Interval)	*P* Value	Regression Coefficient	Odds Ratio (95% Confidence Interval)	*P* Value
Age per year increase	−0.07	0.94 (0.91–0.96)	<0.001	−0.07	0.94 (0.91–0.96)	<0.001
Male sex	−0.65	0.52 (0.30–0.92)	0.03	−0.70	0.45 (0.28–0.86)	0.01
Current or stable angina pectoris	0.98	2.68 (1.61–4.48)	<0.001	0.94	2.56 (1.56–4.20)	<0.001
Previous myocardial infarction	0.81	2.70 (1.80–4.30)	<0.001	0.96	2.61 (1.65–4.11)	<0.001
Heart failure	...	...	...	−0.40	0.67 (0.21–2.18)	0.51
Diabetes mellitus	0.58	1.80 (0.80–4.05)	0.16	0.53	1.70 (0.75–3.77)	0.20
Prior cerebrovascular accident	−0.04	0.95 (0.50–1.83)	0.90	−0.10	0.90 (0.48–1.07)	0.75
Renal dysfunction	0.93	2.52 (1.30–4.92)	0.01	0.94	2.57 (1.33–4.94)	0.005
Chronic pulmonary disease	−0.65	0.52 (0.30–0.92)	0.02	−0.57	0.56 (0.32–0.97)	0.04
Elevated total cholesterol	1.04	2.82 (1.83–4.36)	<0.001	...	...	...

* Characteristics that had an independent relation with the decision to prescribe statins or beta-blockers at $P = 0.25$ were included in the multivariate logistic regression model to form the propensity score.
Ellipses indicate that variables did not reach a *P* value of 0.25 to be included in the multivariate logistic regression models.

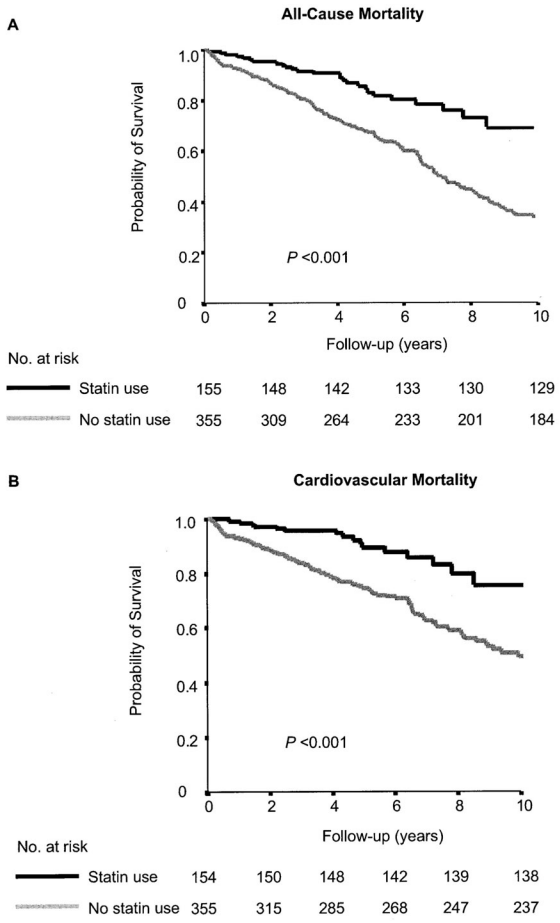

Figure 1. Kaplan-Meier estimates of all-cause (A) and cardiovascular (B) mortality, according to statin use. *P* value (log-rank test) indicates the differences in survival.

certained by reviewing records at the Office of Civil Registry. Cause of death was determined from hospital records and autopsy results for patients who died during follow-up at Erasmus Medical Center, and by contacting the general practitioner for those who died outside of the medical center. If no autopsy was performed, the cause of death was determined from the clinical information provided by the general practitioner. When the cause of death was uncertain, it was classified as "unknown".

The study outcomes were all-cause and cardiovascular mortality. Death was considered to be of cardiovascular etiology if it was directly attributable to myocardial infarction, heart failure, or ventricular arrhythmia in the absence of any other precipitating factor, or if death was sudden and unexpected. In addition, death was attributed to cardiovascular causes if it was due to cerebrovascular accident, aortic aneurysm rupture, or pulmonary embolism. Coronary bypass surgery or coronary angioplasty was not defined as a cardiac event, and patients were censored at the time of these procedures.

Statistical Analysis

The Kaplan-Meier method was used to assess the prognostic importance of statin and beta-blocker use with respect to event-free survival. Differences between survival curves were compared with the log-rank test. Since the decision to start statin or beta-blocker therapy was not randomized, adjustments were made for clinical factors that may have affected the decision to use either medication. Separate propensity scores were calculated by multiple logistic regression analyses. Baseline characteristics that had an independent relation with the decision to prescribe statins or beta-blockers (*P* value of 0.25) were included in the multivariate score. Univariate Cox proportional hazards regression models were used to assess the associations among statin and beta-blocker use, baseline characteristics, and primary outcomes. In analyses of cardiovascular mortality, patients who died of noncardiovascular causes were censored at the time of death.

All variables were entered in the multivariate model, irrespective of the significance level in univariate analyses. The association of statins and beta-blockers with all-cause and cardiovascular mortality was assessed, with adjustments for clinical characteristics as well as for the two propensity scores. Finally, the interactions between statin or beta-blocker use and baseline clinical characteristics were evaluated. Hazard ratios and corresponding 95% confidence intervals are reported. All analyses were performed using SPSS statistical software (SPSS Inc., Chicago, Illinois). *P* values <0.05 were considered significant.

RESULTS

Of the 519 patients who survived surgery, 510 (98%) were followed until February 2003 (Table 1). Thirty percent (n = 154) of patients were long-term statin users. Compared with patients who did not use statins, statin users were younger and more often women, and had a higher body mass index and FEV_1. Statin users also had a higher prevalence of cardiovascular disease and renal dysfunction, but a lower prevalence of pulmonary disease. There were no significant differences in the prevalence of smoking, smoking cessation, and total, low-density lipoprotein (LDL), and high-density lipoprotein cholesterol levels. Statin users more frequently used concomitant cardiac medications. In the patients who were statin users, the most frequently prescribed statins were simvastatin (71% [n = 110]; 10 or 20 mg), atorvastatin (18% [n = 27]; 20 or 40 mg), pravastatin (10% [n = 16]; 20 or 40 mg), and fluvastatin (1% [n = 1]; 20 mg).

