# Perioperative Cardiovascular Risk Stratification and Modification

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# Perioperative Cardiovascular Risk Stratification and Modification

## Perioperatieve cardiovasculaire risicostratificatie en risicomodificatie

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# Contents

# Preface

Worldwide, annually approximately 100 million people undergo some form of non-cardiac surgery. Cardiac events, such as myocardial infarction are a major cause of perioperative morbidity and mortality in these patients. Though the true incidence of perioperative cardiac complications is difficult to assess, it is estimated that approximately 2.0–3.5% of patients undergoing major non-cardiac surgery experience a major adverse cardiac event. Furthermore an estimated 0.5–1.5% of patients die within 30 days after the surgical procedure due to a cardiovascular cause. The pathophysiology of perioperative cardiac events is complex. Similar to the non-operative setting it is thought that approximately half of all perioperative myocardial infarctions are attributable to a sustained coronary oxygen demand/supply mismatch. Coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is thought to be the other important cause of acute perioperative coronary syndromes.

### Part 1. Preoperative cardiovascular risk assessment

The risk of perioperative cardiac complications depends on mainly two conditions: (1) the condition of the patient prior to surgery, i.e. the presence and severity of co-morbidities, and (2) the type of the surgical procedure. The first part of this thesis covers current knowledge and existent data on preoperative cardiac risk assessment. In this part adjustments of current risk indices to improve the predictive ability, the value of additional cardiac testing and possible new preoperative cardiac risk markers are investigated.

### Part 2. Perioperative cardiovascular risk reduction

Once perioperative cardiac risk is assessed, the next step is to treat patients with an increased cardiac risk optimally to minimize the risk of perioperative cardiac complications. In part 2 of this thesis several possible risk reduction strategies are discussed, including beta-blocker therapy, 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitor (statin) therapy, prophylactic coronary revascularization and endovascular treatment modalities.

Beta-blockers have negative chronotropic and negative inotropic effects. Due to the role of sympathetic activation in adverse perioperative cardiac outcomes, beta-adrenergic receptor blocking drugs have been proposed as a means for providing cardioprotection. Potential cardioprotective mechanisms of beta-blockers include a) reduced heart rate and contractility and subsequently

lower myocardial oxygen demand; b) a shift in energy metabolism from free fatty acids to the more energy efficient glucose; c) anti-arrhythmic effects; d) anti-renin/angiotensin properties; and e) anti-inflammatory effects possibly promoting plaque stability. The effects on heart rate, contractility, and energy substrate shift occur almost instantly while the anti-inflammatory effects may only be observed after a prolonged beta-blocker usage. Recently the benefits of perioperative beta-blocker therapy have been questioned. This part of the thesis describes (1) which patients might benefit from perioperative beta-blocker therapy, and (2) what the potential pitfalls of perioperative beta-blocker therapy are.

Numerous clinical trials have clearly demonstrated that statin use is associated with a substantial long-term reduction in the risk for cardiovascular morbidity and mortality in patients with or at risk of coronary heart disease. However, lipid lowering seems not to be the only beneficial effect of statins. Other, so-called pleiotropic, effects of statins have recently been described. One of these pleiotropic effects may be the stabilization of vulnerable coronary plaques during surgical procedures which might result in a substantial reduction of perioperative adverse cardiac events. However, the timing of initiation of statin therapy remained a matter of debate. Should the patient start with statin therapy at the preoperative screening visit while there is (1) a possibly increased risk for perioperative statin-induced side effects such as myopathy, as suggested by the ACC/AHA/NHLBI clinical advisory on the use and safety of statins, (2) a possibly increased cardiac risk if statin therapy has to be interrupted in the perioperative period, as is to be expected in approximately 25% of patients, and (3) the evidence supporting the perioperative use of statins is based on retrospective studies? This part of the thesis tries to answer these questions.



The role of preoperative coronary revascularization in patients at high cardiac risk undergoing non-cardiac surgery is ill-defined. The concept of a beneficial effect of prophylactic coronary revascularization before non-cardiac surgery is based on the assumption that perioperative myocardial infarctions arise at locations in coronary arteries with hemodynamically critical stenosis, elicited by the stress of surgery. Evidence for the use of this potentially cardioprotective procedure is based on the results of two registries which showed an improved outcome in non-cardiac surgical patients with a history of coronary artery bypass grafting (CABG) or percutaneous coronary intervention with stent placement (PCI) compared to a similar patient group without a CABG or PCI. It must be noted however that the time interval between coronary revascularization and the non-cardiac procedure in these registries was 4.1 and 2.4 years respectively. Therefore the indication of prophylactic coronary revascularization immediate prior to the non-cardiac surgical procedure remained speculative. Therefore, the potential benefit of prophylactic coronary revascularization in high risk patients has been investigated and is described in part 2 of this thesis.

### Part 3. Long-term cardiovascular risk reduction

After successful non-cardiac surgery certain patient populations remain at increased risk for cardiac events. Patients who underwent non-cardiac vascular surgery are particular prone to long-term adverse cardiac outcome. The high cardiac risk in this population is attributable to the high prevalence of underlying coronary artery disease. As was already shown in 1984 only 8% of patients undergoing major non-cardiac vascular surgery have a normal coronary artery tree. In part 3 of this thesis the long-term prognosis of patients undergoing non-cardiac vascular surgery is examined. Furthermore several risk reduction strategies are studied such as prophylactic coronary revascularization, the use of endovascular treatment modalities and the importance of aggressive medical therapy in this high-risk group of patients. After all, the patient should live long enough to enjoy the benefits of surgery.

# Part I

## Preoperative Cardiovascular Risk Assessment

# Chapter 1

## Cardiac complications

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Since the landmark publication of Hertzer and colleagues from the Cleveland Clinic in 1984[1] the coexistence of coronary artery disease (CAD) and peripheral arterial disease (PAD) has been accepted with almost religious zeal by physicians treating patients with PAD.

## EPIDEMIOLOGY

### A. Prevalence of cardiac disease

Hertzer's seminal study, in which 1000 consecutive patients undergoing operations for PAD underwent preoperative cardiac catheterizations (whether or not they had symptoms of CAD), is unlikely ever to be repeated, and the published article is one of the most widely quoted articles in the medical and surgical literature. These investigators reported that only 8% of their patients (who were roughly divided into thirds—aortic, infrainguinal, and carotid disease) had normal coronary arteries, and approximately one third had severe-correctable or severe-inoperable CAD. More recent studies using functional tests for CAD such as dobutamine stress echocardiography confirmed these findings. In a study population of 1097 vascular surgical patients, the incidence of rest wall motion abnormalities was nearly 50%, while one-fifth of patients had stress-induced myocardial ischaemia[2].

### B. Definition of cardiac complications

Numerous undesirable cardiac events have been evaluated and considered as endpoints in clinical reviews of peripheral vascular surgery, including (1) unstable angina pectoris, (2) congestive heart failure, (3) arrhythmias, (4) myocardial ischemia (overt and "silent"), (5) nonfatal myocardial infarction, and (6) cardiac death. Of these adverse events, the first four endpoints are relatively "soft" compared with the last two.

Unstable angina is included as one of the acute coronary syndromes (ACS); however, it does not routinely produce lasting cardiac damage, and its definition is variable, ranging from a mere change in frequency of chest pain to unrelenting pain unresponsive to standard therapeutic maneuvers, such as administration of nitroglycerin and rest.

Congestive heart failure may be the result of fluid overload, which often occurs after vascular procedures or the use of a narcotic agent as the primary anesthetic. The diagnosis of congestive heart failure is often subjective with no consensus regarding the criteria required to confirm the diagnosis (i.e. jugular venous distention, dyspnea, rales, gallop rhythm, typical chest x-ray findings, pedal or sacral edema, objective measurement of decreased cardiac output—in variable combinations).

Arrhythmias may be brief, self-limiting, hemodynamically benign, and due to factors other than cardiac disease, including hypoxia, drug toxicity, or metabolic derangements.

Myocardial infarction and cardiac death are more serious cardiac complications. The Joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) Committee for the Redefinition of Myocardial Infarction has made a clear definition of myocardial infarction (TABLE 1.1)[3]. The definition includes the rise and fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia; ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block); development of pathological Q waves on ECG; imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities.

| **Table 1.1** | Definition of myocardial infarction. |
|---|---|
| | Diagnosis of myocardial infarction if any one of the following criteria is met: |
| (1) | Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:<br>(1) Symptoms of ischemia;<br>(2) ECG changes indicative of new ischemia, i.e. new ST-T changes or new left bundle branch block (LBBB)<br>(3) Development of pathological Q waves in the ECG;<br>(4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. |
| (2) | Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. |
| (3) | Pathological findings of an acute myocardial infarction. |

Cardiac death was defined in the same document: sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new left bundle branch block, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

*Biomarkers*

This definition of myocardial infarction and cardiac death might be sufficient for non-surgical patients. However it should be noted that up to 75% of perioperative myocardial infarctions remain asymptomatic and may therefore be difficult to assess[4]. This might be attributable to the disguising effects of sedation and the simultaneous occurrence of symptoms directly related to surgery such as nausea. This implies a serious underestimation of the true incidence of so-called "hard" cardiac endpoints in vascular surgery patients. It also implies a call for routine postoperative measurement of cardiac biomarkers in patients scheduled for major vascular surgery since cardiac complications are most common in these patients and these patients are most likely the ones not able to indicate symptoms of acute coronary syndromes.

Cardiac troponin (I or T) is the preferred biomarker for myocardial injury. It has nearly absolute myocardial tissue specificity as well as high clinical sensitivity[5]. As stated in the consensus document an increased value for cardiac troponin is defined as a measurement exceeding the 99th percentile of a normal reference population. Detection of a rise and fall of the measurements is essential to the diagnosis of acute myocardial infarction[6]. The 99th percentile must be determined for each specific assay with appropriate quality control. The values for the 99th percentile can be found on the International Federation for Clinical Chemistry website[7]. Blood samples for the measurement of troponin should be drawn on first assessment (often some hours after the onset of symptoms) and 6–9 hours later[8]. To establish the diagnosis of myocardial infarction, one elevated value above the decision level is required. The demonstration of a rising and/or falling pattern is needed to distinguish background elevated troponin levels, e.g. patients with chronic renal failure, from elevations in the same patients which are indicative of myocardial infarction[6].

CKMB is the best alternative if troponin assays are not available. As with troponin, an increased CKMB value is defined as a measurement above the 99th percentile.[9] As with troponins, CKMB measurements should be recorded at the time of the first assessment of the patient and 6–9 hours later in

order to demonstrate the rise and/or fall exceeding the 99th percentile URL for the diagnosis of myocardial infarction.

*ECG*

The ECG is an integral part of the diagnostic work-up of patients with suspected myocardial infarction and also a cornerstone in the consensus document on myocardial infarction[10]. The acute or evolving changes in the ST-T waveforms and the Q-waves when present potentially allow the clinician to date the event, to suggest the infarct-related artery, and to estimate the amount of myocardium at risk. The diagnosis of myocardial infarction is difficult in the presence of LBBB even when marked ST-T abnormalities or ST elevation are present that exceed standard criteria[11,12]. In such cases a previous, preoperative ECG may be helpful to determine the presence of acute myocardial infarction in this setting. In patients with right bundle branch block (RBBB), abnormalities in leads V1–V3 are common, making it difficult to assess the presence of ischemia in these leads; however, when ST elevation or Q-waves are found in the postoperative period, myocardial ischemia or infarction should be considered[10].

## C. Incidence of cardiac complications

Although the widespread prevalence of CAD in patients requiring peripheral vascular surgery is well accepted, the frequency of adverse cardiac outcomes in unselected groups of vascular patients is more controversial. Comparison of cardiac morbidity of vascular operations between different studies is often misleading because the frequency of cardiac complications depends on the vigor with which the diagnosis is pursued. Prospective trials tend to include only specific patient groups while large registries might be less accurate in scoring cardiac complications. Since "soft" cardiac endpoints are difficult to assess in a uniform way, in particular in retrospective series, it is probably more accurate to look at "hard" cardiac endpoints such as cardiac death and myocardial infarction. Therefore only a crude estimate of the magnitude of cardiac complications after vascular and endovascular surgery can be given.

Objective measurements such as continuous 12-lead ECG recording in the perioperative period combined with rigorous screening of cardiac biomarkers might give a more accurate estimation of the true incidence of perioperative cardiac complications. A few studies have used this modality though

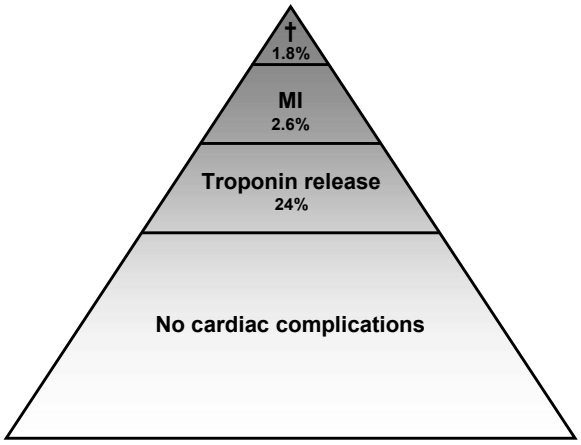



**Figure 1.1** Incidence of perioperative cardiac complications based on a recent study by Poldermans et al.[54]
† = cardiac death, MI = Myocardial infarction

it must be noted that only major vascular procedures were included (FIGURE 1.1). One of these studies is a study by Landesberg et al. in which 447 patients scheduled for elective abdominal aortic surgery (n=70), peripheral arterial bypass surgery (n=163) or carotid artery surgery (n=214) were followed using continuous 12-lead ECG recording and cardiac troponin T and I and CK/CK-MB measurement on the first three postoperative days[13]. In 14.8% of these patients perioperative ST-segment changes were observed. Furthermore, 23.9% of patients experienced cardiac troponin T or I release.

Cohort studies tend to report a lower incidence of cardiac events. In a recent report by Welten et al. 30-day mortality in a group of 2,730 patients undergoing non-cardiac vascular surgery was 1% for patients undergoing CEA, 6% for patients undergoing AAA repair and 3% for patients undergoing lower extremity arterial revascularization[14]. Importantly in all three patient groups approximately 75% of deaths were related to cerebrocardiovascular causes. The percentage of approximately 5% cardiac events has been confirmed in the prospective Euro Heart Survey including over 700 patients undergoing elective arterial vascular surgery[15]. In 2002 Krupski et al reviewed all major series reporting 100 or more patients, and the average MI rate after aortic, carotid, and infrainguinal operations were 2.2% (7500 patients), 1.0% (28,000 patients), and 4% (6000 patients), respectively[16]. To demonstrate the difference attributable to the vigor of postoperative screening for cardiac events: in prospective studies with routine measurement of cardiac troponins and continuous ECG monitoring perioperative myocardial infarction occurs in as many as 20% of patients as has been shown by Landesberg et al[13].

Carotid artery surgery seems to be associated with the lowest incidence of adverse cardiac events despite the limitations described above. The incidence of myocardial infarction in patients undergoing carotid endarterectomy is estimated to be approximately 1% as has recently been reported by Greenstein et al in a group of 9,308 patients (MI 1.1%)[17] and the CEA National Surgical Quality Improvement Program including 13,622 patients with a cardiac event rate of 1.1%[18]. In the recently published randomized controlled trials carotid stenting does not seem to be superior to endarterectomy in terms of cardiac outcome. Only in the SAPPHIRE trial stenting tended to be associated with less perioperative myocardial infarctions 2.4% vs. 6.1% (p=0.1)[19]. The CAVATAS trial did not find a significant difference in the incidence of myocardial infarctions in patients randomized to either open (n=253) or endovascular (n=251) treatment, 1% and 0% respectively[20]. Unfortunately both SPACE and EVA-3S did not report perioperative myocardial infarctions separately[21,22]. Furthermore, a recent Cochrane review did not show any advantage of either procedure in terms of cardiac outcome[23]. Considering the relatively low incidence of major cardiac complications in extracranial carotid surgery it is unlikely that there is a clinically relevant difference in cardiac outcome in patients without an extremely high preoperative cardiac risk.

Aortic aneurysm repair is a high-risk surgical procedure. Patients scheduled for AAA repair seem to have a clear perioperative survival benefit of endovascular repair, indicating a possible cardiac advantage of endovascular treatment. Interestingly this was not confirmed in the two major randomized controlled trials on this subject. Though the overall complication rate was significantly lower in the endovascular treated group in the DREAM trial, the incidence of perioperative cardiac complications was similar in patients undergoing open or endovascular repair (5.7% vs. 5.3%)[24]. Also, in a systematic review by Drury et al in 2005 no perioperative cardiac benefit could be found in patients undergoing endovascular AAA repair (HR 0.81, 95% CI 0.35-1.86)[25]. In the EVAR 1 trial overall mortality was significantly reduced in patients treated with endovascular stent grafts (1.7% vs. 4.7%), indicating a lower perioperative cardiac risk in these patients though nonfatal MIs were not reported[26]. It is unclear why in some reports no perioperative benefit of endovascular procedures was found while

in the vast majority of cohort series endovascular repair is associated with less perioperative cardiac complications. This has recently been confirmed in the large Medicare database (22,830 patients) of Schermerhorn et al.: myocardial infarction occurred in 7.0% and 9.4% in endovascular and open procedures respectively ($p<0.001$)[27]. To compare open surgical procedures and endovascular procedures for lower extremity arterial revascularization proves to be even more difficult. Indications for open or endovascular treatment differ substantially and cardiac complications rates can therefore only be considered separately.

Though a reliable figure for perioperative cardiac complications in patients scheduled for elective vascular surgery can not be given, overall it is estimated that extracranial carotid procedures are less prone to cardiac complications than abdominal aortic and peripheral arterial bypass procedures (1% vs. 3-5%).

## II. PATHOGENESIS OF PERIOPERATIVE ACUTE CORONARY SYNDROMES

Although the pathophysiology of perioperative acute coronary syndromes is not entirely clear, it is now well accepted that coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is an important cause of acute perioperative coronary syndromes (FIGURE 1.2A and 1.2B). This is similar to the nonoperative setting.

The perioperative surgical stress response includes a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability[28]. In patients with significant coronary artery disease (CAD), perioperative myocardial infarction (PMI) may also be caused by a sustained myocardial supply/demand imbalance due to tachycardia and increased myocardial contractility[28].

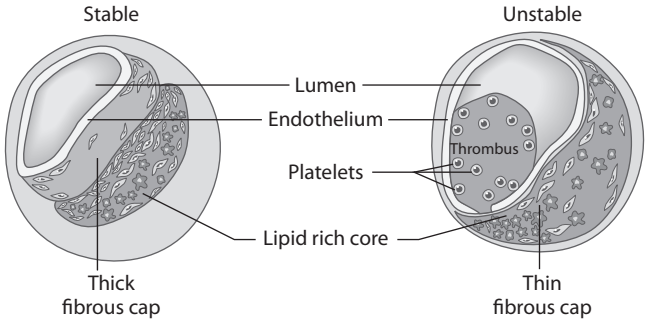



**FIGURE 1.2A** In contrast to atherosclerotic disease of peripheral arteries, in which complications are usually directly related to the degree of stenosis and hypoperfusion (e.g., high-grade carotid artery stenoses), lesions within the coronary arteries may cause acute events even when stenoses are not critical. This is due to relatively unstable or "vulnerable" plaques with a large lipid pool and a thin, weakened fibrous cap (shown in the second diagram) infiltrated by macrophages. These plaques are most susceptible to disruption and development of platelet-derived thrombosis. Infiltration by macrophages and other inflammatory cells produces a vulnerable cap most vulnerable to disruption. Cytokines and proteases involved in the balance between synthesis and degradation of collagen and elastin determine structural integrity and play an important role in acute coronary events. Identification of and intervention for hemodynamically significant coronary artery lesions may not provide secure protection against perioperative adverse cardiac events after vascular surgery.

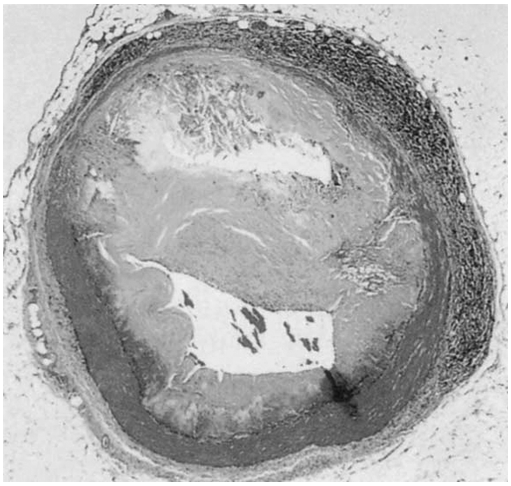


**FIGURE 1.2B** Electron micrograph showing extraordinary infiltration of myeloperoxidase-laden neutrophils into a section of coronary artery from a patient with unstable angina. This is a diffuse process, not localized to a single vulnerable plaque. The implications are that focused therapy (e.g., percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery) may not be protective against coronary events in the vascular patient; instead, anti-inflammatory (e.g., antiplatelet therapy) treatment, stabilization with antilipid treatments, and beta blockers to decrease myocardial oxygen consumption may be more beneficial than mechanical approaches.



Episodes of perioperative ST-segment depression, indicating subendocardial myocardial ischemia, have been described in up to 41% of vascular surgery patients, mostly occurring within the first 2 days after surgery[29]. The association of PMI with myocardial ischemia and nontransmural or circumferential subendocardial infarction supports this mechanism. Landesberg demonstrated that 85% of postoperative cardiac complications were preceded by prolonged ST-segment depression[30]. Fleisher et al. found that 78% of patients with cardiac complications had at least 1 episode of prolonged myocardial ischemia (i.e. >30 minutes), either before or at the same time as the cardiac event. In the majority of cases, it presents without Q waves[31]. The hypothesis that ST-segment depression can lead to PMI is further supported by increased troponin T levels during or shortly after prolonged ST-segment depression ischemia[32]. ST-segment elevation–type ischemia is considered to be relatively uncommon, confirmed by the incidence (12%) of intraoperative ST-segment elevation in a study by London et al[33].

Plaque disruption, defined as fissure or rupture of plaque and hemorrhage into the plaque cavity[34], is the cause of fatal PMIs in approximately half of the cases as was demonstrated in the autopsy study by Dawood et al. Similar autopsy results were found in the study by Cohen and Aretz[35]; a plaque rupture was found in 46% of patient with post-operative MI. "Unstable" plaques have a large lipid core and a thin, weakened fibrous cap infiltrated by macrophages (FIGURE 1.2A and 1.2B). It is hypothesized that these plaques with a large lipid pool and a thin, weakened fibrous cap infiltrated by macrophages and other inflammatory cells are the most vulnerable to disruption. Cytokines and proteases involved in the balance between synthesis and degradation of collagen and elastin, which determines the structural integrity of the plaque cap, play an important role in perioperative acute coronary events.

In a study of Feringa et al., vascular surgery patients were evaluated by continuous 12-lead electrocardiographic monitoring during surgery and studied for the presence and location of ischemia. The relationship with the pre-operatively assessed culprit coronary artery lesion using noninvasive cardiac imaging was studied. In patients with perioperative ST-segment depression, the location corresponded with the pre-operatively assessed coronary lesion in 89%, and only in 53% of those with ST-segment elevation ($p<0.001$). This study showed one of the limitations of pre-operative cardiac risk assessment focusing on the identification of the culprit coronary artery lesion. Using cardiac testing, one can identify the patient at risk; however, the location of the PMI is difficult to foresee owing to the unpredictable progression of (asymptomatic) coronary artery lesions toward unstable plaques owing to the stress of surgery.

## III. CLINICAL PRESENTATION

In postoperative patients, symptoms of cardiac complications might very well be atypical or absent even when ECG and/or biomarkers are abnormal. It is important to realize that myocardial infarction might occur with atypical symptoms, or even without symptoms, being detected only by ECG, biomarker elevations, or cardiac imaging. An estimated 75% of patients who have objective evidence of MI are not diagnosed as such because symptoms are masked by residual anesthetic effects, administration of analgesic agents, competing somatic stimuli such as incisional pain, and other factors.

Classical symptoms of myocardial ischemia include various combinations of chest, upper extremity, jaw, or epigastric discomfort with exertion or at rest. Often, the discomfort is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnea, diaphoresis, nausea, or syncope. Considering these classical symptoms it is hardly surprising that such a large number of episodes of myocardial ischemia and infarction are missed in the perioperative period. Physicians should therefore be liberal in the ordering of laboratory tests such as cardiac troponin measurements in patients who underwent vascular surgery. This becomes even more important as even asymptomatic troponin release has severe implications for patients' outcome (see below).

## IV. PREOPERATIVE CARDIAC EVALUATION

### A. Clinical risk factor indices

Adequate preoperative cardiac risk assessment is essential for identifying high-risk patients for perioperative cardiac events. Several risk indices were developed to stratify vascular surgical patients, based on clinical cardiac risk factors.

The cardiac risk index of Goldman et al in 1977 was the first multifactorial model specifically for perioperative cardiac complications to be widely used[36]. This risk index was developed in a non-cardiac surgical population. The authors identified nine independent risk factors correlated with postoperative serious or fatal cardiac complications: (1) preoperative third heart sound or jugular venous distention; (2) MI in the preceding 6 months; (3) >5 premature ventricular contractions per minute documented at any time before operation; (4) rhythms other than sinus rhythm or the presence of premature atrial contractions on preoperative electrocardiogram (ECG); (5) age >70 years; (6) an intraperitoneal, intrathoracic, or aortic operation; (7) emergency operation; (8) important valvular aortic stenosis; and (9) poor general medical condition. This index was modified by Detsky et al in 1986[37], who added the presence of angina and a remote history of MI to the original model of Goldman et al.

They used a Bayesian approach involving pretest probabilities, and presented the modified cardiac risk index in a simple normogram.

The Glasgow aneurysm score, described in 1994, was one of the first cardiac risk scores only intended for vascular surgical procedures. In a retrospective study of 500 randomly chosen patients scheduled for open abdominal aortic aneurysm repair, potential preoperative risk factors were related to postoperative in-hospital mortality[38]. One year later, the Leiden Risk Model for perioperative mortality in patients with an abdominal aortic aneurysm was developed by Steyerberg et al[39]. This clinical prediction rule was based on several risk factors obtained from the literature, and validated in a cohort of 246 patients undergoing open abdominal aortic aneurysm repair.

In 1996, L'Italien et al developed and validated a Bayesian model for preoperative cardiac risk assessment in a total of 1081 consecutive patients undergoing elective major vascular surgery[40]. This study had a combined endpoint of nonfatal MI or cardiac death. Using 567 patients as a derivation cohort, the following risk factors were identified as predictors of adverse postoperative outcome: myocardial infarction, congestive heart failure, angina pectoris, prior coronary revascularization, diabetes mellitus, and age >70 years. Importantly, the validation cohort (514 patients) exhibited a prognostic accuracy of 74%. Patients classified as low-risk, intermediate-risk, and high-risk had cardiac event rates of 3%, 8%, and 18%, respectively.

Lee et al developed the largest and currently most widely used model of risk assessment, the Revised Cardiac Risk Index in 1999[41]. This index identifies six predictors of major cardiac complications: (1) high-risk type of surgery, (2) history of ischemic heart disease, (3) history of congestive heart failure, (4) history of cerebrovascular disease, (5) preoperative treatment with insulin, and (6) preoperative serum creatinine >2.0 mg/dL. Based on the presence of none, 1, 2, or ≥ 3 predictors, the rate of major cardiac complications in the validation cohort (n = 1422) was estimated to be 0.4%, 0.9%, 7%, and 11%, respectively.



The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE) I Trial identified comparable independent clinical risk factors associated with major vascular surgery: a history of myocardial infarction, angina, congestive heart failure, diabetes, renal dysfunction, cerebrovascular events, and age >70 years[2]. Recently, Kertai et al developed a Bayesian model for the prediction of all-cause perioperative mortality in 1537 patients undergoing all types of open vascular surgery (TABLE 1.2)[42]. Risk factors associated with postoperative all-cause death included ischemic heart disease, congestive heart failure, cerebrovascular events, hypertension, renal dysfunction, chronic pulmonary disease, and type of vascular surgery, i.e. ruptured aneurysm of the abdominal aorta (AAA), elective AAA, lower extremity, and carotid vascular surgery. The final logistic regression model with nine independent predictors (including beta-blocker and statin use) of perioperative mortality was used to create a variable-weight index, the Customized Probability Index, where scores were assigned based on parameter estimates of individual predictors. The sum of scores of surgical risk (0-46 points), medical history (0-67 points), and cardioprotective medication (statins -10 points and beta-blockers -15 points) was calculated for an overall cardiac risk.

### B. Laboratory

Apart from those measurements indicating clinical risk factors (for example, serum creatinine for renal failure, fasting glucose for diabetes mellitus, etc) currently no routine laboratory measurements are related to perioperative cardiac complications. Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP) have been shown to be associated with adverse

**TABLE 1.2** Customized Probability Index (derived from Kertai et al.[42])

Estimated Probability of Perioperative All-Cause Mortality

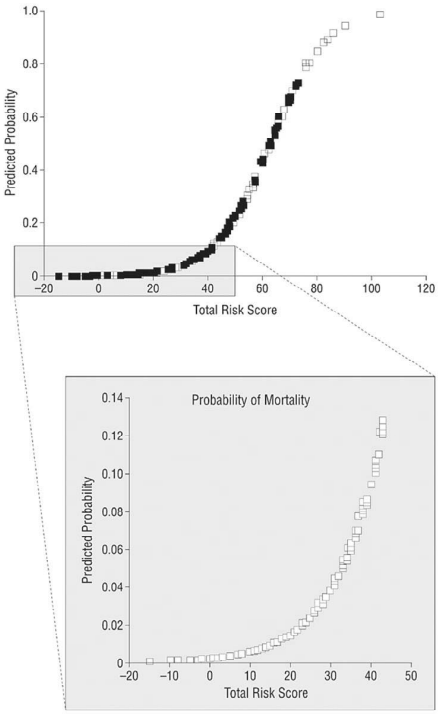
Assign scores as indicated for each characteristic according to type of vascular procedure, medical history, and long-term medication use.

| Vascular Surgical Procedures | Scores |
|---|---|
| High risk | |
| Acute abdominal aortic aneurysm rupture | +43 |
| High-intermediate risk | +26 |
| Thoracoabdominal surgery | |
| Abdominal aortic surgery | |
| Low-intermediate risk | +15 |
| Infrainguinal bypass | |
| Low risk | 0 |
| Carotid endarterectomy | |

| Medical History | Scores |
|---|---|
| Cardiovascular morbidity | |
| Ischemic heart disease | +13 |
| Congestive heart failure | +14 |
| History of cerebrovascular event | +10 |
| Hypertension | +7 |
| Renal dysfunction | +16 |
| Chronic pulmonary disease | +7 |
| Long-term Medication | |
| β-Blocker use | - 15 |
| Statin use | - 10 |

Calculate the total score by summing the individual scores from the given characteristics and, using the total risk score, read the corresponding estimated probability of perioperative all-cause mortality.

| Characteristics | Scores |
|---|---|
| Vascular surgery procedures | |
| Medical history | |
| Long-term medication | |
| Total Risk Score | |




postoperative outcome in recent studies. NT-proBNP is increased in patients with left ventricular dilatation caused by fluid overload (e.g. heart failure and renal dysfunction), pressure overload (e.g. aortic valve stenosis), and myocardial ischemia, which might explain the excellent relation with adverse postoperative outcome. In a study by Dernellis et al. of 1590 patients scheduled for all types of non-cardiac general surgery elevated levels of BNP, i.e. >189 pg/mL, were independently associated with a staggering 34-fold increased risk for postoperative cardiac events[43]. Similar results were found by Feringa et al in their report on the prognostic value of NT-proBNP in 170 patients scheduled for major vascular surgery[44]. Patients with a NT-proBNP level >533 pg/mL had an independent 17-fold increased risk for postoperative cardiac events, even after adjustment for preoperative dobutamine stress echocardiography results. Gibson et al confirmed the predictive value of BNP in 149 major vascular surgical patients: using receiver-operator curve analysis a BNP concentration of 108.5 pg/mL best predicted the likelihood of cardiac events, with a sensitivity and specificity of 87%[45]. The true value of either BNP or NT-proBNP in the preoperative screening setting must be confirmed in large scale prospective trials such as the recently started multinational DECREASE VI trial.

Diabetes mellitus is a common risk factor in patients scheduled for vascular surgery with a prevalence of approximately 50% if all patients are thoroughly screened[46]. Diabetes mellitus is known to be a strong predictor for perioperative events. Therefore fasting glucose values should be obtained in all patients scheduled for vascular surgery and glucose loading testing should be considered in all. Recently it was shown that the level of preoperative glycosylated hemoglobin in diabetic patients is strongly related to perioperative cardiac outcome. In the same patient population it was also shown that in patients with high preoperative glycosylated hemoglobin it is more difficult to regulate

glucose values in the perioperative period[47,48]. This might partly explain the strong relation between preoperative glycosylated hemoglobin and outcome, since it is known from critically ill patients and patients with myocardial infarction that tight glucose control is of imminent importance. In a large case-control study by Noordzij et al. in non-cardiac nonvascular surgical patients it was also shown that random preoperative glucose levels were associated with postoperative outcome[49]. Those with a random glucose level ≥ 11.1 mmol/L had a 4-fold increased risk for perioperative cardiovascular death. Importantly, glucose levels of 5.6-11.1 mmol/L were independently associated with a 3-fold increased risk for perioperative cardiovascular events.

Preoperative asymptomatic troponin release in patients with symptomatic peripheral arterial disease is associated with a poor postoperative prognosis[50]. Preoperative troponin release may occur because of asymptomatic myocardial ischemia, a condition often observed in patients scheduled for major vascular surgery. As was already noted by Landesberg et al. in 1993, over 40% of patients planned for major vascular surgery experience silent myocardial ischemia preoperatively as assessed by continuous 12-lead ECG recording, including in asymptomatic patients[30]. Notably, both Landesberg et al. and Kertai et al. previously showed that even low levels of asymptomatic troponin elevations in the perioperative period are associated with worse long-term outcome in patients undergoing major vascular surgery[13,51].

Renal insufficiency is taken into account in most risk indices. For example, the serum creatinine cut-off value Lee et al used was 2.0 mg/dL (177 mmol/L)[41]. However, it might be argued that patients with less pronounced renal insufficiency also do worse compared to patients with normal serum creatinine values. A continuous variable for creatinine would probably be better, though not very user-friendly in every day practice. Recent studies have also shown that glomerular filtration rate might be a better predictor than serum creatinine since this takes into account the different creatinine concentrations between sexes[52].



### C. Non-invasive (stress) testing

Once the assessment of risk factors indicates an increased cardiac perioperative risk, or if there is a suspicion of CAD upon examination, further cardiac testing is warranted. According to the current guidelines of the American College of Cardiology/American Heart Association, preoperative cardiac exercise or pharmacologic stress testing is recommended for (1) patients with an intermediate pretest probability of CAD, (2) patients undergoing initial evaluation for suspected or proven CAD, (3) subjects with a significant change in clinical status, (4) demonstration of proof of myocardial ischemia before coronary revascularization, (5) evaluation of adequacy of medical treatment, and (6) prognostic assessment after an acute coronary syndrome.[53]

One of the main issues in preoperative cardiac risk assessment is to identify those patients who should undergo additional stress testing before surgery. The randomized, multicenter DECREASE II study[54] assessed the value of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart-rate control. In total, 1476 vascular surgical patients were divided into three risk groups based on the risk score of Boersma et al[2]. All 770 intermediate-risk patients were randomly assigned to preoperative cardiac stress testing or no testing. Importantly, all patients in the DECREASE II study received beta-blocker therapy, irrespective of stress-test results, aiming at tight heart-rate control, i.e. a heart rate of 60 to 65 beats per minute. This study demonstrated no differences in cardiac death and MI at 30 days between patients assigned to no testing versus cardiac stress testing (1.8% versus 2.3%; odds ratio [OR], 0.78; 95% confidence interval [CI], 0.28 to 2.1). These results indicate that intermediate-risk patients undergoing major vascular surgery are at a relatively

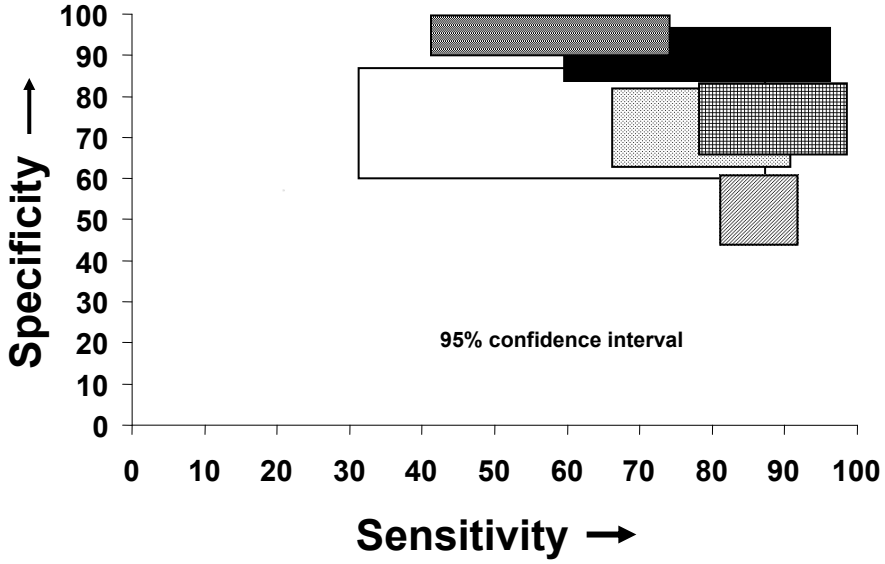



**FIGURE 1.3** Sensitivity and specificity of different types of preoperative non-invasive cardiac testing modalities (derived from Kertai et al.[57])
= Dipyridamole stress echo; = ST analysis; = Ejection fraction;
= Dobutamine stress echo; = Exercise ECG; = Dipyridamole thallium scan

low perioperative risk and do not benefit from preoperative cardiac testing when receiving beta-blocker therapy with tight heart-rate control.

For those patients who require cardiac testing, several noninvasive and physiological (and nonphysiological) stress tests are available for the evaluation of perioperative risk. Nonphysiological stress tests are especially recommended to detect preoperative myocardial ischemia in asymptomatic vascular surgery patients (FIGURE 1.3).

*C1. Rest Electrocardiography*

Different studies have shown an association between abnormal ECG findings and perioperative cardiac complications[36,37]. In a large prospective study by Lee et al involving 4315 patients undergoing major non-cardiac surgery, a history of ischemic heart disease was one of the six independent predictors of major cardiac complications[41]. Pathological Q-waves, as an electrocardiographic sign of MI in the past, were found in 17% of patients, with a 2.4-fold increased risk of perioperative events. A recent retrospective study confirmed the prognostic value of routine preoperative electrocardiography in 22,457 non-cardiac operations[55]. Patients with abnormal ECG findings had a higher incidence of 30-day cardiovascular death compared with patients with a normal ECG (1.8% versus 0.3%; adjusted OR, 3.4; 95% CI, 2.4 to 4.5). In addition, it was demonstrated that a preoperative ECG is also predictive of long-term outcome, independent of clinical findings and perioperative ischemia, in CAD patients undergoing major non-cardiac surgery[56].