Table 4. Univariate Predictors and Estimated Risks of Long-term All-Cause and Cardiovascular Mortality

Variable	No. of Patients (n = 510)	All-Cause Mortality			Cardiovascular Mortality		
		No. of Events (%)	Hazard Ratio (95% Confidence Interval)	*P* Value	No. of Events (%)	Hazard Ratio (95% Confidence Interval)	*P* Value
Statins				<0.001			<0.001
Yes	154	27 (18)	0.4 (0.3–0.5)		17 (11)	0.3 (0.2–0.6)	
No	356	178 (50)	1		122 (34)	1	
Beta-blockers				0.003			0.03
Yes	265	80 (30)	0.6 (0.5–0.9)		57 (21)	0.7 (0.4–0.9)	
No	245	125 (51)	1		83 (34)	1	
ACE inhibitors				0.6			0.7
Yes	165	62 (38)	0.9 (0.7–1.2)		47 (29)	1.1 (0.8–1.5)	
No	338	142 (42)	1		92 (27)	1	
Aspirin				0.6			0.8
Yes	119	43 (36)	1.1 (0.8–1.5)		29 (24)	1.0 (0.7–1.6)	
No	383	160 (42)	1		110 (29)	1	
Age (years)							
≥70	274	135 (49)	2.9 (1.6–5.4)	<0.001	93 (34)	2.4 (1.3–4.7)	0.008
60–69	176	58 (33)	1.7 (0.9–3.2)	0.08	37 (21)	1.3 (0.7–2.6)	0.4
<60	60	12 (20)	1		10 (17)	1	
Sex				0.8			0.3
Male	436	177 (41)	0.9 (0.6–1.4)		117 (27)	0.8 (0.5–1.2)	
Female	74	28 (38)	1		23 (31)	1	
Current or stable angina pectoris				0.8			0.4
Yes	99	37 (37)	1.1 (0.7–1.5)		28 (28)	1.2 (0.8–1.8)	
No	411	168 (41)	1		112 (27)	1	
Previous myocardial infarction				0.02			0.008
Yes	130	59 (45)	1.4 (1.1–1.9)		45 (35)	1.6 (1.1–2.3)	
No	380	146 (38)	1		95 (25)	1	
Heart failure				0.7			0.7
Yes	17	8 (47)	1.2 (0.6–2.4)		6 (35)	1.2 (0.5–2.7)	
No	493	197 (40)	1		134 (27)	1	
Diabetes mellitus				0.8			0.2
Yes	30	12 (40)	1.1 (0.6–1.9)		11 (37)	1.4 (0.8–2.7)	
No	480	193 (40)	1		129 (27)	1	
Prior cerebrovascular accident				0.03			0.007
Yes	68	33 (49)	1.5 (1.0–2.2)		26 (38)	1.8 (1.2–2.8)	
No	442	172 (39)	1		114 (26)	1	
Renal dysfunction				0.05			0.1
Yes	50	24 (48)	1.5 (1.0–2.3)		17 (34)	1.5 (0.9–2.4)	
No	460	181 (39)	1		123 (27)	1	
Chronic pulmonary disease				<0.001			0.03
Yes	118	62 (53)	1.8 (1.3–2.4)		38 (32)	1.5 (1.1–2.2)	
No	392	143 (37)	1		102 (26)	1	

ACE = angiotensin-converting enzyme.

Follow-up

The median follow-up was 4.7 years (interquartile range, 2.7 to 7.3 years). Of the 205 patients (40%) who died during follow-up, 140 died of cardiovascular causes (Table 2). An autopsy was performed in 53 patients (26%), including 28 whose death was of cardiac origin. Seventeen patients (3%) underwent a second vascular operation during follow-up, including peripheral vascular surgery due to worsening claudication (n = 7), carotid endarterectomy (n = 3), repair of the thoracic aortic aneurysm (n = 2), and removal of the infected vascular prosthesis (n = 5). Coronary bypass surgery or coronary angioplasty was performed in 11 patients who were censored from follow-up at this time.

Propensity to Prescribe Statins or Beta-blockers

The propensity score for statin use revealed that patients were more likely to be prescribed statins if they were

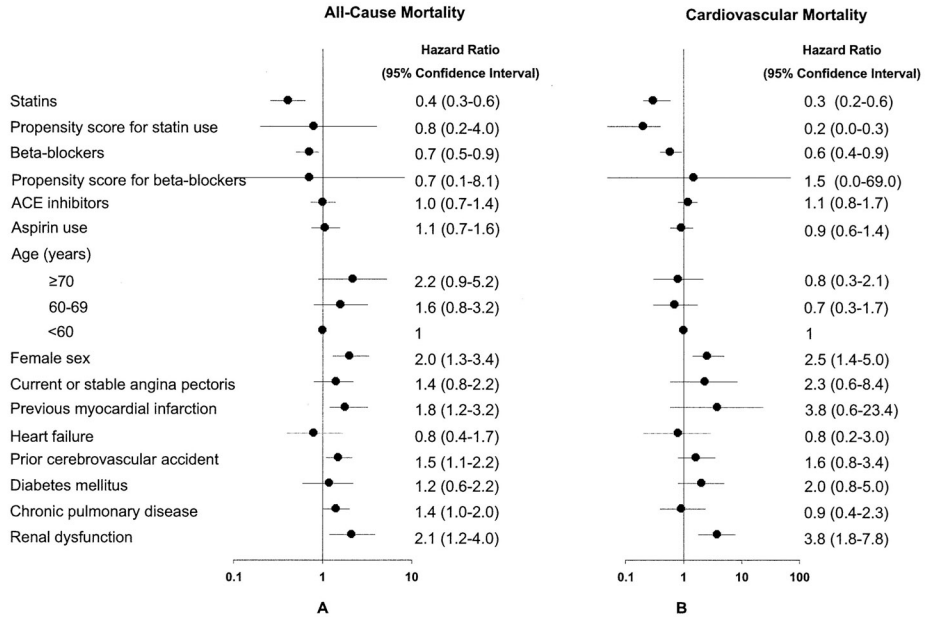

Figure 2. Multivariate associations among clinical characteristics, propensity scores, and all-cause (A) and cardiovascular (B) mortality. ACE = angiotensin-converting enzyme.

younger, had a history of coronary artery disease or renal dysfunction, or had elevated serum total cholesterol levels (Table 3). Similarly, the propensity score for beta-blocker use showed that beta-blockers were used more often if patients were younger or had a history of coronary artery disease, but were used less often in those with chronic pulmonary disease (Table 3).

Relation between Statin Use and Long-term Outcome

Survival was significantly improved in patients who used statins compared with those who did not (Figure 1). Compared with nonusers, patients using statins had a 2.5-fold reduction in the risk of all-cause mortality (hazard ratio [HR] = 0.4; 95% confidence interval [CI]: 0.3 to 0.5) and more than a threefold reduction in the risk of cardiovascular mortality (HR = 0.3; 95% CI: 0.2 to 0.6) (Table 4). This association remained unchanged after adjusting for other covariates and the propensity score (Figure 2). Beta-blocker use was also associated with an approximately 1.5-fold reduction in all-cause and cardiovascular mortality compared with nonuse (Table 4; Figure 3). There were no associations between use of aspirin or angiotensin-converting enzyme inhibitors and either all-cause or cardiovascular mortality.

Other predictors of all-cause and cardiovascular mortality in the univariate analysis included age ≥70 years, previous myocardial infarction, prior cerebrovascular accident, and chronic pulmonary disease (Table 4). In a multivariate analysis (Figure 2), female sex, previous myocardial infarction, prior cerebrovascular accident, and renal dysfunction were significant predictors of all-cause mortality. When a separate multivariate analysis for cardiovascular mortality was performed, only female sex and renal dysfunction remained significant multivariate predictors of cardiovascular mortality (Figure 2).

Additional Beneficial Effects of Statin Use

Tests for heterogeneity revealed no evidence of a differential effect of statin use in patients who used beta-blockers ($P = 0.5$) or aspirin ($P = 0.4$), who were older ($P = 0.7$), or who had a history of myocardial infarction ($P = 0.4$), prior cerebrovascular accident ($P = 0.3$), renal dysfunction ($P = 0.10$), or chronic pulmonary disease ($P = 0.6$) in relation to all-cause mortality. When the same analysis was repeated for cardiovascular mortality, there was no evidence of a differential effect of statin use in these categories.

DISCUSSION

Our data suggest that long-term statin use after successful repair of an abdominal aortic aneurysm is associated with a substantial reduction in all-cause and cardiovascular mortality. Even though statin users had different clinical characteristics associated with an adverse long-term outcome as compared with nonusers, including a higher prevalence of cardiovascular disease, the association between statin use and reduced mortality remained after adjustment for clinical risk factors and beta-blocker use.

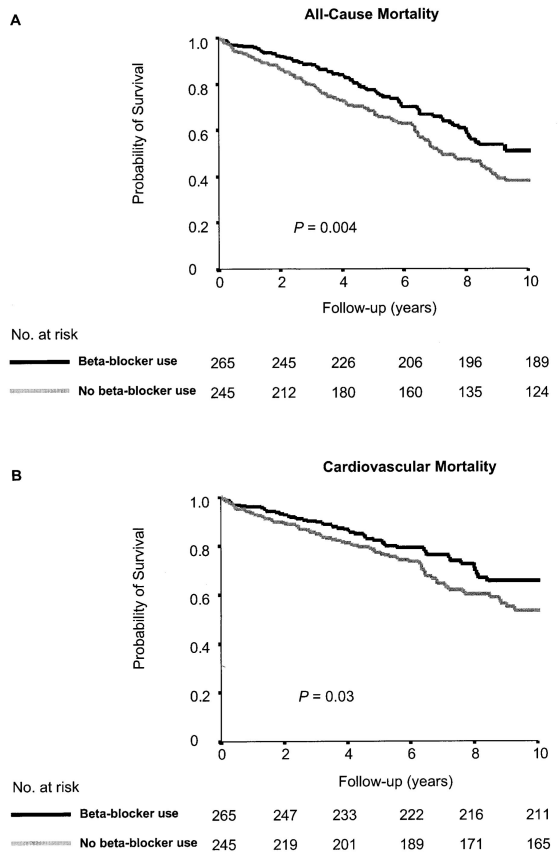

Figure 3. Kaplan-Meier estimates of all-cause (A) and cardiovascular (B) mortality, according to beta-blocker use. *P* value (log-rank test) indicates the differences in survival.

There is considerable literature on the late survival of patients who undergo successful abdominal aortic aneurysm repair, with several studies indicating that the primary cause of late death is often cardiovascular (11–14). Similarly, 68% of deaths in our study was due to cardiovascular causes. There is also growing evidence of an association between the presence of an abdominal aortic aneurysm and atherosclerosis (15,16), which may explain the high proportion of late mortality due to cardiovascular causes.

Some have suggested that prophylactic myocardial revascularization preceding abdominal aortic aneurysm surgery may improve late survival in patients undergoing abdominal aortic aneurysm repair (3,14). Noninvasive tests or routine coronary angiography identify patients with clinically silent but anatomically important coronary artery disease in whom myocardial revascularization might be highly successful. However, only one third of acute cardiovascular events are caused by stenotic plaques, and the remainder results from disrupted but nonstenotic plaques. Indeed, the distribution of myocardial infarction is not necessarily related to the location of hemodynamically critical coronary artery lesions (17). This may indicate the presence of coronary artery disease in numerous locations throughout the coronary tree, and the possibility that myocardial infarction may result from plaque rupture and thrombosis at the site of a hemodynamically unimportant but unstable atherosclerotic plaque (18). In that respect, lipid-lowering medications such as statins may be beneficial in the prevention of late cardiac complications. In addition to being effective in lowering LDL cholesterol levels, statins may also attenuate plaque inflammation and influence plaque stability (19), effects that may also affect the coronary and noncoronary circulation (20).

Consistent with previous studies, we also found an association between beta-blocker use and a reduction in all-cause and cardiovascular mortality (21,22). In patients who used beta-blockers and statins, there was no evidence of a differential beneficial effect of statin use on beta-blocker therapy. Thus, statin use appears to be independently associated with a reduced incidence of long-term complications even in the presence of beta-blockers. Beta-blockers reduce inflammation via a reduction in sympathetic tone (23), whereas statins target inflammation through the downregulation of cytokine production in the endothelium and leukocytes (24), which may explain some of the independent effects of these drugs in the prevention of long-term cardiac complications.

Data from large prospective studies of the effect of statin use on future coronary events provide some evidence that may be applicable to patients undergoing abdominal aortic aneurysm repair (25–31). These studies have demonstrated the protective, anti-inflammatory effects of statins against first and subsequent myocardial infarction, and cardiovascular mortality. They have also found that statin use decreases the risk of subsequent mortality and coronary events in patients with known coronary artery disease (25,26). Patients with average or "normal" lipid levels also benefit from statin use (27–29). Additional evidence has also indicated that statins slow the progression of coronary artery disease (30,31).

Several limitations should be kept in mind when interpreting our results. The study was observational and patients were not randomly assigned to statin therapy, which limits the ability to establish a causal relation. Although we adjusted for potential confounders, there may have been unmeasured confounders. Additionally, statin use might not have been noted in some patients, as not all patients systematically received statin therapy based on elevated plasma lipid levels. If this had been the case, however, the beneficial effect of statin use would have been underestimated and its protective effect would have been even stronger.

In conclusion, our results reveal that long-term statin use in patients who underwent successful abdominal aor-

tic aneurysm surgery is associated with reduced all-cause and cardiovascular mortality irrespective of clinical risk factors and beta-blocker use. It seems likely, therefore, that long-term statin use should be considered in patients following this type of surgery.