*C2. ST-segment Holter recording*

The use of ambulant 24-hour ST-segment registration for evaluation of perioperative cardiac risk was first described by Raby et al.[57] They reported a sensitivity of 75% and a specificity of 83% for the prediction of a combined endpoint of cardiac death and nonfatal MI. A large meta-analysis showed

lower values, comprising eight studies with a total of 893 patients, with a weighted sensitivity of 52% (95% CI, 21% to 84%) and a specificity of 70% (95% CI, 57% to 83%)[58]. The advantages of ST-segment Holter include its low cost and wide availability.

*C3. Exercise Electrocardiogram*

The most commonly used physiologic stress test for detecting myocardial ischemia uses a treadmill or cycle ergometer. Among its advantages, this test provides an estimate of functional capacity, and hemodynamic response, and detects myocardial ischemia through ST-segment changes. The accuracy of an exercise ECG varies widely among studies. A meta-analysis by Kertai et al for the detection of myocardial ischemia with treadmill testing in vascular surgery patients showed a rather low sensitivity (74%; 95% CI, 60% to 88%) and specificity (69%; 95% CI, 60% to 78%) (FIGURE 1.3) comparable to daily clinical practice[58]. However, important limitations in patients with peripheral vascular disease involve their frequently limited exercise capacity. Furthermore, preexisting ST-segment deviations, especially in the precordial leads V5 and V6 at the rest ECG, make a reliable ST-segment analysis more difficult[59].

*C4. Stress Echocardiography*

Because most patients with peripheral vascular disease are unable to exercise maximally, stress echocardiography with pharmacologic stressors (such as dobutamine) is a good alternative. Although vasodilators (e.g. dipyridamole or adenosine) may have advantages for the assessment of myocardial perfusion, dobutamine is the preferred pharmacological stressor when the test is based on an assessment of regional wall-motion abnormalities[60].



Dobutamine is a synthetic catecholamine with predominantly β1-receptor-stimulating properties, resulting in a strong positive inotropic effect and modest chronotropic effect on the heart. During the stress test, dobutamine is intravenously administered. A graded dobutamine infusion starting at 5 µg/kg/min, and increasing at 3-minute intervals to 10, 20, 30, and 40 µg/kg/min, is the standard for dobutamine stress echocardiography (DSE). During dobutamine infusion, contractility and heart rate increase, leading to increased myocardial oxygen demand. Myocardial ischemia leading to systolic contractile dysfunction, detectable by echocardiography, occurs in regions supplied by hemodynamically significant stenotic coronary arteries.

Tissue harmonic imaging is advised for stress echocardiography. This special imaging setting reduces near-field artifacts, improves resolution, enhances myocardial signals, and is superior to fundamental imaging for endocardial border visualization. The improvement in endocardial visualization is further enhanced by the use of contrast agents for left-ventricular (LV) opacification. Contrast agents increase the number of interpretable LV wall segments. These recent developments exhibit decreased interobserver variability, and have improved the sensitivity of stress echocardiography[61].

Many reports demonstrated that DSE predicts perioperative events in patients undergoing vascular surgery[62,63]. The negative predictive value of dobutamine stress tests is high, although the positive predictive value is much lower.

Kertai et al reported a weighted sensitivity of 85% (95% CI, 74% to 97%) and a specificity of 70% (95% CI, 62% to 69%) for DSE in 850 patients from eight studies (FIGURE 1.3).[58] A recent meta-analysis by Beattie et al analyzed the predictive value of pharmacological stress testing compared with myocardial perfusion scintigraphy[64]. This report included 25 studies (3373 patients) of mainly dobutamine as well as dipyridamole stress echocardiography. The likelihood ratio of a perioperative event with a positive stress echocardiography was 4.09 (95% CI, 3.21 to 6.56).

*C5. Myocardial Perfusion Scintigraphy*

Myocardial perfusion scintigraphy (MPS) is a widely used technique in the preoperative risk assessment of patients undergoing vascular surgery. The technique involves intravenous administration of a small quantity of a radioactive tracer. The detection of CAD is based on a difference in blood-flow distribution through the LV myocardium. These differences in perfusion can be explained by insufficient coronary blood flow based on coronary stenosis. Nowadays, technetium-99m-labeled radiopharmaceutical is the most widely used tracer.

Myocardial perfusion scintigraphy is used in combination with exercise or pharmacologic stress testing to diagnose the presence of CAD. If there is a decrease or loss in regional perfusion after maximal vasodilatation with, for example, adenosine, as seen in hemodynamically significant CAD or in transmural MI, a reduced radiopharmaceutical signal is observed. Stress and rest MPS are compared for reversible abnormalities. A positive MPS is associated with an increased risk of perioperative and postoperative cardiac complications. A meta-analysis by Etchells et al investigated the prognostic value of semiquantitative dipyridamole MPS for perioperative cardiac risk in patients undergoing non-cardiac vascular surgery[65]. They included nine studies, involving a total of 1179 vascular surgery patients, with a 7% cardiac complication rate. One of the most important findings in this study was that reversible ischemia in <20% of the myocardial segments did not change the likelihood of perioperative complications. The previously mentioned meta-analysis which assessed the prognostic value of six diagnostic tests reported a sensitivity of 83% (95% CI, 77% to 89%) and a much lower specificity of 47% (95% CI, 41% to 57%) for MPS (FIGURE 1.3).[58]

## D. Invasive testing

Guidelines of the American College of Cardiology /American Heart Association (ACC/AHA) recommend coronary angiography for patients with high-risk noninvasive test results, and myocardial revascularization in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved[53]. This recommendation was supported by the Coronary Artery Surgery Study that showed a reduced incidence of non-fatal myocardial infarctions after previous bypass surgery among vascular surgery patients compared to those treated medically, 8.5% versus 0.6% (p=0.001)[66]. More recently, the data from the Bypass Angioplasty Revascularization Investigation trial showed that patients undergoing coronary bypass surgery and percutaneous coronary intervention experienced similar low rates of postoperative cardiac events in non-cardiac surgery[67]. However, these studies were not designed to assign the optimal strategy in severely ill patients with extensive coronary artery disease immediately prior to major non-cardiac surgery. In addition, these studies could not address the concern of delaying the non-cardiac surgical procedure because of testing, revascularization, and initiation of antiplatelet therapy since the time between revascularization and non-cardiac surgery in these studies was 4.1 and 2.4 years, respectively. These concerns raise the question whether invasive test results would alter pre- and perioperative management.

The randomized Coronary Artery Revascularization Prophylaxis (CARP) trial was the first study that addressed the strategy of prophylactic revascularization, the ultimate consequence of invasive testing, compared to optimal medical therapy in patients with clinically stable coronary artery disease who were scheduled for major non-cardiac vascular surgery[68]. This trial showed that prophylactic revascularization was safe but did not improve perioperative or long-term outcome. The long-term (median follow-up 2.7 years) mortality was 22% in patients allocated to prophylactic coronary revascularization, compared to 23% in the medical only strategy, p=0.92 (FIGURE 1.4). Also, the incidence of perioperative non-fatal myocardial infarction was similar, respectively 12% and 14%, p=0.37. However, it must be noted that the majority of patients in the CARP trial had only 1 or 2 vessel disease.

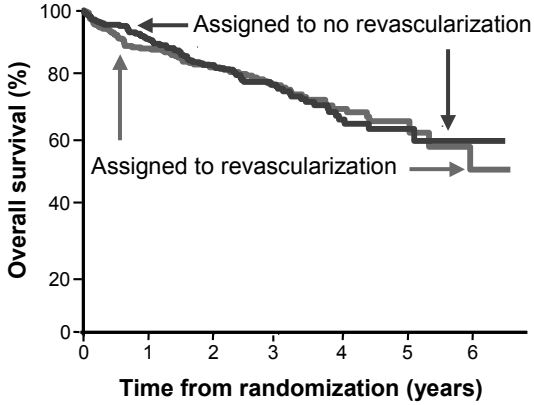



**FIGURE 1.4** Results of the CARP trial[68].
At a median follow-up of 2.7 years there was no survival benefit in patients who underwent preoperative coronary revascularization (RR=0.98 95% CI 0.70-1.37, p=0.92).

The recently conducted DECREASE V randomized pilot study in which the majority of patients had 3-vessel disease also showed no perioperative and long-term (follow-up 1 year) benefit of prophylactic coronary revascularization[69]. The findings of both CARP and DECREASE V support the current guidelines of the ACC/AHA on perioperative management in high-risk patients to reserve revascularization only for cardiac unstable patients. After successful non-cardiac surgery these patients should be regularly screened for the presence of ischemic complaints and aggressive anti-ischemic therapy, both medical and invasive, should be considered. In these patients at high risk scheduled for major non-cardiac vascular surgery prophylactic revascularization might be switched to late revascularization, thus obviating the delay of surgery.



## V. PREVENTION

### Medical management

*A1. Beta-blockers*

Although beta-blockers are widely prescribed as a means for reducing perioperative cardiac events, randomized controlled trials of beta-blockers have shown divergent results.

Evidence supporting the use of beta-blockers is based mainly on two small, prospectively randomized clinical trials and several observational studies. In the first study, Mangano et al. randomized 200 patients with either known or suspected coronary artery disease undergoing high-risk non-cardiac surgery to receive atenolol (50 mg or 100 mg) or placebo[70]. Atenolol therapy was not associated with an improved in-hospital outcome (cardiac death or MI); however, it was associated with a 50% reduction in electrocardiogram evidence of myocardial ischemia detected with continuous 3-lead Holter monitoring during the first 48 h after surgery. Interestingly, patients receiving perioperative atenolol had a reduced rate of cardiac events 6 to 8 months after surgery compared with the placebo group, suggesting a delayed beneficial response[71].

In the second trial, the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study)-I trial, of 112 vascular surgery patients with evidence of myocardial ischemia

on preoperative dobutamine stress-echocardiography, Poldermans et al. showed a 10-fold reduction in the incidence of perioperative cardiac death and MI with perioperative bisoprolol use compared with placebo (3.4% versus 34%; $P < 0.001$)[72]. The high incidence of perioperative cardiac events was explained by the selection of high-risk patients for study. From a population of 1351 patients, only 112 met entrance criteria of inducible myocardial ischemia.

In the POBBLE (PeriOperative Beta-BLockadE) trial, only low-risk patients (history of ischemic heart disease was an exclusion) scheduled for vascular surgery were studied[73]. This low-risk population was randomized to receive either metoprolol 25 mg or 50 mg (n = 55) or placebo (n = 48) starting the day before surgery and continued during the first 7 days after surgery. There was no difference in the incidence of perioperative cardiovascular events between the placebo and metoprolol groups (34% versus 32%). The duration of hospitalization though was shorter for those patients receiving metoprolol versus placebo (10 days versus 12 days).

In the DIPOM (Diabetic Postoperative Mortality and Morbidity) study the cardioprotective effect of 100 mg metoprolol started the evening before major non-cardiac surgery was compared with placebo in 921 diabetic patients[74]. In that study, there were no differences in 30-day morbidity and mortality (21% versus 20%; $p = 0.66$). A limitation of the DIPOM study was that it was only powered to detect a 10% difference in mortality after 1 year of follow-up.

Recently the results of the large randomized POISE trial were presented. A total of 8351 patients were randomized to controlled-release oral metoprolol succinate or placebo. The primary endpoint of cardiac death, myocardial infarction, or cardiac arrest was reduced in the metoprolol group, compared to placebo (5.8% vs. 6.9%, hazard ratio 0.83, 95% CI 0.70-0.99, p=0.04), driven by a reduction of non-fatal myocardial infarctions, albeit, at the costs of an increased incidence of total mortality and stroke. Stroke was associated with perioperative bradycardia, hypotension, and bleeding in patients randomized to metoprolol with a diseased cerebrovascular tree, suggestive of an over treatment effect.

There are several explanations for the divergent findings from randomized trials of perioperative beta-blockers, including the use of a fixed versus individualized dose titrated to the patients heart rate. In a study of 150 patients, Raby et al. assessed the heart rate threshold for myocardial ischemia before surgery using Holter monitoring[75]. Patients with myocardial ischemia (n = 26) were then randomized to receive IV esmolol titrated to aiming at tight heart rate 20% less than the ischemic threshold but >60 bpm or placebo. Of the 15 patients receiving esmolol, 9 had mean heart rates below the ischemic threshold and none experienced postoperative ischemia. Four of 11 patients receiving placebo had a mean heart rate below the ischemic threshold, and 3 of the 4 had no postoperative ischemia. Together, of the 13 patients with heart rates below the ischemic threshold, 1 (7.7%) had postoperative myocardial ischemia versus 12 of 13 (92%) patients with heart rates exceeding the ischemic threshold. Feringa et al. found similar results in a study of 272 patients receiving beta-blocker therapy and undergoing vascular surgery[76]. In that study it was shown that higher doses of beta-blockers and lower heart rate were associated with reduced Holter monitoring-detected perioperative myocardial ischemia (HR, 0.40; 95% confidence interval [CI] 0.21-0.56) and troponin T release (HR, 0.65; 95% CI 0.49-0.86). These data suggest that monitoring of the heart rate and consequent beta-blocker dose adjustment is of critical importance.

The conflicting results of perioperative beta-blocker trials might be further explained by varying durations of therapy. As mentioned, although the sympathico-inhibitory effects of beta-blockers occur

almost instantly, the anti-inflammatory effects may be observed only after prolonged treatment. As mentioned, in the Mangano et al. study, the major benefits of atenolol were observed in the months after surgery[70]. In the DIPOM, POBBLE and POISE trials, beta-blocker therapy was initiated on the day before surgery. The DECREASE-I trial showed the largest effect of perioperative beta-blocker therapy. The time between beta-blocker therapy initiation and surgery was 37 days in this trial[72].

Further, withdrawal of beta-blocker therapy shortly before surgery, or in the immediate postoperative period, might contribute to adverse myocardial effects resulting from a "rebound" effect resulting in increased arterial blood pressure, heart rate, and plasma noradrenalin concentrations[77]. Redelmeier et al. have recently shown that the long-acting agent atenolol was superior to the short-acting drug, metoprolol, when given perioperatively, probably as the result of acute withdrawal effects from missed doses of short-acting beta-blockers[78]. On the other hand care should be taken not to over treat the patient. In the POISE study, metoprolol succinate, a long-acting β-blocker, dose was used with a starting dose of 100 mg, 2 to 4 hours prior to surgery, again 100 mg 0 to 6 hours after surgery, and a dose of 200 mg 12 hours after the first postoperative dose. Thereafter the daily maintenance dose was started at 200 mg. Medication was withheld if blood pressure dipped below 100 mmHg or heart rate was below 50 bpm. So, on the first day of surgery metoprolol succinate could have been administered at a dose up to 400 mg on the day of surgery, 100% of the maximum daily therapeutic dose (MDTD). In the non-surgical setting, much lower starting doses are recommended, for instance in patients with NYHA Class II heart failure 12.5 to 25 mg daily is started for two weeks and for hypertension the initial dose is 25 to 100 mg, usually increased at weekly intervals.



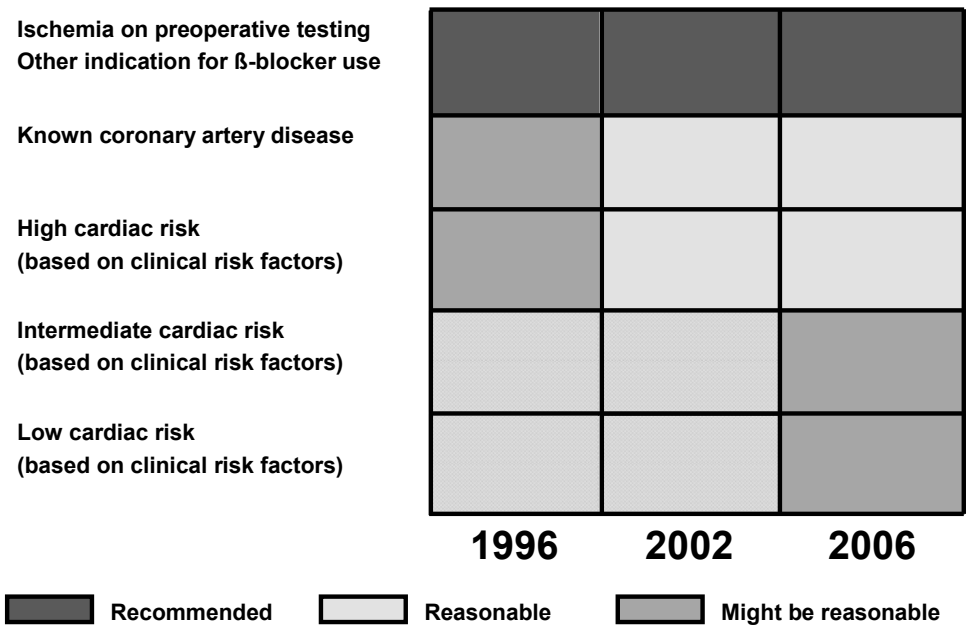



**Figure 1.5** Evolving guideline recommendations on the use of perioperative beta-blockade in the last decade. Based on the ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for non-cardiac surgery: focused update on perioperative beta-blocker therapy: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.

*Proposed recommendations.* In patients with Class I indications for β-blockers for secondary prevention of heart disease, therapy is recommended independent of the non-cardiac surgery (FIGURE 1.5). However, further study is required to determine the optimal dose and time to initiate the drug before surgery. This is particularly relevant in patients with cerebrovascular disease.

We believe that the protocol utilized in the DECREASE studies (low dose long-acting agents titrated to effect at least 7 days in advance) is associated with overall benefit compared to risk, while high dose therapy started the morning of surgery is associated with greater risk than benefit.

What do we do for those with indications for perioperative β-blocker therapy, but in whom there is insufficient time to appropriately titrate the medication? The overriding theme is that tachycardia due to perioperative events, i.e. bleeding, hypovolemia, inadequate control of pain or infection, should not be initially treated with additional β-blocker; the underlying cause of these conditions should be treated first. If tachycardia persists, then β-blocker can be used cautiously in high-risk patients with proven or suspected coronary artery disease, preferable supervised in the perioperative setting by physicians who have experience with perioperative hemodynamics.

*A2. Statins*

Several recent retrospective studies have shown a beneficial effect of statins on perioperative cardiac outcome with adjusted Hazard ratio's ranging from 0.20 to 0.62 (TABLE 1.3).[79-81,83,84] Importantly, Kertai et al also found the effect of statins to be independent of β-blocker use.[81] The first blinded, placebo-controlled, randomized trial that investigated the influence of statin use on perioperative cardiovascular complications has been reported by Durazzo et al.[82] This research group randomly assigned 100 patients to treatment with either 20 mg of atorvastatin or placebo. Patients received treatment for 45 days and at least 2 weeks before surgery. One month after surgery, patients with

**TABLE 1.3** Studies of the effectiveness of perioperative statin use in major vascular, non-cardiac surgery.

| Author | Year | Type of study | N | Type of surgery | Rx prior to surgery |
|---|---|---|---|---|---|
| Poldermans et al.[80] | 2003 | Case-control | 480 | Vascular | Chronic use |
| Kertai et al.[81] | 2004 | Cohort | 570 | Vascular | Chronic use |
| Durazzo et al.[82] | 2004 | RCT | 100 | Vascular | 30 days |
| Lindenauer et al.[83] | 2004 | Cohort | 780,591 | General | Chronic use |
| O'Neil-Callahan et al.[84] | 2005 | Cohort | 1,163 | Vascular | Chronic use |

| Cont'd | End Point | Event rate in controls | Odds Ratio | NNT |
|---|---|---|---|---|
| Poldermans et al.[80] | 30-day all cause mortality | Not reported | 0.22 | Not reported |
| Kertai et al.[81] | 30-day mortality or nonfatal MI | 11.0% | 0.24 | 14 |
| Durazzo et al.[82] | Death, nonfatal MI, ischemic stroke, unstable angina within 6 months after surgery | 26% | 0.31 | 6 |
| Lindenauer et al.[83] | In-hospital all cause mortality | 3.2% | 0.71 | 109 |
| O'Neil-Callahan et al.[84] | Composite of death, MI, ischemia, congestive heart failure, ventricular tachycardia during hospitalization | 16.5% | 0.52 | 15 |

RCT = Randomized Controlled Trial; CEA = Carotid Endarterectomy; MI = Myocardial Infarction; NNT = Number Needed to Treat

elevated cholesterol levels were advised to continue or start statin therapy. The outcome of this trial was the end point of cardiovascular events, defined as cardiac death, nonfatal myocardial infarction, stroke, or unstable angina pectoris. Patients were monitored up to 6 months after the surgical procedure. Of 100 patients, 44 statin users and 46 nonusers underwent elective vascular surgery. The 6-month incidence of cardiovascular events was reduced by 3.1-fold in statin users compared with nonusers (p=0.022).