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Summary and conclusions

In this thesis, the prognostic value of clinical risk factors, the use of noninvasive testing for risk stratification, and pharmacologic risk reduction strategies are described for the perioperative and long-term management of patients undergoing major vascular surgery.

Part 1: Preoperative risk evaluation-clinical risk factors

In chapter 1, a systematic review is given summarizing the issue of perioperative risk evaluation and management of patients undergoing major vascular surgery. This chapter describes the burden of peripheral artery disease, pathophysiology of perioperative cardiac events, risk assessment and risk reduction strategies. The summarized data from published literature show that patients without cardiac risk factors are considered to be at low risk and no additional evaluation for coronary artery disease is recommended; beta-blockers may reduce perioperative cardiac events in this patient population; patients with one or more cardiac risk factors represent an intermediate to high-risk population. Additional noninvasive testing for the evaluation of coronary artery disease is recommended. Beta-blockers should be prescribed to all patients and coronary artery revascularization should be reserved for patients who have a clearly defined need for revascularization, independent of the need for surgery.

In chapter 2, a comparison is made between serum creatinine and creatinine clearance for the prediction of postoperative mortality in patients undergoing major vascular surgery. The results show that preoperative creatinine clearance derived from serum creatinine, age, body weight and gender had additional prognostic value compared to serum creatinine to predict postoperative mortality in patients undergoing major vascular surgery. Measures that may improve or preserve the renal function during and after surgery may help to reduce postoperative mortality in this high-risk patient population.

In chapter 3, we describe a relation between the presence of aortic stenosis and an increased risk of perioperative mortality. Aortic stenosis is the most common valvular heart disease affecting 2% to 9% of adults over 65 years of age. Earlier studies showed that patients with aortic stenosis were at increased risk of life-threatening or fatal cardiac complications. Later, three studies reported that selected patients with aortic stenosis who were not candidates for, or refused, aortic valve replacement could undergo noncardiac surgery with a reasonably low event rate. However, a more recent study reported that peak instantaneous gradients were associated with increased cardiovascular mortality. Therefore, in this chapter we compared the incidence of perioperative mortality and nonfatal myocardial infarction in a large group of patients with moderate to severe aortic stenosis who were undergoing elective noncardiac surgery to patients without aortic stenosis. We found that patients with aortic stenosis were at five-fold increased risk for cardiac complications compared to patients without aortic stenosis.

In chapter 4, the safety of dobutamine stress echocardiography in patients with aortic stenosis is described. Low-dose dobutamine stress echocardiography is a recommended investigation in patients with low-gradient aortic stenosis and reduced left ventricular function to assess whether the aortic stenosis is fixed or dynamic. Patients with aortic stenosis and normal or mildly reduced left ventricular function may be referred for dobutamine stress echocardiography for the diagnosis of coronary artery disease, or for risk stratification before noncardiac surgery. However, only few data are available relating to the safety of dobutamine stress echocardiography in these patients. Therefore, in this chapter the safety of dobutamine stress echocardiography was studied in 75 patients with aortic stenosis and with severely reduced or moderate to normal left ventricular function. The mean pressure gradient, valve area and side effects after dobutamine stress echocardiography were evaluated. Serious cardiac arrhythmias occurred in 10 patients. Among 20 patients with evidence of ischemia on dobutamine stress echocardiography, three developed adverse side effects. The results showed that patients with a low-gradient aortic stenosis and left ventricular dysfunction were susceptible to potentially life-threatening arrhythmias during dobutamine stress echocardiography. In these patients an alternative noninvasive test for the diagnosis of coronary artery disease, such as myocardial perfusion scintigraphy should be

considered. In patients with mild to moderate aortic stenosis, and with normal or mildly reduced left ventricular function, dobutamine stress echocardiography was relatively safe, but arrhythmias and hypotension were noted during a high-dose dobutamine challenge.

In chapter 5, the long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after successful major vascular surgery is studied. A follow-up study was conducted between 1996 and 2000 in 393 patients who underwent successful aortic or infrainguinal vascular surgery and routine sampling of cardiac troponin T. Patients were followed for on average period of four years and the incidence of all-cause mortality was evaluated. The presence of cardiac troponin T elevations was associated with an almost two-fold increased risk of long-term mortality in patients undergoing successful major vascular surgery, independent of the presence of risk factors for coronary artery disease, renal dysfunction, cardiac medication use, and elevated CK levels. Additional clinical studies are required to determine the most optimal approach and management for patients with abnormal cardiac troponin T levels to improve their long-term outcome.

In chapter 6, the relation between clinical risk factors and perioperative mortality is studied in patients who underwent elective abdominal aortic aneurysm surgery. Patients undergoing elective open abdominal aortic surgery are at increased risk for perioperative mortality. Identification of preoperative factors associated with increased risk of mortality may initiate preoperative interventions and influence decisions about the type and also the timing of the surgery. A number a risk factors of perioperative mortality in elective abdominal aortic aneurysm surgery have been identified. These risk factors have been incorporated in clinical risk models such as the Leiden and the United Kingdom Small Aneurysm Trial risk scores. However, the performance of these risk models were not evaluated in other more recent datasets. In this chapter we studied the performance of the Leiden and the United Kingdom Small Aneurysm Trial risk scores. Our results show that the Leiden risk model could identify a low-risk population of patients. The United Kingdom Small Aneurysm Trial risk model had only relatively poor performance and, hence, was not a suitable alternative to the Leiden risk model.

In chapter 7, we use data of 75,581 patients who underwent 108,613 noncardiac surgical procedures between 1991-2000 at the Erasmus MC to examine trends in the incidence of fatal perioperative cardiovascular complications over time, and study the relationship between clinical and electrocardiographic variables and fatal cardiovascular outcome. There were no significant changes in cardiovascular mortality over time in either men or in women. Advanced age, male gender, type of surgery, diabetes mellitus, hypertension, ischemic heart disease, heart failure, stroke, and renal failure were identified as important clinical risk factors for cardiovascular death. An abnormal ECG was also associated with increased perioperative cardiovascular mortality. Based on these results, a score was developed to estimate an individual patient's risk of cardiovascular death in relation to a specific surgical procedure. The results showed that the developed multivariable risk models showed excellent ability to discriminate between patients at low, intermediate and high risk of cardiovascular complications, and can readily be applied in routine perioperative management.

Part 2: Preoperative cardiac risk evaluation-noninvasive testing

In chapter 8, in a scientific letter we propose that the decision about to perform early surgery for abdominal aortic aneurysm or institute ultrasonographic surveillance should be made on an individual basis, after an evaluation of the perioperative risk. Based on data of 661 patients operated for abdominal aortic aneurysm surgery between 1991 and 2000 at the Erasmus MC, patients without chronic pulmonary disease or cardiac risk factors represent a population at low risk for operative death. Patients with one or more cardiac risk factors could be further stratified by the absence or presence and extent of myocardial ischemia, as determined by dobutamine stress echocardiography. In this way risk assessment and modification could be undertaken for each patient.

In chapter 9, the additional prognostic value of dobutamine stress echocardiography, dipyridamole stress echocardiography and dipyridamole perfusion scintigraphy are compared in patients undergoing major vascular surgery. We used data of 2,204 consecutive patients who underwent either of these noninvasive tests before major vascular surgery. We found no statistically significant difference in the

predictive value of a positive test result for dobutamine stress echocardiography and dipyridamole stress echocardiography (Odds ratio of 37.1 [95% CI, 8.1-170.1] versus 9.6 [95% CI, 4.9-18.4]; p=0.12), whereas a positive test for dipyridamole perfusion scintigraphy had significantly lower prognostic value (Odds ratio of 1.95 [95% CI, 1.2-3.2]). In further analyses the additional prognostic value of these tests modalities were studied on clinical risk factors. Our results show that dobutamine or dipyridamole stress echocardiography had more favorable prognostic performance, irrespective of clinical risk profile. In contrast, the prognostic value of dipyridamole perfusion scintigraphy is more likely to be dependent on patients' clinical risk score.

In chapter 10, a meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery is described. The identification of clinical risk factors and the role of noninvasive diagnostic testing to predict perioperative cardiac risk have been evaluated over recent decades. These have included multifactorial clinical scoring systems based upon, noninvasive tests such as ambulatory electrocardiography, exercise electrocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy, and dipyridamole or dobutamine stress echocardiography. Using a novel meta-analytic method we systematically summarized data for the available literature. In all, 58 studies with a total of 8,119 patients met the inclusion criteria. Dobutamine stress echocardiography showed a positive trend towards better diagnostic performance than the other tests, but reached only statistical difference in comparison with myocardial perfusion scintigraphy. However, dobutamine stress echocardiography could be the favoured test if there is a suspicion about valvular and left ventricular dysfunction.

Part 3: Perioperative pharmacological therapy

In chapter 11, in an editorial review the possible reasons to withhold beta-blockers from high-risk patients with coronary artery disease are described. In this editorial, we analyzed issues such as how often beta-blockers are underused, the possible reasons for withholding beta-blockers and recommendations.

Next in chapter 12, the first study is described that revealed an association between statin use and a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Patients undergoing major vascular surgery are at increased risk of perioperative mortality due to underlying coronary artery disease. Statins may reduce perioperative mortality through the improvement of lipid profile, but also through the stabilization of coronary plaques on the vascular wall. To evaluate this association a case-control study was performed among the 2,816 patients who underwent major vascular surgery from 1991 to 2000 at the Erasmus MC. Case subjects were all 160 (5.8%) patients who died during the hospital stay after surgery. From the remaining patients, two controls were selected for each case and were stratified according to calendar year and type of surgery. The data showed that statin therapy was significantly less common in cases than in controls (8% versus 25%; P<0.001). The adjusted odds ratio for perioperative mortality among statin users as compared with nonusers was 0.22 (95% CI, 0.10-0.47). This study provided evidence for the first time that statin use reduces perioperative mortality in patients undergoing major vascular surgery.

In chapter 13, the combined effect of perioperative statin and beta-blocker use in relation to perioperative mortality is described. Five hundred seventy patients who underwent elective abdominal aortic aneurysm surgery were studied between 1991-2000 at the Erasmus Medical Center. Patients were evaluated for clinical risk factors, statin and beta-blocker use. The main outcome measure was a composite of all cause mortality and nonfatal myocardial infarction within 30 days of surgery. The findings of this study revealed that the incidence of the composite endpoint was significantly lower in statin users compared to non-statin users (3.7% vs. 11.0%; adjusted odds ratio: 0.24, 95% CI, 0.10-0.70; p=0.01). Beta-blocker use was also associated with a significant reduction in the composite endpoint (adjusted odds: 0.24, 95% CI, 0.11-0.54). Despite the fact that beta-blocker users were more often statin users there was no evidence of differential beneficial effect of statin use on beta-blocker therapy. Thus, statin use appears to be independently associated with a reduced incidence of perioperative mortality and nonfatal myocardial infarction even in the presence of beta-blockers.

Part 4: Long-term pharmacological therapy

In chapter 14, the optimal long-term cardiac management after major vascular surgery is described. This study was performed based on the long-term follow-up data of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography study. The follow-up study was conducted in 1,286 patients of the 1,351 patients who survived surgery for at least 30 days. The results of the present study shows that stress-induced ischemia during dobutamine stress echocardiography has additional prognostic value, irrespective of the clinical risk profile. Patients receiving beta-blockers had significantly lower risk than patients not receiving them. However, the cardioprotective effect of beta-blockers was more likely to depend on the presence or absence of cardiac risk factors and stress-induced myocardial ischemia during dobutamine stress echocardiography testing.

In chapter 15, we studied the association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. The main finding of this study is that the incidence of all-cause and cardiovascular mortality was significantly lower in statin users than in nonstatin users. After adjusting for clinical risk factors and beta-blocker use, the association between statin use and reduced all-cause (hazard ratio: 0.4, 95% CI, 0.3-0.6) and cardiovascular (hazard ratio: 0.3, 95% CI, 0.2-0.6) mortality persisted. It seems, therefore, that long-term statin use should be considered in patients following abdominal aortic aneurysm surgery.

In conclusion, perioperative and long-term cardiac risk assessment and management of patients undergoing major vascular surgery is one of the most challenging and controversial areas of clinical medicine. With the help of our research we showed that by applying appropriate preoperative risk stratification tools and perioperative and long-term risk reduction strategies these patients may safely undergo surgery and survive the perioperative period in order to benefit from their surgery in the short and long-term.

Samenvatting en conclusies

In dit proefschrift worden de prognostische waarde van klinische risicofactoren, het gebruik van niet-invasieve onderzoekstechnieken voor risicostratificatie, farmacologische risicoreductie strategieën beschreven voor peri-operatieve en lange termijn beleid bij patiënten die een grote vaatoperatie hebben ondergaan.