A major concern of perioperative statin therapy has been the risk of statin-induced elevated serum transaminases, myopathy, and rhabdomyolysis. An important potential risk factor in the perioperative setting is the use of concomitant medications. The risk of myopathy might increase with concomitant drugs that are myotoxic or increase serum statin levels. Besides concomitant medication use, numerous other factors in the perioperative setting might increase the risk of statin-induced myopathy, including impairment of renal function after major surgery, the use of analgesic agents, and postoperative pain that might mask signs of myopathy. Failure to detect statin-induced myopathy may then lead to continuous statin use and the subsequent development of rhabdomyolysis and acute renal failure. In a retrospective study of 885 consecutive patients undergoing major vascular surgery, no case of rhabdomyolysis or a significant higher creatine kinase level in the 211 statin users was observed[87]. Considering that the risk of cardiovascular complications is far greater than the risk of statin-induced myopathy and rhabdomyolysis, the potential benefits of perioperative statin use seem to outweigh the potential hazards. The safety of statins should be confirmed in blinded, randomized trials, however.

*A3. Antiplatelet therapy*

Studies on the effectiveness of antiplatelet therapy to prevent cardiac complications in patients undergoing vascular surgery are non-existent. However, a large proportion of patients with peripheral arterial disease are on antiplatelet therapy as a means of secondary prevention.




What should be done with antiplatelet therapy in the perioperative setting? In their extensive review on the impact of antiplatelet therapy on perioperative bleeding complications, Harder et al. concluded that monotherapy with aspirin or clopidogrel alone usually does not have to be discontinued in the perioperative period[88]. This conclusion was confirmed in the meta-analysis of Burger et al.[89] In 41 studies including a total of 49 590 patients undergoing a variety of non-cardiac surgical procedures (14 981 on perioperative aspirin and 34 609 not on aspirin) they found that aspirin continuation led to a 1.5 times increased risk of bleeding complication, but not to a higher level of the severity of bleeding complications. They concluded that based on their meta-analysis aspirin should only be discontinued perioperatively if bleeding risks with increased mortality or sequels are comparable to the observed cardiovascular risks after aspirin withdrawal.

This issue is of particular relevance to patients with (recent) coronary stent placement. Surgery increases the in-stent thrombosis risk in these patients due to a perioperative stress response including sympathetic activation promoting sheer stress on arterial plaques, enhanced vascular reactivity conducive to vasospasm, reduced fibrinolytic activity, platelet activation, and hypercoagulability. In addition, while the surgical patient is in a hypercoagulable state dual antiplatelet therapy is often interrupted because of the fear for excessive bleeding complications during surgery. This double-edged sword of dual antiplatelet therapy, prevention of cardiac complications on one hand and an excess of bleeding risk on the other, remains a controversial issue in perioperative management. Is has recently been suggested that non-cardiac surgery after PCI with stenting should be delayed at least 6 weeks and dual antiplatelet therapy is associated with improved outcome[90]. It is advisable to

continue at least single antiplatelet therapy in patients with a history of coronary stent placement. Obviously for each patient a personalized decision should be made based on the possibility and anticipated severity of perioperative bleeding complications and the risk of in-stent thrombosis with subsequent myocardial infarction and cardiac death.

### Preoperative coronary revascularization

The randomized Coronary Artery Revascularization Prophylaxis (CARP) trial was the first study that addressed the strategy of prophylactic revascularization compared to optimal medical therapy in patients with clinically stable coronary artery disease who were scheduled for major non-cardiac vascular surgery[68]. This trial showed that prophylactic revascularization was safe but did not improve perioperative or long-term outcome. The long-term (median follow-up 2.7 years) mortality was 22% in patients allocated to prophylactic coronary revascularization, compared to 23% in the medical only strategy, p=0.92 (FIGURE 1.4). In addition, the incidence of perioperative non-fatal myocardial infarction was similar, respectively 12 and 14%, p=0.37. However, it must be noted that the majority of patients in the CARP trial had only 1 or 2 vessel disease. In the nonrandomized cohort of the CARP trial 48 patients (4.6%) had left main stenosis. In this cohort, patients who had undergone preoperative revascularization did seem to have an improved 2.5 year survival (84% vs. 52%). In a post-hoc analysis coronary artery bypass grafting was associated with fewer myocardial infarctions and a shorter hospital stay compared to percutaneous coronary interventions in patients receiving multivessel coronary artery revascularization as prophylaxis[91]. However, more complete revascularization accounted for these intergroup differences.

For the DECREASE V study, a total of 1880 patients scheduled for major non-cardiac vascular surgery were screened[69]. Those with 3 or more clinical risk factors (age > 70 yrs, myocardial infarction, angina pectoris, congestive heart failure, diabetes mellitus, renal failure, and cerebrovascular events) all underwent preoperative cardiac stress testing. Those with extensive stress-induced ischemia (≥ 5 segments or ≥ 3 walls) were randomly assigned for additional revascularization. All received beta-blockers aiming at a heart rate of 60-65 bpm and antiplatelet therapy was continued during surgery. Of 430 high-risk patients, 101 (23%) showed extensive ischemia and were randomly assigned to revascularization (N=49) or no-revascularization (n=52). Coronary angiography showed 2-vessel disease in 12 (24%), 3-vessel disease in 33 (67%), and left main in 4 (8%). This study population reflects the patients at highest cardiac risk in the perioperative period. Compared to the CARP trial the perioperative cardiac risk in the DECREASE V population was even higher; all patients had extensive stress induced myocardial ischemia and 75% had 3-vessel or left main disease. If a beneficial effect on postoperative outcome could have been expected of prophylactic coronary revascularization, then it would be seen at least in this group of patients. However, the results of the trial were disappointing. Two patients died after revascularization, but prior to operation because of a ruptured aneurysm. Revascularization did not improve perioperative outcome, the incidence of cardiac death and myocardial infarction was 43 vs. 33%, OR 1.4, 95% CI 0.7-2.8 (p=0.30). Also no benefit during 1-year follow-up was observed after coronary revascularization, 49 vs. 44%, OR 1.2, 95% CI 0.7-2.3 (p=0.48).

The apparent lack of benefit of prophylactic coronary revascularization is not fully understood. Most likely patients with stress induced ischemia not only suffer from a blood flow limiting coronary lesion but also from (multiple) non-significant lesions which are vulnerable to rupture due to the stress of surgery. The perioperative stress response, which includes a cytokine response, catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation and consequent hypercoagulability triggers coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion.

Autopsy results have shown that this mechanism is responsible for at least half of all perioperative infarctions. These findings are in line with dobutamine echocardiography results that show a correlation between the assessment of the preoperative culprit coronary lesion and the location of the perioperative myocardial infarction in only half of all cases. Surgical or percutaneous treatment of the culprit coronary lesion(s) apparently provides insufficient extra protection on top of medical treatment for rupture of these instable lesions.

## VI. TREATMENT

The treatment of perioperative cardiac complications often is more challenging and less straightforward compared to the treatment of acute coronary syndromes in the nonoperative setting. Where aggressive anti-coagulation or antiplatelet therapy is standard in nonoperative patients, in those who recently underwent vascular surgery a delicate balance between bleeding and thrombotic complications must be found. In this setting the choice of treatment for cardiac complications in vascular surgery should be appreciated.

For patients in the non-operative setting, recently new guidelines have been developed for acute coronary syndromes[92-95]. One of the criteria upon which the treatment decision is based is the type of acute coronary syndrome; i.e. non ST-segment elevation myocardial infarctions or ST-segment elevation myocardial infarctions.

In general for patients with non-ST segment elevation infarction, medical therapy is sufficient. This should consist of adequate beta-blockade, and anticoagulation in addition to antiplatelet therapy and statin therapy. In case of non-ST segment elevation infarction in the perioperative setting a physician experienced in this type of complications should be consulted.



The ST-segment elevation myocardial infarction is an absolute emergency both in nonoperative and operative patients. Depending on several factors immediate reperfusion strategies, e.g. fibrinolytic therapy and PTCA with stenting, should be considered. The indications for therapy are described in the ESC and ACC guidelines and a cardiologist should be consulted immediately to discuss the pros and cons of the different treatment strategies for each individual postoperative patient.

## VII. IMPACT OF CARDIAC COMPLICATIONS ON OUTCOME

### A. Acute

The acute impact of cardiac complications, in particular myocardial infarction, is significant. Sprung and colleagues analyzed 6948 vascular operations at the Cleveland Clinic and found 107 patients with postoperative transmural MIs[96]. The overall in-hospital mortality rate was 20.6% with the highest mortality on postoperative day 0. In a similar series, Badner and coworkers reported a 17% post-MI mortality rate after non-cardiac surgery[97]. Although these mortality rates are better than rates reported in older series (presumably owing to improved anesthetic care, beta blockers, and so forth), a death rate from MI of almost one in five remains startlingly high.

### B. Long-term

Some authors have questioned the long-term clinical importance of non–Q wave MIs (i.e. "chemical" MIs) in vascular surgery patients. Yeager and colleagues followed 8 of 31 patients who sustained a

perioperative MI with "chemical MIs" in which enzyme elevation was the sole indicator of postoperative MI. At a mean follow-up of 27.7 months, survival for patients with nonfatal perioperative MI at 1 and 4 years was 80% and 51%, which did not differ significantly from that of control patients (90% and 60%; p>0.05)[98]. Although these investigators concluded that "a perioperative chemical MI" may not be a clinically significant event, patients surviving nonfatal perioperative MIs after peripheral vascular surgery did have a higher incidence of subsequent adverse cardiac events and subsequent coronary artery revascularization. Similarly, McFalls and coworkers reported that even in vascular patients with perioperative transmural MIs, nonfatal perioperative MI was only a marginally significant independent predictor of 1-year mortality (p=0.06), whereas the extent of vascular disease at presentation was a more important determinant of survival[68]. However after 2.5 years of follow-up survival of patients without a perioperative MI turned out to be significantly better than in those with a perioperative MI[99].

These optimistic reports have not been supported by more recent publications using more sensitive cardiac biomarkers such as cardiac troponin. As was already shown in a series of 2003 patients, a perioperative troponin T release >0.03 ng/ml and/or a troponin I release >0.6 ng/ml had a significant independent 2-fold increased risk for long-term mortality during a mean follow-up of 32 months[13]. This has been confirmed in a study of 393 vascular surgery patients by Kertai et al.: an increase in troponin T level > 0.1 ng/ml was associated with a 1.9-fold increased risk for all-cause mortality during a median follow-up of 4 years[51]. Overall, the incidence of death, myocardial infarction, stroke, or severe myocardial ischemia requiring coronary reperfusion after perioperative troponin release within 1 year after hospital discharge is as high as 20-40% in several studies.

Finally it should be emphasized that patients undergoing non-cardiac vascular surgery are at high risk for long-term cardiac events, even those without perioperative cardiac complications. In fact, patients

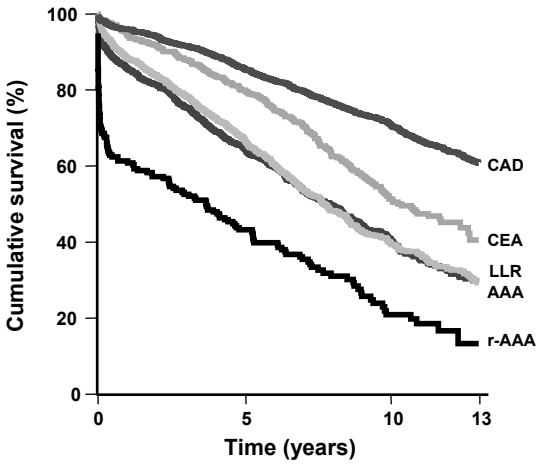



**FIGURE 1.6** Long-term survival after vascular surgery or after an acute coronary event (derived from Welten et al.[14]).
CAD = patients with an acute coronary event but without vascular surgery
CEA = patients who underwent carotid endarterectomy
LLR = patients who underwent lower limb arterial reconstructions
AAA = patients who underwent abdominal aortic aneurysm repair
r-AAA = patients who underwent ruptured abdominal aortic aneurysm repair

who undergo vascular surgery have a worse prognosis compared to patients who experienced an acute coronary event (FIGURE 1.6). This difference is partially caused by a marked undertreatment of patients with PAD compared to patients with established, symptomatic coronary artery disease. Optimal medical treatment of these patients is of critical importance and recent guidelines such as the ACC/AHA guidelines and the TASC2 guidelines should be adhered to so that the patient lives long enough to enjoy the benefits of vascular surgery[100,101].

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# Chapter 2

## Cardiac risk in non-cardiac surgery

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Cardiac complications are a major cause of perioperative morbidity and mortality in patients undergoing non-cardiac surgery. It is estimated that the incidence of such complications is between 0.5 and 1.0 per cent[1]. Worldwide, about 100 million adults undergo some form of non-cardiac surgery each year, and so between 500,000 and 1,000,000 people will suffer from perioperative cardiac complications; one of four of them will die from this cause.

In recent years the scope of perioperative cardiac risk stratification and cardioprotective therapy has changed. In addition to localized treatment of culprit coronary artery lesions, systemic therapy focusing on coronary plaque stabilization has been introduced. Although the pathophysiology of perioperative myocardial infarction (MI) is not entirely clear, plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is implicated in a similar manner to that causing MI in the non-operative setting. The incidence of plaque rupture may be increased by the stress response to major surgery. This response includes sympathetic activation promoting sheer stress on arterial plaques, enhanced vascular reactivity conducive to the development of vasospasm, reduced fibrinolytic activity, platelet activation and hypercoagulability. Heightened sympathetic tone also increases myocardial oxygen requirements (for example through tachycardia and increased contractility), leading to a mismatch between oxygen supply and demand that, when sustained, can lead to infarction. Several studies of the pathophysiology of perioperative MI using non-invasive tests, coronary angiography and autopsy have shown that coronary plaque rupture and thrombus formation occur in 50 per cent of all fatal MIs, whereas a sustained oxygen supply-demand mismatch is responsible for the other 50 per cent. Lesions causing stenosis severe enough to lead to an oxygen supply-demand mismatch are also considered to be a marker for the presence of other non-obstructive lesions. These other lesions are also at risk of inflammation and rupture, and are likely to trigger a perioperative acute coronary syndrome. These findings explain why patients at risk can be identified by preoperative cardiac stress testing and why the site promoting the perioperative event may not be identical to the culprit coronary artery lesion identified before surgery.

The unpredictability of vulnerable coronary plaque rupture produces new challenges in perioperative cardiac risk stratification and cardiac risk modification in the surgical setting. Traditionally, stratification has been based on a combination of clinical risk factors and additional cardiac testing, and indices such as the Revised Cardiac Risk Index have proven their reliability and reproducibility in clinical practice[1]. For patients suspected to be at high cardiac risk, additional tests, such as dobutamine stress echocardiography, may further refine risk stratification[2].

Although traditional imaging tools identify major coronary stenoses, they generally overlook those relatively mild coronary lesions that, as noted above, are responsible for half of all perioperative cardiac events. Inflammation is one of the key features of these unstable, vulnerable coronary plaques. In the non-operative setting, the role of several inflammatory biomarkers for the prediction of coronary events has been studied both in healthy people and in patients with stable coronary artery disease, acute coronary syndromes or requiring secondary prevention. These markers include C-reactive protein, interleukin 6, serum amyloid A, tumor necrosis factor, soluble intercellular adhesion molecule 1, macrophage inhibitory cytokine 1, soluble P-selectin and CD40 ligand. However, studies of inflammatory biomarkers for the prediction of adverse perioperative cardiac events are scarce; future research into perioperative cardiac risk prediction must focus on these biomarkers.

The nature of perioperative cardiac events has implications for perioperative cardioprotective therapy. Local therapy may be the best option for the culprit lesion. In high-risk patients myocardial oxygen-supply mismatch might be counteracted by beta-blockers, and in this context it is important

to appreciate that only adequate beta-blocker use (that achieving a target heart rate of less than 65 beats per min) seems to lower the perioperative cardiac event rate[3]. However, for those with multiple coronary artery lesions suggestive of left main or three-vessel disease, beta-blocker therapy alone may prove sufficient. Although previously considered as an appropriate preoperative treatment for these patients, prophylactic preoperative coronary revascularization is now known not to reduce the incidence of perioperative cardiac events sufficiently[4,5]. This is probably because such revascularization cannot prevent the rupture of vulnerable plaques.

Systemic therapy should be considered for the prevention of vulnerable plaque rupture and it is noteworthy in the non-operative setting that the recently published Medicine, Angioplasty, or Surgery Study (MASS) II and Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation (COURAGE) trials[6,7] both found no additional benefit from coronary revascularization over best medical treatment only in patients with stable multivessel coronary artery disease. Medical treatment in both trials included rigorous statin and aspirin therapy. Recent literature also suggests an important role for this type of anti-inflammatory medication in surgical patients. For example, perioperative statin therapy in vascular surgical patients seems to be safe and effective for the prevention of perioperative cardiac events[8]. This cardioprotective effect of statins is independent of their lipid-lowering effect and is attributed to their so-called pleiotropic potential. The pleiotropic effects of statins depend on several possible plaque-stabilizing mechanisms, such as increased production of endothelin 1 and generation of reactive oxygen expression of endothelial nitric oxide synthase, reduced species, improvement of thrombogenic profile and, importantly, reduction in inflammation by reduced expression of inflammatory cytokines, chemokines and adhesion molecules, and a lowering of C-reactive protein levels.



What are the implications of these new insights for surgical practice? Recent improvements in perioperative medical therapy have diminished the need for extensive cardiac assessment in most patients; this reduces any delay to surgery. Medical therapy to improve the balance of myocardial oxygen supply and demand, such as beta-blockade, does not interfere with any planned operation; cardioselective beta-blockers, in particular, are safe even for patients with chronic obstructive pulmonary or peripheral arterial disease. Statin therapy aimed at coronary plaque stabilization also seems to be safe. The use of antiplatelet agents in the perioperative period is more controversial. A meta-analysis of 41 studies, including a total of 49 590 patients undergoing a variety of non-cardiac operations, has shown that aspirin continuation is associated with a 1.5-fold increased risk of bleeding complications but not with a higher level of severity of such complications[9].

In summary, to improve postoperative cardiac outcome after non-cardiac surgery a dual approach is required. First, one must focus on correcting the mismatch of myocardial oxygen supply and demand. Second, one must stabilize the coronary artery atheromatous plaque. At present, these needs are best met with a combined medical therapy of cardioselective beta-blockers, statins and, if possible, aspirin.

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# Chapter 3

## Coronary risk assessment in the management of patients undergoing non-cardiac vascular surgery

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## INTRODUCTION

Patients scheduled for non-cardiac vascular surgery are at significant risk of cardiovascular morbidity and mortality due to underlying symptomatic or asymptomatic coronary artery disease. As was shown by Hertzer et al. in their landmark study in 1984 of 1000 patients undergoing non-cardiac vascular surgery, 61% of all patients did have at least one coronary artery with a stenosis of 50% or more[1]. In fact, only 8% of all patients did have a normal coronary angiogram. Importantly, there was no difference between patients who presented with an abdominal aortic aneurysm, lower extremity ischemia, or cerebrovascular disease. More recent studies using functional tests such as dobutamine stress echocardiography confirmed the high incidence of coronary artery disease in vascular surgical patients. In a study population of 1097 vascular surgical patients with at least one cardiac risk factors, the incidence of wall motion abnormalities at rest was nearly 50% while one fifth of patients had stress induced myocardial ischemia[2].

The high prevalence of coronary artery disease in vascular surgical patients explains the high incidence of perioperative cardiac events in this patient population. Though recent developments in anesthesiological and surgical techniques, e.g. locoregional anesthesia and endovascular treatment modalities, have improved postoperative cardiac outcome considerably, perioperative cardiac complications remain a significant problem. The incidence of perioperative myocardial infarction is around 5% and the prevalence of (a-) symptomatic perioperative myocardial ischemia as assessed by serum troponin I or serum troponin T in major vascular surgery is even 15 to 25%[2-4].

Patients undergoing vascular surgery are also susceptible to cardiovascular events during long-term follow-up after the surgical procedure. Over half of all long-term deaths in this population are attributable to cardiac events. The preoperative work up of vascular patients should be considered as an excellent opportunity to identify patients at increased long-term risk and treat them appropriately to lower the long-term risk for cardiovascular events. After all, the patient should live long enough to enjoy the benefits of the vascular surgical intervention.

This review will provide an overview of the current status of preoperative work-up of patients undergoing non-cardiac vascular surgery.

## CLINICAL CARDIAC RISK SCORES

### Non-cardiac surgery

The first, most simple and least costly step in preoperative cardiac risk stratification is the identification of clinical cardiac risk factors. In the last three decades much attention has been given to the identification of patients at risk by using simple clinical cardiac risk factors. This research has led to numerous cardiac risk indices for non-cardiac surgical procedures (TABLE 3.1).

In 1977 Goldman et al. proposed the first cardiac risk stratification model based on prospectively collected data[5]. In this study of 1001 patients, nine independent predictors were found to be correlated with postoperative life-threatening and fatal cardiac complications: preoperative third heart sound or jugular venous distention; myocardial infarction in the preceding six months; more than five premature ventricular contractions per minute documented at any time before operation; rhythm other than sinus rhythm or presence of premature atrial contractions on preoperative electrocardiogram; age over 70 years; intraperitoneal, intrathoracic or aortic operation; emergency operation; important

**TABLE 3.1** Risk factors according to the classifications of Goldman, Lee, and Boersma for adverse postoperative outcome in patients undergoing all types of non-cardiac surgical procedures.

| **Goldman et al.[5] 1977** *Life-threatening and fatal cardiac complication* | **Lee et al.[7] 1999** *Major adverse cardiac event* | **Boersma et al.[8] 2005** *Cardiovascular death* |
|---|---|---|
| Third heart sound or jugular venous distention | Congestive heart failure | Congestive heart failure |
| Myocardial infarction in the preceding six months | Ischemic heart disease | Ischemic heart disease |
| > 5 PVCs per minute at any time before operation | Cerebrovascular disease | Cerebrovascular disease |
| Other than sinus rhythm or presence PACs | Insulin dependent diabetes mellitus | Insulin dependent diabetes mellitus |
| Age over 70 years | Renal failure | Renal failure |
| Intraperitoneal, intrathoracic or aortic operation | High-risk surgery | Surgical risk according to the AHA/ ACC classification |
| Emergency operation | | Age: <40 yrs, 40-50, 50-60, 60-70,70-80, ≥80 |
| Important valvular aortic stenosis | | |
| Poor general medical condition | | |
| No. patients in original report: 1001 | No. patients in original report: 2893 | No. patients in original report: 108 593 |
| | AUC in original report: 0.77 | AUC in original report: 0.85 |

PVC = Premature Ventricular Contraction; PAC = Premature Atrial Contraction



valvular aortic stenosis; and poor general medical condition. The incidence of adverse cardiac events was 1% in the group at lowest risk (class I), and increased to 7%, 14%, and 78% in class II, III, and IV patients respectively. However, it must be noted that only 18 patients were in the group at highest risk. The Goldman index has a 96.8% negative predictive value, and thus is an excellent tool to rule out CAD. The value of the Goldman index for diagnosing patients with CAD on the other hand was less optimal, i.e. a positive predictive value of 21.6%.

In 1986 Detsky et al. prospectively validated and modified the Goldman index and presented a simple normogram, introducing the pre-test likelihood of perioperative cardiac events for cardiac risk stratification[6]. The Detsky modified multifactorial risk index has been in use ever since and is considered to be a good and practical index.

In 1999 Lee et al. reviewed the performance of several clinical risk indices in patients who underwent elective non-cardiac surgery[7]. They found that the Goldman risk index and the Detsky modified cardiac risk index had a similar performance for predicting major cardiac complications. However, when the Goldman risk index was revised and validated, the predictive value of the risk index had substantially improved. In the validation cohort the ROC area improved form 0.70 for the original Goldman index to 0.81 for the Revised Cardiac Risk Index by Lee et al. The Revised Cardiac Risk Index identified 6 predictors (high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, insulin dependent diabetes mellitus, and renal failure) of major cardiac complications, and based on the presence of 0, 1, 2, or 3 or more of these predictors, the rate of major cardiac complications was estimated to be 0.4%, 0.9%, 7%, and 11%, respectively. Interestingly the Lee index has better prognostic value than the Goldman and Detsky indices though the number of cardiac risk factor variables in the Lee index is smaller. This might be explained by the improvement of perioperative

care in the time between the development of the Goldman and Lee risk indices. Nowadays, the Lee index is considered the most relevant index for predicting perioperative cardiac risk in non-cardiac surgery by many clinicians and researchers. However, the patients studied by Lee et al. can hardly be considered as an average non-cardiac surgical population. Thoracic, vascular and orthopedic patients were overrepresented in this study population.

Recently, Boersma et al. developed the Erasmus Risk Index, a further refinement of the Revised Cardiac Risk Index[8]. This index was based on an administrative database of 108 593 patients undergoing all types of non-cardiac surgery during a period of 10 years at a university medical center in the Netherlands. Of these patients 1877 (1.7%) died in hospital, including 543 cardiovascular deaths. Applying the Revised Cardiac Risk Index in this population the corresponding odds ratios for patients without risk factors, 1, 2, or ≥ 3 were 1 (reference), 2.0, 5.1, and 11.0 respectively, with a C statistic for the prediction of cardiovascular mortality of 0.63. Importantly, if more precise data about the type of operation was introduced in the model the C statistic significantly increased to 0.79. Adding age resulted in an even better C index of 0.83. These data suggest that the Revised Cardiac Risk Index by Lee et al. is probably suboptimal for identifying patients with greater cardiac risk, perhaps because it excluded emergency operations and perhaps because the type of surgery, which is one of the main determinants of adverse cardiovascular outcome, was considered in only 2 subtypes: high risk, including intraperitoneal, intrathoracic and suprainguinal vascular procedures; and all remaining nonlaparascopic procedures, mainly including orthopedic, abdominal, and other vascular procedures. In the study by Boersma et al. it was found that a more subtle classification, as suggested by the American Heart Association/American College of Cardiology guideline committee, resulted, at least retrospectively, in a substantially better risk discrimination.

### Non-cardiac vascular surgery

Patients undergoing non-cardiac vascular surgery are at high risk for postoperative cardiac complications due to underlying coronary artery disease. Several risk indices have been developed to stratify vascular surgical patients based on clinical cardiac risk factors (TABLE 3.2). In general, patients undergoing carotid artery stenosis repair have the least cardiac risk, followed by lower extremity revascularization procedures and abdominal aortic procedures. Some risk indices only describe major non-cardiac vascular surgical procedures, a term commonly used for lower extremity and abdominal aortic surgery.

The Glasgow aneurysm score, described in 1995, was one of the first cardiac risk scores dedicated to only vascular surgical procedures[9]. In a retrospective study of 500 randomly chosen patients scheduled for open abdominal aortic aneurysm repair potential preoperative risk factors were related to postoperative in-hospital mortality. In multivariate analysis age, shock, myocardial disease, cerebrovascular disease, and renal disease were independently associated with adverse perioperative outcome.

One year after the introduction of the Glasgow aneurysm score, the Leiden Risk Model was proposed by Steyerberg et al.[10] This study group composed a clinical prediction rule for perioperative mortality, using several risk factors obtained from literature. These risk factors included age, gender, a history of myocardial infarction, congestive heart failure, ischemia on the electrocardiogram, pulmonary disease, and renal dysfunction. Data from 246 patients undergoing open abdominal aortic aneurysm repair were used to validate the prediction rule. In the prediction rule, cardiac, renal, and pulmonary co-morbidity were found to be the most important risk factors, while age had only a moderate effect on perioperative mortality.

**Table 3.2** Risk factors in vascular surgical procedures.

| Glasgow Aneurysm Score[9]<br>1994, major vascular surgery<br>*All-cause perioperative mortality* | Leiden Risk Model[10]<br>1995, major vascular surgery<br>*All-cause perioperative mortality* | L'Italien et al.[11]<br>1996, major vascular surgery<br>*Cardiac death and nonfatal MI* |
|---|---|---|
| Myocardial disease | Myocardial Infarction | Myocardial Infarction |
| Cerebrovascular disease | Congestive Heart Failure | Congestive Heart Failure |
| Renal dysfunction | ECG evidence of ischemia | Angina Pectoris |
| Age | Female gender | Prior Coronary Revascularization |
| | Renal dysfunction | Diabetes Mellitus |
| | Chronic pulmonary disease | Age > 70 years |
| | Age (<60; 60-70; >70 years) | |
| No. patients in original report: 500 | No. patients in original report: 246 | No. patients in original report: 1081 |
| | | AUC in original report: 0.74 |

| Boersma et al.[2]<br>2001, major vascular surgery<br>*Cardiac death and nonfatal MI* | Customized Probability Index[12]<br>2005, vascular surgery<br>*All-cause perioperative mortality* |
|---|---|
| Myocardial Infarction | Ischemic heart disease |
| Congestive Heart Failure | Congestive heart failure |
| Angina Pectoris | Cerebrovascular events |
| Cerebrovascular events | Hypertension |
| Renal dysfunction | Renal dysfunction |
| Diabetes Mellitus | Chronic pulmonary disease |
| Age > 70 years | Type of vascular surgery (ruptured AAA; elective AAA; lower extremity; carotid) |
| No. patients in original report: 1097 | No. patients in original report: 2310 |
| AUC in original report: 0.78 | AUC in original report: 0.85 |



A total of 1081 consecutive patients undergoing major elective vascular surgery were used for the development and validation of a Bayesian model for preoperative cardiac risk assessment by L'Italien et al. in 1996[11]. The outcome for this study was a combination of nonfatal myocardial infarction and cardiac death. Using 567 patients as a derivation cohort the following risk factors were identified as predictors for adverse postoperative outcome: myocardial infarction, congestive heart failure, angina pectoris, prior coronary revascularization, diabetes mellitus, and age > 70 years. Importantly, the validation cohort of 514 patients showed a prognostic accuracy of 74%. Patients classified as low, intermediate and high risk had cardiac event rates of 3%, 8%, and 18% respectively.

Patients enrolled in the DECREASE I trial were used for the development of a risk score for elective major vascular surgery in 2001[2]. This study identified 7 independent clinical risk factors for the combination of postoperative cardiac death and nonfatal myocardial infarction: a history of myocardial infarction, angina pectoris, congestive heart failure, diabetes mellitus, renal dysfunction, cerebrovascular events, and age > 70 years. For patients not on beta-blocker therapy the risk of perioperative cardiac events increased by each risk factor added, ranging from 1.0% in patients without risk factors, to 2.2%, 4.5%, 9.2%, 18.0%, and 32.0% for 1, 2, 3, 4, and ≥ 5 risk factors respectively.

Recently Kertai et al. used a total of 2310 patients to develop a Bayesian model for the prediction of all-cause perioperative mortality in patients undergoing all types of open vascular surgery, including

emergent surgery[12]. 1537 patients were used to develop the risk score: the "customized probability index". Risk factors associated with postoperative all-cause death were ischemic heart disease, congestive heart failure, cerebrovascular events, hypertension, renal dysfunction, chronic pulmonary disease, and type of vascular surgery, i.e. ruptured AAA, elective AAA, lower extremity, and carotid. The final logistic regression model with the 9 independent predictors (including beta-blocker and statin use) of perioperative mortality was used to create a variable-weight index where scores were assigned on the basis of parameter estimates of the individual predictors. The type of surgery was a strong risk factor; patients with a ruptured abdominal aortic aneurysm had the worst outcome (43 points), followed by elective thoracoabdominal and abdominal aortic surgery (26 points), lower extremity arterial bypass surgery (15 points), and carotid surgery (0 points). It should be noted that all procedures in the risk model were open surgical procedures. Risk factors based on medical history, ordered in descending risk, were: renal dysfunction (16 points), congestive heart failure (14 points), ischemic heart disease (13 points), cerebrovascular event (10 points), hypertension (7 points), and pulmonary disease (7 points). Based on the sum of scores of surgical risk (0-46 points), medical history (0-67 points), and the score for cardioprotective medication (statins -10 points and beta-blockers -15 points) an overall cardiac risk can be calculated.

## ADDITIONAL LABORATORY TESTING

Apart from those measurements indicating clinical risk factors (for example, serum creatinine for renal failure, fasting glucose for diabetes mellitus, etc) currently no routine laboratory measurements are related to perioperative cardiac complications.

Recent studies showed that increased plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP) are associated with adverse postoperative outcome[13-16]. NT-proBNP is increased in patients with left ventricular dilatation caused by fluid overload (e.g. heart failure and renal dysfunction), pressure overload (e.g. aortic valve stenosis) and myocardial ischemia, which might explain the excellent relation with adverse postoperative outcome. In a study of 1590 patients scheduled for all types of non-cardiac general surgery by Dernellis et al. raised levels of BNP, i.e. > 189 pg/ml, were independently associated with a staggering 34 fold increased risk for postoperative cardiac events[14]. Similar results were found by Feringa et al. in their report on the prognostic value of NT-proBNP in 170 patients scheduled for major vascular surgery. Patients with a NT-proBNP level > 533 pg/ml had an independent 17-fold increased risk for postoperative cardiac events, even after adjustment for preoperative dobutamine stress echocardiography results[13]. Gibson et al. confirmed the predictive value of BNP in 149 major vascular surgical patients: using receiver-operator curve analysis a BNP concentration of 108.5 pg/ml best predicted the likelihood of cardiac events, with a sensitivity and specificity of 87%[15]. The true value of either BNP or NT-proBNP in the preoperative screening setting must be confirmed in large-scale prospective trials such as the recently started multinational DECREASE VI trial.

Diabetes mellitus is a common risk factor in patients scheduled for vascular surgery with prevalence of approximately 50% if all patients are thoroughly screened[17]. Diabetes mellitus is known to be a strong predictor for perioperative events. Therefore fasting glucose values should be obtained from all patients scheduled for vascular surgery and glucose loading testing should be considered in all. Recently it was shown that the level of preoperative glycosylated hemoglobin in diabetic patients is strongly related to perioperative cardiac outcome[18,19]. In the same patient population it was also shown that in patients with high preoperative glycosylated hemoglobin it is more difficult to regulate

glucose values in the perioperative period. This might partly explain the strong relation between preoperative glycosylated hemoglobin and outcome, since it is known from critically ill patients and patients with myocardial infarction that tight glucose control is of imminent importance. In a large case-control study by Noordzij et al. in non-cardiac nonvascular surgical patients it was also shown that random preoperative glucose levels were associated with postoperative outcome[20]. Those with a random glucose level > 11.1 mmol/l had a 4-fold increased risk for perioperative cardiovascular death. Importantly, also glucose levels of 5.6-11.1 mmol/l were independently associated with a 3-fold increased risk for perioperative cardiovascular events.

Recently Sarveswaran et al. found that preoperative asymptomatic troponin release in patients with symptomatic peripheral arterial disease is associated with a poor postoperative prognosis[21]. Preoperative troponin levels may be elevated because of asymptomatic myocardial ischemia, a condition often observed in patients scheduled for major vascular surgery. As was already noted by Landesberg et al. in 1993, over 40% of patients planned for major vascular surgery experience silent myocardial ischemia preoperatively as assessed by continuous 12-lead ECG recording, also in asymptomatic patients[22]. Notably, both Landesberg et al. and Kertai et al. previously showed that even low levels of asymptomatic troponin elevations in the perioperative period are associated with worse long-term outcome in patients undergoing major vascular surgery[23,24].

In most risk indices renal insufficiency is taken into account. For example, the serum creatinine cut-off value Lee et al used is 2.0 mg/dL (177 mmol/l)[7]. However, it might be argued that patients with less pronounced renal insufficiency also do worse compared to patients with normal serum creatinine values. A continuous variable for creatinine would probably be better, though not very user-friendly in every day practice. Recent studies have also shown that glomerular filtration rate might be a better predictor than serum creatinine since this takes into account the different creatinine concentrations between sexes[25].



## ADDITIONAL NONINVASIVE CARDIAC TESTING

If there is evidence or suspicion of CAD at physical examination, e.g. valve abnormalities or left ventricular dysfunction, or a high cardiac risk score further cardiac testing might be required. The most simple, inexpensive form of cardiac imaging is resting echocardiography, for the detection of impaired left ventricular function and valve stenosis and sclerosis. Impaired left ventricular function was long considered a strong predictor for adverse perioperative cardiac events. However, due to improved perioperative care it is no longer a strong predictor for short-term outcome but remains a significant predictor for long-term adverse cardiac events. The presence of aortic stenosis is associated with a fivefold increased risk of perioperative cardiac events[26]. Also, the severity of aortic stenosis is related to an increased risk of perioperative events. Considering this, it is important to detect the presence and significance of valve disease. Though physical examination is reliable in detecting abnormal heart sounds, the estimation of the severity of stenosis by physical examination alone is difficult and echocardiography is recommended in patients with abnormal heart sounds.

## ADDITIONAL NONINVASIVE CARDIAC STRESS TESTING

According to the guidelines of the American College of Cardiology/American Heart Association, preoperative cardiac exercise or pharmacological stress testing is recommended for: patients with

intermediate pre-test probability of CAD; prognostic assessment of patients undergoing initial evaluation for suspected or proven CAD; evaluation of subjects with significant change in clinical status; demonstration of proof of myocardial ischemia before coronary revascularization; evaluation of adequacy of medical treatment; and prognostic assessment after an acute coronary syndrome[27]. For stress testing, the evaluation of exercise capacity when subjective assessment is unreliable seems to be a valid reason as well. Patients with CAD or at risk for CAD can be frequently found in the group of patients with limited every day exercise—for example, patients with severe intermittent claudication. In these patients pharmacological stress echocardiography or nuclear imaging are elegant ways to exclude subclinical CAD.

The sensitivity and specificity of available exercise and pharmacological stress tests were compared in several meta-analyses. The meta-analysis of Kertai et al showed a trend in favor of dobutamine stress echocardiography, though other tests had satisfying sensitivity and specificity as well[28]. An upcoming elegant new diagnostic tool is dobutamine stress magnetic resonance imaging, though no randomized trials or large series have reported the sensitivity and specificity of this test yet.