Part 1: Pre-operatieve risico-evaluatie – klinische risicofactoren

In hoofdstuk 1 wordt de peri-operatieve risico-evaluatie en de behandeling van patiënten, die een grote vaatoperatie ondergaan, samengevat. Dit hoofdstuk beschrijft de last van perifeer vaatlijden, de pathosfysiologie van peri-operatieve cardiale events, risicoschatting en strategieën voor risicoreductie. De resultaten van huidige publicaties laten zien dat patiënten zonder cardiale risicofactoren beschouwd worden als een laagrisico groep en voor deze groep wordt geen aanvullende evaluatie van het coronairlijden aanbevolen. Verder zouden beta-blokkers in deze groep patiënten het risico op peri-operatieve cardiale events kunnen verlagen. Daarentegen, patiënten met een of meerdere cardiale risicofactoren worden beschouwd als een groep met een gemiddeld tot hoog risico. Aanvullende non-invasieve testen voor de evaluatie van het coronairlijden wordt in deze groep wel aanbevolen. Bèta-blokkers zouden moeten worden voorgeschreven aan alle patiënten en coronaire revascularisatie zou moeten worden geïndiceerd voor patiënten waarvoor een duidelijke noodzaak voor revascularisatie bestaat, onafhankelijk van de noodzaak tot operatie.

In hoofdstuk 2 wordt een vergelijking gemaakt tussen serum creatinine en de creatinine-klaring voor het voorspellen van peri-operatieve sterfte in patiënten die een grote vaatoperatie ondergaan. De resultaten laten zien dat de peri-operatieve creatinine-klaring afkomstig van het serum-creatinine, leeftijd, lichaamsgewicht en geslacht een aanvullende prognostische waarde hebben in vergelijking tot het

serum-creatinine om de peri-operatieve sterfte te voorspellen in patiënten die een grote vaatoperatie ondergaan. Maatregelen die de nierfunctie mogelijk zouden kunnen behouden tijdens en na de operatie zouden de peri-operatieve sterfte in hoogrisico patiënten kunnen verlagen.

In hoofdstuk 3 wordt de relatie beschreven tussen de aanwezigheid van een aorta-stenose en het verhoogde risico op peri-operatieve sterfte. Aorta-stenose is de meest voorkomende klepaandoening en treft 2% tot 9% van de volwassen boven de 65 jaar. Eerdere studies hebben aangetoond dat patiënten met een aorta-stenose een verhoogd risico hebben op levensbedreigende of zelfs fatale cardiale complicaties. Drie latere studies hebben aangetoond dat bepaalde patiënten met aorta-stenose die niet in aanmerking kwamen voor aorta-klep vervanging of die dit weigerde, non-cardiale operaties kunnen ondergaan met een redelijk laag aantal events. Een meer recente studie heeft echter laten zien dat peak aorta-stenose gradiënt geassocieerd zijn met een toename van de cardiovasculaire sterfte. Daarom wordt in dit hoofdstuk de incidentie van peri-operatieve sterfte en non-fataal myocardinfarct vergeleken in een grote groep patiënten met een matig tot ernstige aorta-stenose in patiënten zonder aorta-stenose die een electieve non-cardiale operatie ondergaan. De resultaten van onze studie laten zien dat patiënten met een aorta-stenose een 5 keer hoger risico hebben op cardiale complicaties in vergelijking tot patiënten zonder aorta-stenose.

In hoofdstuk 4 wordt de veiligheid van dobutamine stress echocardiografie beschreven in patiënten met een aorta-stenose. Lage-dosering dobutamine stress echocardiografie wordt aanbevolen in patiënten met een lage-gradient aorta-stenose en een verminderde linker-ventrikel functie om te bepalen of de aorta-stenose gefixeerd is of dynamisch. Patiënten met een aorta-stenose en een normale of licht verminderde linker-ventrikel functie kunnen worden doorverwezen voor een dobutamine stress echocardiografie voor de diagnose van coronairlijden of voor risicostratificatie voor een non-cardiale operatie. Er zijn echter maar weinig gegevens beschikbaar met betrekking tot de veiligheid van dobutamine stress echocardiografie in deze groep patiënten. In dit hoofdstuk wordt daarom de veiligheid van dobutamine stress echocardiografie bestudeerd in 75 patiënten met een aorta-stenose en een ernstige verminderde of matig tot normale linker-ventrikel functie. Er is gekeken naar

de gemiddelde druk-gradient, klepoppervlak en de bijwerkingen na de dobutamine stress echocardiografie. In 10 patienten was er sprake van ernstige arhytmieen en van de 20 patiënten met bewezen ischemie op de dobutamine stress echocardiografie ontwikkelde 3 patienten ongunstige bijwerkingen. De data laten zien dat patiënten met een lage-gradient aorta-stenose en een linker-ventrikel dysfunctie gevoelig waren voor eventuele levensbedreigende arytmieën. In deze groep patienten zou een alternatieve non-invasieve test moeten worden overwogen voor de diagnose coronairlijden, zoals bijvoorbeeld myocardial perfusie scintigrafie. In patiënten met een milde tot matige aorta-stenose en met een normale of slechts lichte vermindering van de linker-ventrikel-functie was de dobutamine stress echocardiografie relatief veilig, maar was er tijdens een hoge-dosering dobutamine stress echocardiografie wel sprake van arhytmieën en hypotensie.

In hoofdstuk 5 is de lange-termijn prognostische waarde van asymptomatisch cardiale troponine T verhogingen na een geslaagde grote vaatoperatie bestudeerd. In de periode tussen 1996 en 2000 is er een lange-termijn follow-up studie uitgevoerd in 393 patiënten die een geslaagde operatie van de aorta of infrainguinale vaatoperatie hadden gehad en waarbij routinematig cardiaal troponine T was bepaald. Deze patiënten werden gemiddeld 4 jaar gevolgd en er is gekeken naar de incidentie van totale sterfte. Een verhoging van troponine T was geassocieerd met een bijna 2 keer zo hoog risico op sterfte op de lange-termijn in patienten die een geslaagde grote vaatoperatie hadden gehad, onafhankelijk van de aanwezigheid van risicofactoren voor coronairlijden, dysfunctioneren van de nieren, cardiale medicatiegebruik en verhoogde CK-waarden. Aanvullende klinische studies zijn nodig om de meest optimale benadering en behandeling te bepalen voor patiënten met abnormale troponine T waarden om hun uitkomst op lange-termijn te verbeteren.

In hoofdstuk 6 wordt de relatie tussen klinische risicofactoren en peri-operatieve sterfte bestudeerd in patiënten die een electieve abdominale aorta aneurysma operatie ondergaan. Patiënten die een electieve abdominale aorta aneurysma operatie ondergaan hebben een verhoogd risico op peri-operatieve strefte. Identificatie van de pre-operatieve factoren die geassocieerd zijn met een verhoogd risico op sterfte kunnen aanleiding geven tot pre-operatieve interventies en beslissingen beïnvloeden met betrekking tot type en tijdstip van de operatie. Er zijn

een aantal klinische risicofactoren geïdentificeerd voor de peri-operatieve sterfte in electieve abdominale aneurysma operaties. Deze factoren zijn ingebouwd in klinische risicomodellen zoals de Leiden en United Kingdom Small Aneurysm Trial risicoscores. De uitvoering van deze risicomodellen zijn echter nog niet geëvalueerd in andere, meer recente databases. In dit hoofdstuk hebben we de uitvoering van de Leiden en United Kingdom Small Aneurysm Trial risico-scores bestudeerd. De resultaten laten zien dat Leiden risicomodel een laagrisico patienten-populatie zou kunnen identificeren. Het United Kingdom Small Aneurysm Trial risicomodel geeft een relatief slecht resultaat en is dus geen geschikt alternatief voor het Leiden risicomodel.