In this era of new cardioprotective medical therapies, i.e. beta-blockers and statins, the key question is which patient should undergo additional stress testing and which patient can be send for surgery without prior cardiac stress testing. The recently published Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo Study II (DECREASE II) evaluated the value of preoperative cardiac testing in intermediate-risk patients on beta-blocker therapy with perioperative tight heart rate control scheduled for major vascular surgery[29]. A total of 1476 vascular surgical patients were screened for this study. Based on the risk score of Boersma et al. patients were divided into 3 risk groups: low cardiac risk (no risk factors), intermediate cardiac risk (1 or 2 risk factors), and high cardiac risk (> 3 risk factors). All 770 intermediate risk patients were randomly assigned to preoperative cardiac stress-testing or no-testing. Results of preoperative testing and coronary revascularization were discussed with the attending physicians, and hemodynamic management was implemented accordingly. Importantly all patients in the DECREASE II study received beta-blocker therapy aiming at a tight heart rate control, i.e. a heart rate of 60–65 beats per minute, irrespective of stress test results. Of the 386 patients randomized to cardiac stress-testing, 287 (74%) had no stress inducible myocardial ischemia, 65 (17%) had limited ischemia, and 34 (9%) had extensive ischemia. No difference in 30-day outcome was observed in intermediate-risk patients with and without testing, 2.3 vs. 1.8 percent (odds ratio 0.78, 95 percent confidence interval 0.28 to 2.1). The upper limit of the 90 percent confidence interval of the absolute risk difference in favor of cardiac testing was 1.2%, indicating non-inferiority of the no-testing strategy. In intermediate-risk patients with extensive ischemia revascularization did not improve 30-day outcome (25.0 versus 9.1 percent events, odds ratio 3.3, 95 percent confidence interval 0.5 to 24; p=0.32). Also, no difference in 2-year outcome was observed in intermediate-risk patients with and without testing, 4.3 versus 3.1 percent (p-value 0.30). The DECREASE II study indicates that cardiac testing of intermediate-risk patients prior to major vascular surgery, as recommended by the guidelines of the ACC/AHA, provided no benefit in patients on beta-blocker therapy with tight heart rate control. Importantly, the strategy of no-testing brought the operation almost 3 weeks forward.

## ADDITIONAL INVASIVE CARDIAC TESTING

Guidelines of the American College of Cardiology /American Heart Association (ACC/AHA) recommend coronary angiography for patients with high-risk noninvasive test results, and myocardial

revascularization in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved[27]. This recommendation was supported by the Coronary Artery Surgery Study that showed a reduced incidence of non-fatal myocardial infarctions after previous bypass surgery among vascular surgery patients compared to those treated medically, 8.5 vs. 0.6% (p=0.001)[30]. More recently, the data from the Bypass Angioplasty Revascularization Investigation trial showed that bypass surgery and percutaneous coronary intervention had similar low rates of postoperative cardiac events in non-cardiac surgery[31]. However, these studies were not designed to assign the optimal strategy in severely ill patients with extensive coronary artery disease immediately prior to major non-cardiac surgery. In addition, these studies could not address the concern of delaying the non-cardiac surgical procedure because of testing, revascularization, and initiation of antiplatelet therapy since the time between revascularization and non-cardiac surgery in these studies was respectively 4.1 and 2.4 years.

The randomized Coronary Artery Revascularization Prophylaxis (CARP) trial was the first study that addressed the strategy of prophylactic revascularization compared to optimal medical therapy in patients with clinically stable coronary artery disease who were scheduled for major non-cardiac vascular surgery[32]. This trial showed that prophylactic revascularization was safe but did not improve perioperative or long-term outcome. The long-term (median follow-up 2.7 years) mortality was 22% in patients allocated to prophylactic coronary revascularization, compared to 23% in the medical only strategy, p=0.92. Also the incidence of perioperative non-fatal myocardial infarction was similar, respectively 12 and 14%, p=0.37. However, it must be noted that the majority of patients in the CARP trial had only 1 or 2 vessel disease. The recently conducted DECREASE V randomized pilot study in which the majority of patients had 3-vessel disease also showed no perioperative and long-term (follow-up 1 year) benefit of prophylactic coronary revascularization[33]. The findings of both CARP and DECREASE V support the current guidelines of the ACC/AHA on perioperative management in high-risk patients to reserve revascularization only for cardiac unstable patients. After successful non-cardiac surgery these patients should be regularly screened for the presence of ischemic complaints and aggressive anti-ischemic therapy, both medical and invasive, should be considered. In these patients at high risk scheduled for major non-cardiac vascular surgery prophylactic revascularization might be switched to late revascularization, preventing the delay of surgery.



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# Chapter 4

## Assessment of cardiac risk before non-cardiac general surgery

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## INTRODUCTION

In the last decades developments in anesthesiological and surgical techniques, i.e. loco-regional anesthesia and minimally invasive surgery, have improved postoperative cardiac outcome considerably. For example patients with a severely reduced left ventricular function used to be at increased risk, but because of the implementation of these new techniques are now scheduled for surgery at relatively low risk. In other words, the improvement of perioperative care has altered the impact of established cardiac risk factors.

However, as more patients with cardiac co-morbidity survive surgery, long-term cardiac outcome has gained interest. Therefore, the focus of preoperative risk evaluation should also take into consideration the impact of cardiac co-morbidity on long-term survival. After all, patients should live long enough to enjoy the benefits of surgery.

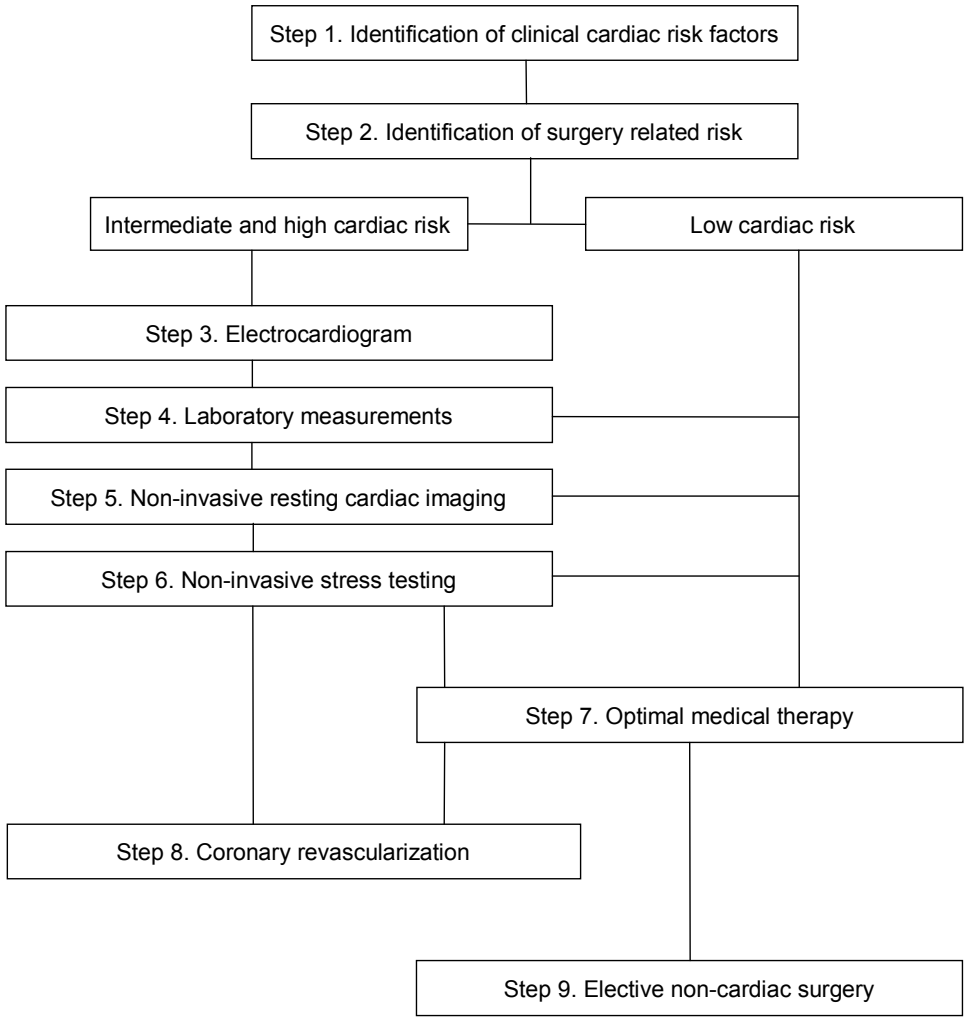
It is estimated that the incidence of cardiac complications after non-cardiac surgical procedures is between 0.5% and 1.0%[1,2]. Annually around 100 million adults undergo some form of non-cardiac surgery. Consequently, approximately 500,000 to 1,000,000 people will suffer from perioperative cardiac complications. Moreover, one out of every four of these patients will die. For the prevention of perioperative cardiac complications it remains of critical importance to identify those at increased risk and treat them accordingly, to improve both perioperative and long-term survival.

This article gives an overview of the current status of preoperative cardiac screening. In a step-wise approach the use and prognostic value of clinical cardiac risk factors, laboratory measurements, non-invasive and invasive coronary testing, and consequently medical and interventional strategies to alter cardiac risk will be discussed (TABLE 4.1).

## STEP 1. IDENTIFICATION OF CLINICAL RISK FACTORS

The first, most simple and least costly step in preoperative cardiac risk stratification is the identification of clinical cardiac risk factors. In the last three decades much attention has been given to the identification of patients at risk by using simple clinical cardiac risk factors. This research has led to numerous cardiac risk indices for non-cardiac surgical procedures. In 1977 Goldman et al. proposed the first cardiac risk stratification model based on prospectively collected data[3]. In this study of 1001 patients, nine independent predictors were found to be correlated with postoperative life-threatening and fatal cardiac complications: preoperative third heart sound or jugular venous distention; myocardial infarction in the preceding six months; more than five premature ventricular contractions per minute documented at any time before operation; rhythm other than sinus rhythm or presence of premature atrial contractions on preoperative electrocardiogram; age over 70 years; intraperitoneal, intrathoracic or aortic operation; emergency operation; important valvular aortic stenosis; and poor general medical condition. The incidence of adverse cardiac events was 1% in the group at lowest risk (class I), and increased to 7%, 14%, and 78% in class II, III, and IV patients respectively. However, it must be noted that only 18 patients were in the group at highest risk. As pointed out by Ridley the Goldman index has a 96.8% negative predictive value, and thus is an excellent tool to rule out CAD[4]. The value of the Goldman index for diagnosing patients with CAD on the other hand was less optimal, i.e. a positive predictive value of 21.6%. In 1986 Detsky et al. prospectively validated and modified the Goldman index and presented a simple normogram, introducing the pre-test likelihood of perioperative cardiac events for cardiac risk stratification[5]. The Detsky modified multifactorial risk

**Table 4.1** Nine steps to optimal preoperative cardiac risk evaluation and modification.






index has been in use ever since and is considered to be a good and practical index. In 1999 Lee et al. reviewed the performance of several clinical risk indices in patients who underwent elective non-cardiac surgery[2]. They found that the Goldman risk index and the Detsky modified cardiac risk index had a similar performance for predicting major cardiac complications. However, when the Goldman risk index was revised and validated, the predictive value of the risk index had substantially improved. In the validation cohort the ROC area improved form 0.70 for the original Goldman index to 0.81 for the Revised Cardiac Risk Index by Lee et al. The Revised Cardiac Risk Index identified 6 predictors (high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, insulin dependent diabetes mellitus, and renal failure) of major cardiac complications, and based on the presence of 0, 1, 2, or 3 or more of these predictors, the rate of major cardiac complications was estimated to be 0.4%, 0.9%, 7%, and 11%, respectively. Interestingly the Lee index has better prognostic value than the Goldman and Detsky indices though the number of cardiac risk factor

variables in the Lee index is smaller. This might be explained by the improvement of perioperative care in the time between the development of the Goldman and Lee risk indices. Nowadays, the Lee index is considered the most relevant index for predicting perioperative cardiac risk in non-cardiac surgery by many clinicians and researchers. However, the patients studied by Lee et al can hardly be considered as an average non-cardiac surgical population. Thoracic, vascular and orthopedic patients were overrepresented in this study population.

## STEP 2. TYPE OF SURGERY

After specifying patients' clinical cardiac risk factors it is important to consider the surgical procedure the patient is scheduled for. However, the clinical cardiac risk indices of Lee, Detsky and Goldman include only high-risk surgery in their models as other types of surgery were not associated with adverse outcome. However, this simplification might not be sufficient to accurately predict perioperative cardiac outcome. Recently Boersma et al. validated the Lee risk index in a large cohort (n=108,593) of all types of non-cardiac surgical procedures[1]. When the Lee index was adapted and more detailed information on the surgical risk of the procedure was added, the predictive value improved substantially (C-statistic improved from 0.63 to 0.85). In this model surgical procedures were classified as low-risk, intermediate-low, intermediate-high, and high-risk surgical procedures.

## STEP 3. ELECTROCARDIOGRAM

Recently, Noordzij et al. showed that the addition of a simple classification of preoperative ECG (i.e. normal or abnormal) improved the predictive value of the combination of clinical cardiac risk factors and type of surgery[6]. An ECG was considered abnormal in case of atrial fibrillation, left or right bundle branch block, left ventricular hypertrophy, premature ventricular complexes, pacemaker rhythm, Q-wave, or ST changes. This study was performed in a group of 23,036 patients undergoing non-cardiac surgery. Though ECGs added extra information on perioperative cardiac risk, it was also shown that in absolute numbers, the increase in predictive value was small in patients undergoing low-risk or intermediate-risk procedures and a "routine preoperative ECG" in this population should be precluded.

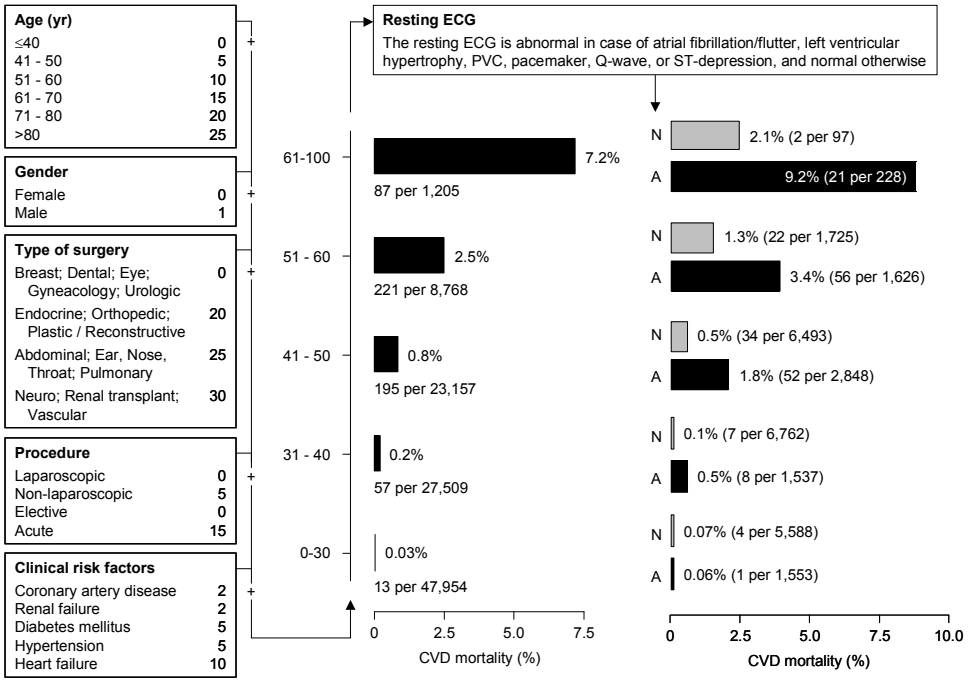
### Summarizing steps 1 to 3

With these simple risk predictors (i.e. clinical risk factors; type of surgery; and ECG) it is possible to make an initial crude assessment of a patient's perioperative cardiac risk. This risk estimation can be used to identify those patients at increased risk who should undergo further cardiac testing. Recently Boersma et al. proposed an interesting risk estimation based on the evaluation of 108,593 non-cardiac surgical procedures[7]. In this model clinical risk factors, type of surgery, and ECG are all included (TABLE 4.2).

## STEP 4. LABORATORY MEASUREMENTS

Apart from those measurements indicating clinical risk factors (e.g. serum creatinine for renal failure, fasting glucose for diabetes mellitus etc.) currently no routine laboratory measurements are related to perioperative cardiac complications. However, two recent studies showed that increased plasma NT-pro-BNP was associated with adverse postoperative outcome[8,9] NT-pro-BNP is increased in patients

**TABLE 4.2** Example of a risk model including clinical risk factors, type of surgery, and ECG to assess perioperative cardiac risk (derived from Boersma *et al*). CVD, cardiovascular disease; PVC, premature ventricular contractions.






with left ventricular dilatation due to fluid overload (i.e. heart failure and renal dysfunction), pressure overload (i.e. aortic valve stenosis) and myocardial ischemia, which might explain the excellent relation with adverse postoperative outcome[10]. Diabetes mellitus is known to be a strong predictor for perioperative events. Therefore fasting glucose levels should be obtained from all patients. Recently it was shown that the level of preoperative glycosylated hemoglobin in diabetic patients is strongly related to perioperative cardiac outcome[11]. In the same patient population it was also shown that in patients with high preoperative glycosylated hemoglobin it is more difficult to regulate glucose levels in the perioperative period. This might in part explain the strong relation between preoperative glycosylated hemoglobin and outcome since it is known from critically ill patients and patients with myocardial infarction that tight glucose control is of imminent importance.

In the Lee risk index renal insufficiency is taken into account. The serum creatinine cut-off value Lee et al. used is 2.0 mg/dL. However, it might be argued that patients with less pronounced renal insufficiency also do worse compare to patients with normal serum creatinine levels. A continuous variable for creatinine would probably be better, though not very user-friendly in every day practice. Recent studies have also shown that glomerular filtration rate might be a better predictor than serum creatinine since this takes into account the different creatinine levels between sexes[12].

## STEP 5. NON-INVASIVE RESTING CARDIAC IMAGING

If steps 1 to 4 indicate an increased cardiac risk or if there is evidence or suspicion of coronary artery disease at physical examination, e.g. peripheral atherosclerotic disease, valve abnormalities or left ventricular dysfunction further cardiac testing might be required. The most simple, inexpensive form of cardiac imaging is resting echocardiography, for the detection of impaired left ventricular function and valve stenosis and sclerosis. Impaired left ventricular function was long considered a strong predictor for adverse perioperative cardiac events. However, due to improved perioperative care it is no longer a strong predictor for short-term outcome but remains a significant predictor for long-term adverse cardiac events.

The presence of aortic stenosis is associated with a 5-fold increased risk of perioperative cardiac events[13]. Also, the severity of aortic stenosis is related to an increased risk of perioperative events. Considering this, it is important to detect the presence and significance of valve disease. Though physical examination is reliable in detecting abnormal heart sounds, the estimation of the severity of stenosis by physical examination alone is difficult and echocardiography is recommended in patients with abnormal heart sounds.

## STEP 6. NON-INVASIVE STRESS CARDIAC IMAGING

According to the guidelines of the ACC/AHA[14] preoperative cardiac exercise or pharmacological stress testing is recommended for patients with intermediate pretest probability of CAD; for prognostic assessment of patients undergoing initial evaluation for suspected or proven CAD; evaluation of subjects with significant change in clinical status; demonstration of proof of myocardial ischemia before coronary revascularization; evaluation of adequacy of medical therapy; and prognostic assessment after an acute coronary syndrome. For stress testing, the evaluation of exercise capacity when subjective assessment is unreliable seems to be a valid reason as well. Patients with CAD or at risk for CAD can be frequently found in the group of patients with limited every day exercise, e.g. patients with severe intermittent claudication. In these patients pharmacological stress echocardiography or nuclear imaging are elegant ways to exclude sub clinical CAD. However, stress testing should not be performed in asymptomatic patients without evidence of CAD; patients with severe co-morbidity likely to limit the life expectancy or candidacy for revascularization; patients with resting ECG-abnormalities that preclude adequate assessment. The sensitivity and specificity of available exercise and pharmacological stress tests (including exercise electrocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy, and dobutamine stress echocardiography) were compared in several meta-analyses. The meta-analysis of Kertai et al. showed a trend in favor of dobutamine stress echocardiography though other tests had satisfying sensitivity and specificity as well (FIGURE 4.1)[15]. An upcoming elegant new diagnostic tool is dobutamine stress MRI though no randomized trials or large series have reported the sensitivity and specificity of this test yet.

## STEP 7. MEDICAL THERAPY

### Beta-blocker therapy

Although widely prescribed during non-cardiac surgery, the evidence for perioperative beta-blocker use is mainly based on only two landmark studies and several observational studies. The first trial evaluated the effect of atenolol in high-risk patients undergoing non-cardiac surgery[16]. In this study

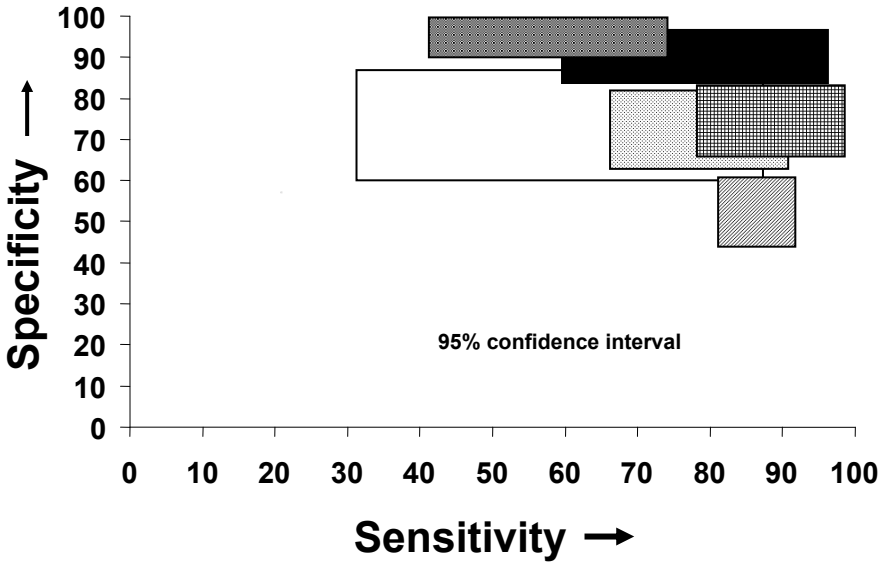



**FIGURE 4.1** Sensitivity and specificity of different types of preoperative non-invasive cardiac testing modalities (derived from Kertai et al[15]).
= Dipyridamole stress echo; = ST analysis; = Ejection fraction;
= Dobutamine stress echo; = Exercise ECG; = Dipyridamole thallium scan



200 patients with risk factors for or known ischemic heart disease were randomized for atenolol or placebo prior to surgery. Atenolol therapy was not associated with an improved in-hospital outcome (cardiac death or myocardial infarction), however, continuous 3-lead Holter monitoring showed a 50% reduction of myocardial ischemia in the atenolol treated group during the first 48 hours after surgery. The second trial showed in a selected high-risk, i.e. stress-induced myocardial ischemia during preoperative dobutamine echocardiography, population of 112 vascular surgery patients a tenfold reduction of incidence of perioperative cardiac death and myocardial infarction, compared to patients without beta-blockers (3.4% vs. 34%)[17]. These promising results were confirmed by a meta-analysis, of prospective randomized studies, evaluating the incidence of perioperative ischemic episodes in 1077 patients in 15 studies (FIGURE 4.2). Beta-blocker therapy was associated with a 65% relative risk (RR) reduction in perioperative myocardial ischemia and a 56% RR reduction in non-fatal MIs. Also, beta-blocker therapy was associated with a significant RR reduction of 67% in the composite endpoint of cardiac death and non-fatal MI. Though other meta-analyses found a similar benefit of beta-blockers[18,19], a recent meta-analysis by Devereaux et al. reported no benefit of beta-blockers on perioperative outcome[20]. However, in that meta-analysis studies that had not yet undergone peer-review were also included which might have seriously influenced the outcome of their meta-analysis.

The promising results were not supported by two recent trials evaluating the effect of beta-blockers in patients at intermediate cardiac risk. In the POBBLE trial low-risk patients, those with a history of ischemic heart disease were excluded, scheduled for vascular surgery were randomized for a fixed dose of metoprolol (n=55) or placebo (n=48). No difference was observed in the incidence of perioperative cardiovascular events. The only difference was observed in the length of hospital stay, which was significantly shorter in those taking metoprolol, 10 vs. 12 days. More recently, the DIPOM study, evaluating the cardioprotective effect of a fixed dose of metoprolol on the evening before major non-

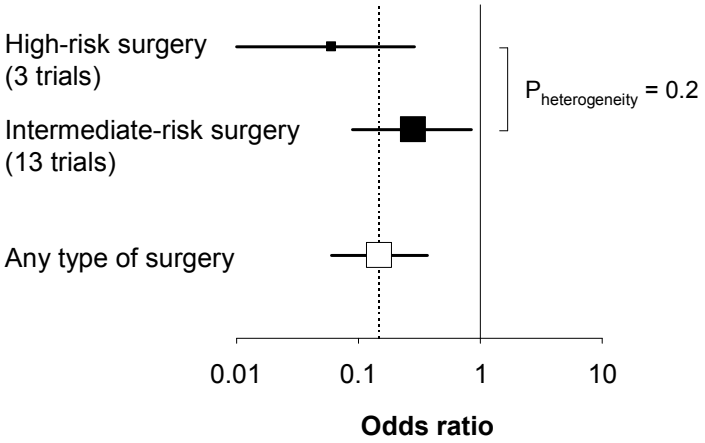



**FIGURE 4.2** Meta-analysis of 15 randomised β-blocker trials. Odds ratio of β-blocker treatment for cardiovascular outcome per type of non-cardiac surgery. Derived from Schouten et al, Cor Artery Dis 2006;17:173–9.

cardiac surgery in 921 diabetics showed no difference in 30-day morbidity and mortality. However, this study was powered for a 1 year follow-up period. Currently at least two large trials, POISE and DECREASE-IV, are ongoing, evaluating the effect of beta-blockers in patients at intermediate risk for perioperative cardiac events. Though the results of these trials have to be awaited, in the mean time, it seems to be safe and effective to prescribe beta-blockers in patients with a Lee index score of 2 or more, as Lindenauer found in a large cohort study of 663,635 patients[21].

### Statin therapy

Several recent studies address the beneficial effect of statin use in patients undergoing non-cardiac surgery (FIGURE 4.3). In a case-control study among 2,816 patients who underwent major vascular surgery statin use was associated with a significant four-fold reduction in all-cause mortality compared to patients with no statin use[22]. The first blinded, placebo-controlled, randomized trial, in which the influence of statin use on perioperative cardiovascular complications was investigated, was reported by Durazzo et al.[23] In their study, 100 patients were randomly assigned to treatment with either 20 mg atorvastatin or placebo. Patients received treatment for 45 days and started at least 2 weeks before surgery. The outcome of this trial was the endpoint of cardiovascular events, defined as cardiac death, non-fatal MI, stroke or unstable angina pectoris. Patients were followed up to 6 months after the surgical procedure. Of 100 patients 90, 44 statin users and 46 non-users, underwent elective vascular surgery. The 6-month incidence of cardiovascular events was 3.1-fold reduced in statin users compared with non-users. Finally, Lindenauer et al.[24] and O'Neil-Callahan et al.[25] confirmed the beneficial effects of statins based on the results of their large-scale retrospective studies. Lindenauer performed a retrospective cohort study based on the hospital discharge and pharmacy records of over 780,000 (70,159 statin users) patients in 329 hospitals throughout the United States. All patients underwent elective major surgical procedures and survived at least the first two postoperative days. After correction for numerous baseline differences, statin users had a 1.4-fold reduced risk of in-hospital mortality. Subsequently, Lindenauer concluded that perioperative statin use might result in a reduced risk of death after major surgical procedures. Though the studies published so far are in favor of perioperative statin treatment, this needs to be confirmed in large, adequately powered randomized trials, such as the recently started DECREASE-IV trial.

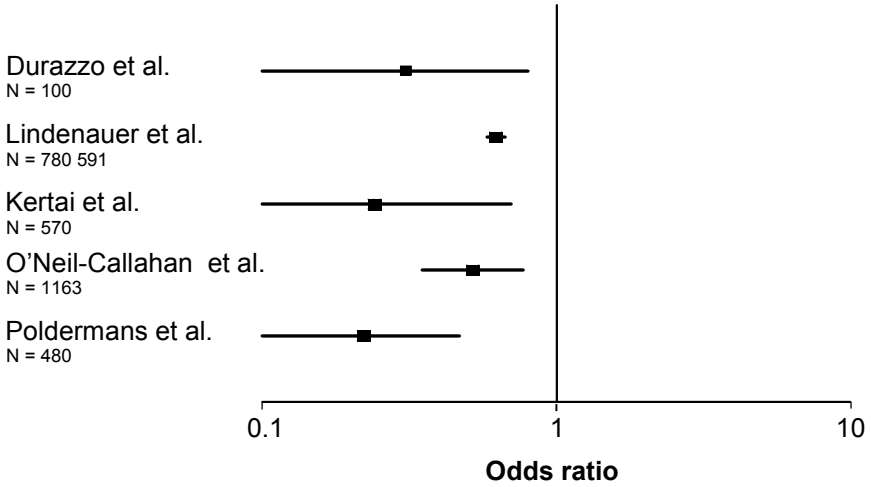



**FIGURE 4.3** Overview of odds ratios and 95% confidence intervals of currently known studies on the influence of statins on perioperative cardiac outcome in non-cardiac surgical procedures.

### Other medical therapy

A meta-analysis by Nishina showed that clonidine, an alpha-2-agonists, use was associated with a reduction in the incidence of perioperative ischemia[26]. However, this study was underpowered (358 non-cardiac surgical patients in two studies) and effects were only reported on ischemia. In two more recent meta-analyses, the beneficial effect of perioperative alpha-2-agonists use was shown for the reduction of myocardial ischemia and perioperative cardiovascular complications. But similarly to the study of Nishina the results of these two meta-analyses were mainly driven by the European Mivazerol trial, the only large-scale study available to date[27]. The results of the European Mivazerol trial showed no overall effect of mivazerol on the pre-specified combined endpoint of cardiac death and myocardial infarction in the total study population of 2,854 patients. Only a post-hoc analysis revealed that in 904 patients who underwent high-risk major vascular surgery mivazerol use was associated with a significantly lower incidence of cardiac death and myocardial infarction.

Nitrates are the most frequently used drugs in case of myocardial ischemia. However, studies about the prophylactic use of intravenous nitroglycerin failed to find any difference in the incidence of intraoperative and perioperative myocardial ischemia in patients receiving nitroglycerin compared to placebo. A potential harmful effect might be a vagal withdraw due to peripheral vasodilatation and subsequent cardiac stimulation and induction of myocardial ischemia in patients with CAD.

In the perioperative setting calcium channel blockers are effectively used in cardiac surgery, reducing myocardial ischemia and arrhythmias. In a meta-analysis Wijeysundera evaluated the use of calcium channel blockers in 11 studies, 1007 patients, all undergoing non-cardiac surgery[28]. Calcium channel blockers significantly reduced perioperative myocardial ischemia (RR 0.49, 95% CI 0.30-0.80) and supra ventricular arrhythmias (RR 0.52, 95% CI 0.37-0.72). However, mortality was not significantly reduced (RR 0.40, 95% CI 0.14-1.16).

## STEP 8. PREOPERATIVE CORONARY INTERVENTIONS

Recent findings of the Coronary Artery Revascularization Prophylaxis Trial showed no survival benefit of preoperative coronary revascularization in cardiac stable patients[29]. Among 5,859 patients scheduled for elective vascular operations a selection was made of patients considered at increased risk for cardiac events with evidence of severe coronary stenosis at coronary angiography. Anatomical criteria of exclusion included: > 50% stenosis of the left main coronary artery, left ventricular ejection fraction < 20% and severe stenosis of the aorta. The 510 patients selected were randomized to optimal medical therapy (more than 80% were on beta-blocker therapy in both groups) with or without coronary revascularization; either percutaneous coronary intervention (59%, mean 18 days prior to surgery) or CABG (41%, mean 54 days prior to surgery). No differences in mortality in the long-term outcome (median follow up of 2.7 years) were found: 22% in the revascularization group vs. 23% in the non-revascularization group. Although the primary end point was late mortality, even the findings at 30 days did not show any difference in terms of mortality or postoperative MI nor did "prophylactic" revascularization result in a reduction of the length of hospital stay. Other, non-randomized studies, on preoperative coronary revascularization are conflicting. The study by Eagle et al. based on the Coronary Artery Surgical Study (CASS) database showed a significant benefit in patients with previous CABG. The same was found by the BARI investigators after both PCI and CABG. However, the time interval between coronary revascularization and non-cardiac surgery in these non-randomized studies was relatively long. Two studies by Kaluza et al. and Wilson et al. showed that perioperative complications after PCI occur mainly when the patient undergoes non-cardiac surgery within 6 weeks after PCI. Placement of coronary stents induces a denudation of the endothelial surface of the coronary artery, thereby greatly increasing the risk of thrombosis. This is further reinforced by the hypercoaguability state during surgery and the problematic use of antiplatelet therapy during surgery.

## CONCLUSION

Clinical cardiac risk markers combined with ECG and the risk of the planned surgical procedure can effectively divide patients in a truly low-risk, intermediate and high-risk population. Low-risk patients probably can be operated without any additional cardiac testing since these tests will not alter perioperative management. Beta-blockers are recommended in patients with ischemic heart disease and should be continued in patients on chronic beta-blocker therapy. Intermediate-risk patients are referred for cardiac testing to exclude extensive stress induced myocardial ischemia, as beta-blockers provide insufficient myocardial protection in this case and preoperative coronary revascularization should be considered taken into account the coronary anatomy and the delay of the index surgical procedure due to revascularization. Whether patients at intermediate risk without ischemic heart disease should be treated with statins and/or beta-blockers is still subject of debate. The currently ongoing POISE and DECREASE IV studies will probably provide us with the necessary evidence for this group of patients. Furthermore preoperative screening should not only focus on perioperative cardiac risk reduction but should also be considered as a unique opportunity to improve patients' long-term cardiac outcome by proper medical therapy such as statins and beta-blockers.

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# Chapter 5

## Perioperative cardiovascular mortality in non-cardiac surgery: validation of the Lee cardiac risk index

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## ABSTRACT

**Background:** The Lee risk index was developed to predict major cardiac complications in non-cardiac surgery. We retrospectively evaluated its ability to predict cardiovascular death in the large cohort of patients who recently underwent non-cardiac surgery in our institution.

**Methods:** The administrative database of the Erasmus MC, Rotterdam, The Netherlands, contains information on 108 593 non-cardiac surgical procedures performed from 1991 to 2000. The Lee index assigns 1 point to each of the following characteristics: high-risk surgery, ischemic heart disease, heart failure, cerebrovascular disease, renal insufficiency, and diabetes mellitus. We retrospectively used available information in our database to adapt the Lee index, calculated the adapted index for each procedure, and analyzed its relation to cardiovascular death.

**Results:** A total of 1877 patients (1.7%) died perioperatively, including 543 (0.5%) classified as cardiovascular death. The cardiovascular death rates were 0.3% (255/75 352) for Lee Class 1, 0.7% (196/28 892) for Class 2, 1.7% (57/3380) for Class 3, and 3.6% (35/969) for Class 4. The corresponding odds ratios were 1 (reference), 2.0, 5.1, and 11.0, with no overlap for the 95% confidence interval of each class. The C statistic for the prediction of cardiovascular mortality using the Lee index was 0.63. If age and more detailed information regarding the type of surgery were retrospectively added, the C statistic in this exploratory analysis improved to 0.85.

**Conclusion:** The adapted Lee index was predictive of cardiovascular mortality in our administrative database, but its simple classification of surgical procedures as high-risk versus not high-risk seems suboptimal. Nevertheless, if the goal is to compare outcomes across hospitals or regions using administrative data, the use of the adapted Lee index, as augmented by age and more detailed classification of type of surgery, is a promising option worthy of prospective testing.

## INTRODUCTION

Patients undergoing major non-cardiac surgery are at high risk of cardiovascular morbidity and mortality. Evidence suggests that perioperative myocardial infarction is commonly caused by rupture of a coronary plaque, leading to thrombus formation and subsequent vessel occlusion, similar to what occurs in nonsurgical settings[1,2]. The clinical importance of perioperative cardiovascular complications is well recognized, and numerous investigations have described the relation between patient's characteristics and the risk of adverse cardiovascular outcome[3-11].

In the 1990s, Lee and colleagues systematically analyzed the risk of major cardiac complications (which included myocardial infarction, cardiogenic pulmonary edema, cardiac arrest, and cardiac death) in 4315 patients undergoing non-cardiac surgery, the largest cohort ever described[8]. The resulting Lee index, which is a modification of the original Goldman index, is now considered by many clinicians and researchers to be the most relevant index to predict cardiac risk. However, the patients studied by Lee and colleagues cannot be considered as an average, unselected surgical cohort because their study included only patients with a several-day expected length of hospital stay and excluded neurologic surgery; as a result, it was relatively dominated by patients undergoing thoracic (12%), vascular (21%), and orthopedic surgery (35%).

The current study evaluates the Lee index in 108 593 patients who underwent non-cardiac surgery in the Erasmus Medical Center from 1991 to 2000. Because we relied on medical records and administrative data gathered as part of routine medical care, rather than duplicating the prospective methods of the Lee study, we used cardiovascular mortality, instead of the broader range of clinical cardiac complications that were considered in the original Lee study, as our primary endpoint.

## METHODS

### Hospital setting, procedures and patients

The Erasmus Medical Center, a metropolitan university hospital that serves a population of approximately 3 million people in the southwestern area of The Netherlands, acts as a tertiary referral center for approximately 30 affiliated hospitals. Between January 1, 1991, and December 31, 2000, 122 860 non-cardiac surgical procedures were performed in patients above the age of 15 years in the Erasmus Medical Center. We excluded 14 267 planned and unplanned procedures that were conducted within 30 days after an initial operation, and analyzed the perioperative course of the remaining 108 593 procedures, which were performed in 75 581 different patients. Over the 10-year observation period, 20 885 patients had multiple surgeries in the Erasmus Medical Center. They were included as many times as they had surgeries that were more than 30 days apart. The median span between 2 successive procedures was 297 days (interquartile range, 123 to 677 days). The operation (not the patient) was the unit of analysis because this approach is consistent with clinical practice, wherein the risk of perioperative complications is assessed in relation to a specific procedure.

### Sources of data

For each patient undergoing surgery, a number of data items are routinely entered into the computerized hospital information system at the time the patient is hospitalized. First, surgical techniques are classified by the treating physician according to a standardized national coding system, which was developed in cooperation 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, with a total of 11 969 procedures (11.0%) classified into multiple categories.