In hoofdstuk 7 hebben we de data van 75.581 patiënten onderzocht die in totaal 108.613 non-cardiale operaties hebben ondergaan in de periode van 1991 en 2000 in het Erasmus Medisch Centrum om het beloop van de incidentie van fatale peri-operatieve cardiovasculaire complicaties te bestuderen. Bovendien is de relatie tussen zowel klinische en electrocardiografische variabelen en fatale cardiovasculaire uitkomsten bestudeerd. Er zijn geen significante veranderingen in cardiovasculaire sterfte in de tijd waargenomen in mannen en vrouwen. Oudere leeftijd, mannelijk geslacht, type operatie, diabetes mellitus, hypertensie, ischemische hartziekte, hartfalen, beroerte en nierfalen zijn geïdentificeerd als belangrijke klinische risicofactoren voor cardiovasculaire sterfte. Een abnormaal ECG was ook geassocieerd met een stijging van de cardiovasculaire sterfte. Gebaseerd op deze resulaten is er een score ontwikkeld om het individuele risico te schatten van een patiënt op cardiovasculaire sterfte in relatie tot een specifieke operatie. De resultaten laten zien dat deze multivariabele risico-modellen goed in staat zijn om onderscheid te maken tussen patiënten die een laag, gemiddeld en hoog risico op cardiovasculaire complicaties en kunnen nu routinematig worden toegepast in peri-operatieve behandeling.

Deel 2: Pre-operatieve cardiale risico evaluatie – niet invasieve onderzoeken

In hoofdstuk 8, wordt aan de hand van een wetenschappelijke brief voorgesteld om op basis van individuele besluitvorming, na evaluatie van het peri-operatieve risico, te kiezen voor vroegtijdige operatie van een abdominalis aorta

aneurisma of een regelmatige echocardiografische controle. Dit voorstel is gebaseerd op de gegevens van 661 patiënten die tussen 1991 en 2000 in het Erasmus MC een operatie ondergingen van een aneurisma aorta abdominalis. Een laag risico op operatieve mortaliteit wordt ingeschat als patiënten geen chronische longaandoening of cardiale risicofactoren heeft. Indien er sprake is van één of meer cardiale risicofactoren wordt verder uitgesplitst op het wel of niet aanwezig zijn van cardiale ischemie en de uitgebreidheid hiervan. Dit wordt bepaald aan de hand van dobutamine stressechocardiografie. Deze wijze van inschatting kon voor iedere patiënt worden uitgevoerd.

In hoofdstuk 9 wordt de toegevoegde prognostische waarde van dobutamine stress echocardiografie, dipyridamol stress echocardiografie en perfusie scintigrafie vergeleken bij patiënten die een grote vaatoperatie ondergingen. Hiervoor werden de gegevens van 2204 opeenvolgende patiënten gebruikt bij wie één van deze niet-invasieve onderzoeken werd verricht voorafgaand aan een grote vaatoperatie. Er werden geen statistisch significante verschillen gevonden tussen de prognostische waarde van een positieve test van de dobutamine stress echocardiografie en dipyridamol stress echocardiografie (Odds ratio: 37.1 [95% CI, 8.1-170.1] versus 9.6 [95% CI, 4.9-18.4]; p=0.12), terwijl een positieve dipyridamole perfusie scintigrafie een significant lagere prognostische waarde had (Odds ratio: 1.95 [95% CI, 1.2-3.2]. Aanvullende analyses werden verricht naar de toegevoegde prognostische waarde van deze onderzoeksmethoden met betrekking tot klinische risicofactoren. Onze resultaten laten zien dat dobutamine of dipyramidamol stress echocardiografie een gunstiger prognostisch beeld liet zien, ongeacht het klinisch risico profiel. Dit in tegenstelling tot de voorspellende waarde van dipyridamol perfusie scintigrafie, waarbij het klinische risico profiel wel van invloed leek te zijn.

In hoofdstuk 10 wordt een meta-analyse beschreven, waarin zes verschillende diagnostische onderzoeken met elkaar worden vergeleken op prognostische accuraatheid om het peri-operatieve cardiale risico te voorspellen bij patiënten die een grote vaatoperatie ondergaan. Ook worden klinische risico factoren geïdentificeerd en de rol van niet-invasieve diagnostische onderzoeken bij het voorspellen van het peri-operatieve cardiale risico. Dit omvatte multifactoriële klinische scoringssystemen die gebaseerd waren op, niet-invasieve onderzoeken

zoals electrocardiografie, inspannings electrocardiografie, radionuclide ventriculografie, myocard perfusie scitigrafie en dobutamine of dipyramidamole stress echocardiografie. Met behulp van een nieuwe meta-analyse methode werd op een systematische wijze de gegevens van de beschikbare literatuur samengevat. Uiteindelijk voldeden 58 onderzoeken met in totaal 8,119 patiënten aan de inclusiecriteria. Dobutamine stress echocardiografie liet een positieve trend zien met betrekking tot een betere diagnostiek in vergelijking met andere onderzoeken, maar verschilde alleen statistisch significant met myocard perfusie scintigrafie. Hoewel, de voorkeur uitgaat naar dobutamine stress echocardiografie is er enige twijfel over de betrouwbaarheid bij patiënten met een hartklepaandoening en linker-ventrikel disfunctie.

Deel 3: Peri-operatieve farmacolgische therapie

In hoofdstuk 11 wordt in een editorial, een overzicht van de mogelijke redenen beschreven waarom in hoog-risisco patienten met coronairlijden geen bèta-blokkers wordt gegeven. In deze editorial worden verschillende kwesties geanalyseerd, zoals hoe vaak er sprake is van ondergebruik van bèta-blokkers, de mogelijke redenen voor het niet geven van bèta-blokkers en aanbevelingen.

Vervolgens wordt in hoofdstuk 12 als eerste, een studie beschreven waarin een verband is aangetoond tussen het gebruik van cholesterolverlagens als statinen en een lagere peri-operatieve sterfte in patiënten die een grote niet-cardiale vaatoperatie ondergaan. Patiënten die een grote niet-cardiale vaatoperatie ondergaan, hebben een verhoogd risico op peri-operatieve sterfte als gevolg van onderliggend coronairlijden. Statinen kunnen de peri-operatieve sterfte enerzijds reduceren door een verbetering van het lipiden profiel en anderzijds door de stabilisatie van de coronaire plaques op de vaatwand. Om deze associatie te evalueren is er een case-control studie uitgevoerd in 2816 patiënten die een grote vaatoperatie hebben ondergaan in het Erasmus MC tussen 1991 en 2000. Voor deze studie zijn alle patiënten bekeken die tijdens of na de operatie overleden zijn in het ziekenhuis (160 patienten, 5.8%). De resultaten laten zien dat deze overleden patiënten significant minder vaak statinen kregen dan de controle patienten (18% versus 25%; $P<0.001$). De gecorrigeerde odds ratio voor peri-operatieve mortaliteit

bij patiënten die statinen krijgen in vergelijking tot diegenen die geen statinen krijgen was 0.22 (95% CI 0.10 – 0.47). Deze studie heeft voor het eerst aangetoond dat het gebruik van statinen de peri-operatieve sterfte reduceert in patiënten die een grote vaatoperatie ondergaan.

In hoofdstuk 13 wordt het gecombineerde effect beschreven van het gebruik van statinen en bèta-blokkers in relatie tot de peri-operatieve sterfte. Er werden 570 patienten bestudeerd die een electieve operatie van de abdominalis aorta aneurysma operatie hebben gehad in het Erasmus MC in de periode tussen 1991 en 2000. In deze patiënten werd gekeken naar klinische risicofactoren en het gebruik van statinen en bèta-blokkers. De belangrijkste uitkomstmaat was een combinatie van totale sterfte en non-fatale hartinfarct binnen 30 dagen na de operatie. De resultaten van deze studie tonen aan dat de incidentie van het bovengenoemde gecombineerde eindpunt significant lager was in diegenen die statinen gebruikten in vergelijking tot diegenen die geen statinen gebruikten (3.7% versus 11.0%; gecorrigeerde odds ratio 0.24, 95% CI 0.10 – 0.70; P=0.01). Het gebruik van bèta-blokkers was ook geassocieerd met een significante reductie in het gecombineerde eindpunt (gecorrigeerde odds-ratio 0.24, 95% CI 0.11 – 0.54). Ondanks het feit dat degenen die bèta-blokkers gebruikten ook statinen gebruikten, is er geen bewijs geleverd dat er een differentieel gunstig effect bestaat van het gebruik van statinen op het gebruik van bèta-blokkers. Dus, het gebruik van statinen lijkt onafhankelijk geassocieerd te zijn met een lagere incidentie van peri-operative sterfte en non-fataal hartinfarct, zelfs wanneer er bèta-blokkers worden gebruikt.

Deel 4: Langdurige farmacologische therapie

In hoofdstuk 14 wordt ingegaan op de optimale lange termijn behandeling na een grote vaatoperatie. Centraal hierin staan de lange termijn follow-up gegevens van de Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography studie. Dit onderzoek werd verricht onder 1286 van de 1351 patiënten die 30 dagen na hun operatie nog in leven waren. De resultaten van dit onderzoek laten zien dat inspanningsgeïndiceerde ischemie tijdens een dobutamine stress echocardiogram van aanvullende prognostische waarde is, ongeacht het klinische risico profiel. Patiënten die een bèta-blokkers kregen bleken een significant

lager risico te hebben dan patiënten die geen bèta-blokker kregen. Hierbij dient wel te worden opgemerkt dat het gunstige effect van bèta-blokkers waarschijnlijk afhankelijk was van het al dan niet hebben van cardiale risicofactoren en inspanningsgeïndiceerde cardiale ischemie tijdens een dobutamine stress echocardiogram.

In hoofdstuk 15 wordt de associatie tussen het langdurig gebruik van statines en sterfte na een succesvolle operatie van een aorta aneurisma beschreven. De belangrijkste resultaten van dit onderzoek betreffen de significant lagere sterfte en cardiovasculaire sterfte tussen patiënten die wel en niet met statines werden behandeld. Na correctie voor klinische risicofactoren en het gebruik van bèta-blokkers, bleef de associatie tussen het gebruik van statines en verminderde sterfte (hazard ratio: 0.4, 95% CI, 0.3-0.6) en cardiovasculaire sterfte (hazard ratio: 0.3, 95% CI, 0.2-0.6) bestaan. Op basis hiervan lijkt het dan ook gerechtvaardigd om langdurig gebruik van statines te overwegen bij patiënten die geopereerd zijn aan een abdominalis aorta aneurisma.

Tot slot kan worden geconcludeerd dat peri-operatieve en lange termijn cardiale risico inschatting en behandeling van patiënten die een grote vaatoperatie ondergaan één van de meest uitdagende en controversiële terreinen is binnen de klinische geneeskunde. Door middel van ons onderzoek hebben we laten zien dat wanneer gebruik gemaakt wordt van geschikte onderzoeksmethoden voor pre-operatieve risicostratificatie en gebruik gemaakt wordt van peri-operatieve en lange termijn risicoreductie strategieën, patiënten niet alleen veilig geopereerd kunnen worden, maar hier ook op de korte en op de lange termijn van kunnen profiteren.

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The second twist in my journey came when I happened to study basic epidemiology at the London School of Hygiene and Tropical Medicine, University of London, Great Britain. I was taught that epidemiology is more than just a science dealing with the transmission and control of infectious diseases. My interest in the field of clinical epidemiology was born and I decided to do a further research training at the Netherlands Institute for Health Sciences, Rotterdam, the Netherlands.

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Curriculum vitae

Miklos David Kertai was born on January 1, 1973 in Szeged, Hungary. He received his medical degree from the Semmelweis Medical University, Budapest, Hungary in 1995. In the same year he started his training in anaesthesiology at the Department of Anaesthesiology and Intensive Care Unit, St. Stephen Hospital, Budapest, Hungary. In 1999 he interrupted his training to complete a Doctor of Science postgraduate course in Clinical Epidemiology at the Netherlands Institute for Health Sciences, Rotterdam, the Netherlands. During his postgraduate studies in Clinical Epidemiology he became a research fellow at the Department of Cardiology of the Thoraxcenter in Rotterdam. The research described in this thesis was performed between 2001 and 2004 under the supervision of Prof. dr. Don Poldermans and Dr. Eric Boersma. Subsequently, the clinical training in anaesthesiology will be continued.

List of publications

Papers

1. **Kertai MD**, Steyerberg EW, Boersma E, Bax JJ, Vergouwe Y, van Urk H, Habbema JDF, Roelandt JRTC, Poldermans D. Validation of two risk models for perioperative mortality in patients undergoing elective abdominal aortic aneurysm surgery. Vasc Endovascular Surg 2003; 37: 13-21.
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