Second, from written information that is provided by the patient's general practitioner, referring physician, or hospital physicians involved in perioperative care, each patient's medical history is classified according to the International Classification of Diseases, Ninth Revision (ICD-9)[12]. The classification and the entry of the data in the electronic database are performed by dedicated administrative personnel who have completed in-depth training on medical data registration. We recorded the following medical conditions: history of diabetes mellitus (ICD-9250), myocardial infarction (ICD-9410, 411, and 412), angina pectoris (ICD-9413 and 414), prior heart failure (ICD-9428), cerebrovascular accident (ICD-9430), and renal disease (ICD-9580). These recorded diagnoses served as surrogates for 5 more detailed criteria used in the Lee index[8] in which ischemic heart disease was defined as a history of myocardial infarction or positive exercise test, current complaint of ischemic chest pain, or use of nitrate therapy, or Q waves on the electrocardiogram, but patients with a history of coronary bypass surgery or angioplasty were included only if they had current complaints of chest pain presumed to be due to ischemia; heart failure was defined as a history of heart failure, pulmonary edema, or paroxysmal nocturnal dyspnea, a physical examination showing an S3 gallop or bilateral riles, or a chest radiograph showing pulmonary vascular redistribution; renal failure was a creatine level >2.0 mg/dL; diabetes was insulin requiring; and cerebrovascular disease was defined as a history of a stroke or transient ischemic attack. For the score criterion, high-risk surgery, we categorized procedures in the same way as the Lee index: retroperitoneal, intrathoracic, or suprainguinal vascular procedures were defined as high risk.



### Endpoint definition

The hospital information system also contains the patient's vital status at hospital discharge and clinical postoperative diagnoses. For example, diagnosed perioperative myocardial infarctions are reported, but the patients do not routinely have serial postoperative electrocardiograms or blood sampling for determination of cardiac biomarkers. Consequently, clinically unsuspected or painless perioperative myocardial infarctions may well be missed. Similarly, clinically apparent strokes were reported, but systematic neurological evaluations were not performed. In view of these limitations, we chose cardiovascular death as the primary endpoint of our analyses. Cardiovascular death, which was defined as any death with a cardiovascular complication as the primary or secondary cause (according to the definitions of the World Health Organization), included deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Noncardiovascular death was defined as any death with a principal noncardiovascular cause, including surgery-related bleeding complications, cancer, trauma, and infection. Sudden death in a previously stable patient was considered as cardiovascular.

To obtain the cause of death, 2 investigators (MDK, DP) independently reviewed all available perioperative data but were blind to preoperative characteristics and aimed to reach consensus. If consensus could not be reached, the opinion of a third, independent investigator (OS) was final. Events were counted until hospital discharge or 30 days after surgery, whichever day came first.

### Data quality and ethical considerations

We should emphasize that the data that we used were collected for administrative purposes and not for the purposes of this study by clinicians using standardized data collection forms. We designed and undertook this study several years after the last patient was enrolled, and we were not able to verify the completeness or the correctness of the data. By necessity, we had to rely on the information that

was provided by the clinicians who took care of the patients during everyday clinical practice. This study was approved by the Medical Ethics Committee of the Erasmus Medical Center. However, given the retrospective nature of our study, informed consent could not be obtained from each patient.

### Statistical analysis

Continuous data are described as median values and corresponding 25th and 75th percentiles, and dichotomous data are described as numbers and percentages. With the limitations noted previously, we estimated the Lee index for each patient in our dataset. Univariable logistic regression analyses were used to evaluate the relation among the adapted Lee index (with individual dummy variables for each score category) as calculated with information in our administrative database, the clinical characteristics that are part of this index, and our primary endpoint, which was cardiovascular death including stroke, rather than the endpoint of Lee and colleagues, who considered the composite endpoint of myocardial infarction, cardiogenic pulmonary edema, cardiac arrest, or cardiovascular death. Crude, unadjusted odds ratios and corresponding 95% confidence intervals are reported. Subsequently, multivariable logistic regression analyses were performed to evaluate if the predictive power of the adapted Lee index could be improved retrospectively in our dataset by adding age or more detailed information on the type of surgery, according to the classification recommended by the American Heart Association/American College of Cardiology[13]. The 4 categories were low risk (breast, carotid, dental, endocrine, eye, gynecology, reconstructive), low-intermediate risk (orthopedic, urologic), intermediate-high risk (abdominal; ear, nose, throat; neurological; pulmonary; renal transplant; vascular, excluding aortic and carotid), and high risk (aortic). Adjusted odds ratios and corresponding 95% confidence intervals were calculated. The performance of risk models was determined by the C statistic, which indicates how well a model rank orders patients with respect to their outcomes, where 0.5 indicates no predictive value and 1.0 indicates perfect performance[14]. Because our dataset involved 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 repeated using generalized estimation equations[15], with "patient" as the classification factor. No relevant differences were observed between the parameter estimates as determined according to both methodologies. Therefore, we concluded that interobservation correlation was not a major issue in our dataset, and we present only the results based on classical methods.

## RESULTS

A total of 52 387 surgical procedures were performed in men, including 12 378 orthopedic surgeries (24%); 9273 ear, nose, and throat surgeries (18%); and 8637 abdominal surgeries (16%). Among the 56 206 procedures in women, gynecological surgery was most common with 15 312 procedures (27%), followed by orthopedic surgery with 9840 (18%), and abdominal surgery with 7816 (14%). Because of reallocation of patients among regional hospitals, the annual volumes of ophthalmic and gynecological procedures decreased in the early 1990s. During the study period, the volume of orthopedic surgery gradually increased, whereas the volume of abdominal surgery decreased slightly.

With a median age of 51 years (25th to 75th percentile: 34-65 years), men were 7 years older than were women (median 44 years; 25th to 75th percentile: 32-62 years). The majority of patients had a score of 0 points on the adapted Lee index (FIGURE 5.1). During the study period, no systematic change in scores on the adapted Lee index was observed in men. By comparison, scores in women worsened slightly in 1993 and remained constant thereafter, a shift that was strongly related to the decline in the number of gynecological procedures.

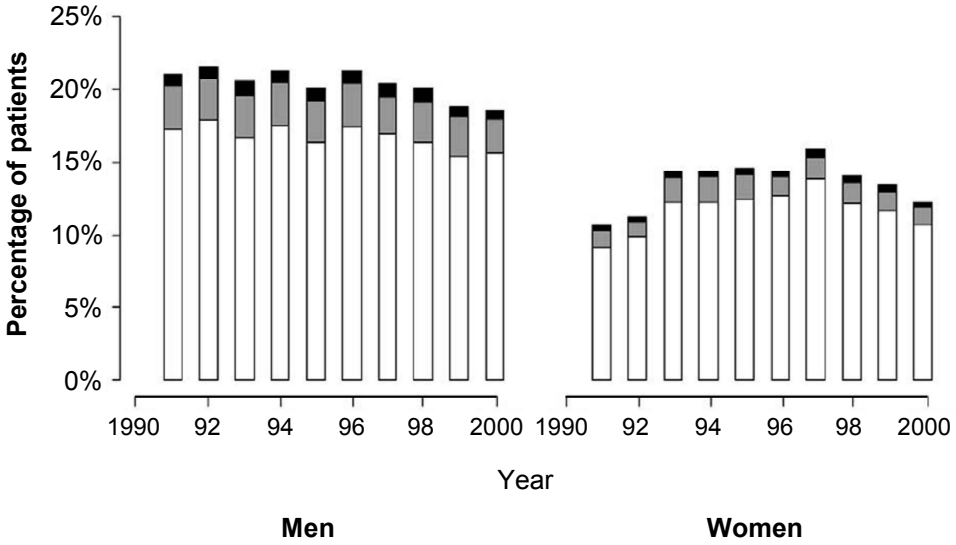


**FIGURE 5.1** Time trends in the cardiovascular risk profile.
Data indicate the percentage of patients with a score of 1 point (white portion of the bar), 2 points (grey portion), and ≥3 points according to the cardiovascular risk index as developed by Lee and colleagues[8].



A total of 1877 patients (1.7%) died perioperatively. A cardiovascular complication was the principal (405 patients) or the secondary (138 patients) cause of death in 543 patients (0.5% of the sample; 29% of deaths). 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

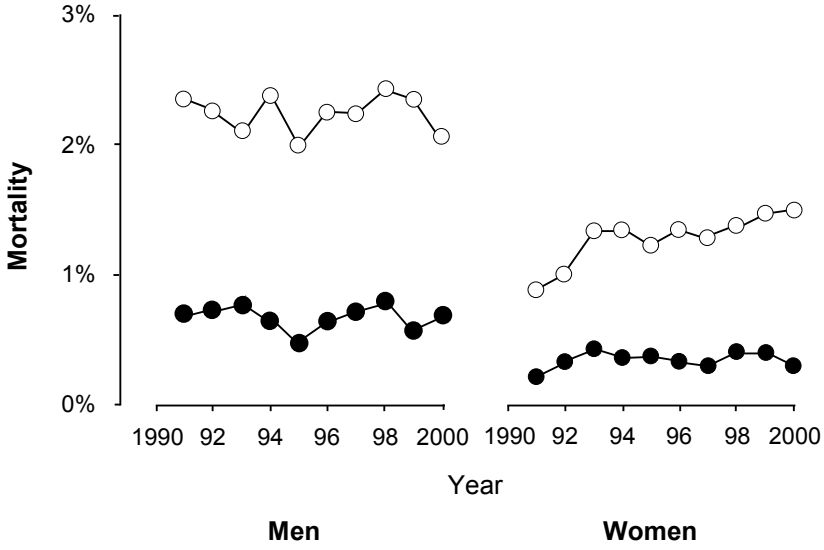


**FIGURE 5.2** Time trends in the incidence of perioperative all-cause mortality (open circles) and cardiovascular death (closed circles).

(37% [122/326] vs. 27% [421/1551] patients; p <0.001). Infection, the most common noncardiovascular cause of death, was the primary cause in 231 patients and the secondary cause in 308 patients, representing 29% of deaths.

All-cause mortality and cardiovascular mortality were higher in men than in women: 2.2% (1167/52 387) versus 1.3% (710/56 206) (p <0.001), and 0.7% (350/52 387) versus 0.3% (193/56 206) (p <0.001). During the study period, no systematic change in all-cause mortality was observed in men (FIGURE 5.2). In contrast, all-cause mortality in women increased significantly from 0.9% (55/6280) in 1991 to 1.3% (69/5151) in 1993 and 1.5% (79/5315) in 2000 (71% increase; p <0.001). There were no significant changes in cardiovascular mortality over time in either men or women.

Important differences in the incidence of perioperative cardiovascular death were observed in relation to type of surgery (TABLE 5.1). Patients undergoing vascular surgery, especially those undergoing aortic surgery, had the highest cardiovascular mortality (1.8%), followed by patients undergoing neurological surgery (1.7%), renal transplant (about 1.1%), and pulmonary surgery (1.1%). Breast, dental, eye, and gynecology surgery were associated with cardiovascular mortality rates below 0.1%. The 15 318 patients (14%) who had laparoscopic procedure had a lower incidence of cardiovascular death than did patients who had open surgery (0.2% vs. 0.6%; p <0.001) (TABLE 5.2). The 774 patients

**TABLE 5.1** Perioperative cardiovascular and all-cause death in patients undergoing non-cardiac surgery for various indications.

| | | Cardiovascular death | | | | | | All-cause death | |
|---|---|---|---|---|---|---|---|---|---|
| | Number of | Primary cause | | Secondary cause | | Total | | | |
| Type of surgery | procedures | Number | (%) | Number | (%) | Number | (%) | Number | (%) |
| Abdominal | 16,453 | 63 | (0.4) | 50 | (0.3) | 113 | (0.7) | 606 | (3.7) |
| Hepatico, pancreatico, biliary | 2752 | 10 | (0.4) | 4 | (0.1) | 14 | (0.5) | 129 | (4.7) |
| Esophagogastric | 11,982 | 53 | (0.4) | 44 | (0.4) | 97 | (0.8) | 488 | (4.1) |
| Other abdominal | 3714 | 12 | (0.3) | 7 | (0.2) | 19 | (0.5) | 122 | (3.3) |
| Breast | 2411 | 0 | | 0 | | 0 | | 0 | |
| Dental | 1225 | 1 | (0.1) | 0 | | 2 | (0.1) | 2 | (0.2) |
| Ear, Nose, Throat | 15,291 | 114 | (0.7) | 22 | (0.1) | 136 | (0.9) | 411 | (2.7) |
| Endocrine | 1029 | 1 | (0.1) | 2 | (0.2) | 3 | (0.3) | 6 | (0.6) |
| Eye | 9163 | 1 | (0.0) | 0 | | 1 | (0.0) | 11 | (0.1) |
| Gynecology | 15,343 | 2 | (0.0) | 1 | (0.0) | 3 | (0.0) | 20 | (0.1) |
| Neurologic | 5797 | 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) |
| Reconstructive | 4157 | 5 | (0.1) | 2 | (0.0) | 7 | (0.2) | 12 | (0.3) |
| Pulmonary | 1965 | 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 | 6234 | 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 | 3854 | 36 | (0.9) | 13 | (0.3) | 49 | (1.3) | 142 | (3.7) |
| Other | 9423 | 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) | 1877 | (1.7) |

**TABLE 5.2** Univariable relation among the Lee index, demographic and clinical characteristics, and perioperative cardiovascular death.

| | | Number of procedures | Cardiovascular death | | Unadjusted odds ratio (95% confidence interval) |
|---|---|---|---|---|---|
| | | | Number | (%) | |
| Adaptation of the Lee index score and its components (see Methods) | | | | | |
| Adapted Lee index | ≥3 | 969 | 35 | (3.6) | 11.0 (7.7-15.8) |
| | 2 | 3380 | 57 | (1.7) | 5.1 (3.8-6.7) |
| | 1 | 28,892 | 196 | (0.7) | 2.0 (1.7-2.4) |
| | 0 | 75,352 | 255 | (0.3) | 1 |
| Type of surgery* | High risk | 29,426 | 224 | (0.8) | 1.9 (1.6-2.3) |
| | Not high risk | 79,167 | 319 | (0.4) | 1 |
| History of ischemic heart disease | Yes | 3588 | 77 | (2.1) | 4.9 (3.9-6.3) |
| | No | 105,005 | 466 | (0.4) | 1 |
| History of heart failure | Yes | 1377 | 50 | (3.6) | 8.2 (6.1-11.0) |
| | No | 107,216 | 493 | (0.5) | 1 |
| History of CVA | Yes | 500 | 11 | (2.2) | 4.6 (2.5-8.3) |
| | No | 108,093 | 532 | (0.5) | 1 |
| Renal insufficiency | Yes | 1894 | 31 | (1.6) | 3.5 (2.4-5.0) |
| | No | 106,699 | 512 | (0.5) | 1 |
| Diabetes mellitus | Yes | 2001 | 36 | (1.8) | 3.8 (2.7-5.4) |
| | No | 106,592 | 507 | (0.5) | 1 |
| Detailed data on type of surgery | | | | | |
| Type of surgery† | High risk | 1078 | 63 | (5.8) | 73.6 (46.9-115) |
| | Intermediate-high risk | 40,985 | 371 | (0.9) | 10.8 (7.4-15.9) |
| | Low-intermediate risk | 33,275 | 81 | (0.2) | 2.9 (1.9-4.4) |
| | Low risk | 33,255 | 28 | (0.1) | 1 |
| Laparoscopic procedure | Yes | 15,318 | 24 | (0.2) | 0.3 (0.2-0.4) |
| | No | 93,275 | 519 | (0.6) | 1 |
| Emergency surgery | Yes | 774 | 47 | (6.1) | 14.0 (10.2-19.0) |
| | No | 107,819 | 496 | (0.5) | 1 |
| Other potential risk determinants | | | | | |
| Age (years) | ≥80 | 5314 | 77 | (1.5) | 23.0 (14.8-35.7) |
| | 70-80 | 12,619 | 165 | (1.3) | 20.7 (13.7-31.1) |
| | 60-70 | 15,742 | 146 | (0.9) | 14.6 (9.7-22.1) |
| | 50-60 | 15,675 | 91 | (0.6) | 9.1 (5.9-14.0) |
| | 40-50 | 16,987 | 37 | (0.2) | 3.4 (2.1-5.6) |
| | <40 | 42,256 | 27 | (0.1) | 1 |

CVA = cerebrovascular accident. *According to the Lee index: high risk = intraperitoneal, intrathoracic, and suprainguinal vascular procedures; not high risk = other procedures. †According to the American Heart Association/American College of Cardiology classification: high risk = aortic; intermediate risk = abdominal; ear, nose, throat; neurologic; orthopedic; pulmonary; renal transplant; urologic; vascular, excluding aortic and carotid; low risk = breast; carotid; dental; endocrine; eye; gynecology; reconstructive. Within the intermediate risk group, patients undergoing orthopedic or urologic surgery had significantly lower risk than patients undergoing other types of surgery. Therefore, we labeled orthopedic and urologic procedures as low-intermediate risk, and the remaining procedures as intermediate-high risk.

(0.7%) who underwent emergency surgery had a significantly higher rate of cardiovascular death than did patients who underwent nonemergency surgery (6.1% vs. 0.5%; p <0.001).

In univariable analyses, the adapted Lee index and its individual components were associated with an increased risk of cardiovascular death (TABLE 5.2). The prospective C statistic for the prediction of cardiovascular mortality in this validation analysis was 0.63. The C statistic for this exploratory analysis was substantially higher in the subset of 66 530 low- to intermediate-risk surgical procedures (including breast, carotid, dental, endocrine, eye, gynecology, orthopedic, reconstructive, and urologic surgery) than in the remaining 42 063 intermediate- to high-risk procedures (0.68 vs. 0.56). When more detailed information, including the type of surgery (defined as low, low-intermediate, intermediate-high, and high), whether it was laparoscopic or open, and whether it was emergent, was added to the Lee index, the retrospective C statistic was 0.79 (TABLE 5.3). If age were included, the C statistic rose further, to 0.85.

**TABLE 5.3** Multivariable relation among the Lee index, type of surgery, age, and perioperative cardiovascular death, based on analyses of 108 593 subjects undergoing non-cardiac surgery.

| | | Odds ratio (95% confidence interval) | | |
|---|---|---|---|---|
| | | Adapted Lee index only | Adapted Lee index and type of surgery | Adapted Lee index, type of surgery and age |
| Model C statistic | | 0.63 | 0.79 | 0.85 |
| Adapted Lee index* | ≥3 | 11.0 (7.7-15.8) | | |
| | 2 | 5.1 (3.8-6.7) | | |
| | 1 | 2.0 (1.7-2.4) | | |
| | 0 | 1 | | |
| Adapted Lee index, excluding type of surgery | ≥3 | | 9.2 (5.5-15.4) | 6.4 (3.8-10.8) |
| | 2 | | 5.6 (4.0-7.9) | 4.0 (2.9-5.6) |
| | 1 | | 2.3 (1.8-3.0) | 1.7 (1.3-2.2) |
| | 0 | | 1 | 1 |
| Type of surgery† | High risk | | 35.7 (22.1-57.6) | 20.0 (12.3-32.5) |
| | Intermediate-high risk | | 10.3 (7.0-15.2) | 10.3 (7.0-15.1) |
| | Low-intermediate risk | | 2.8 (1.8-4.3) | 2.7 (1.7-4.1) |
| | Low risk | | 1 | 1 |
| Laparoscopic procedure | Yes | | 0.3 (0.2-0.4) | 0.3 (0.2-0.4) |
| | No | | 1 | 1 |
| Emergency surgery | Yes | | 4.6 (3.2-6.5) | 4.4 (3.1-6.4) |
| | No | | 1 | 1 |
| Age (years) | ≥80 | | | 19.9 (12.8-31.1) |
| | 70-80 | | | 12.6 (8.3-19.0) |
| | 60-70 | | | 8.5 (5.6-12.9) |
| | 50-60 | | | 5.6 (3.6-8.7) |
| | 40-50 | | | 2.5 (1.5-4.1) |
| | <40 | | | 1 |

*Index that assigns one point to each of the following characteristics: ischemic heart disease, history of heart failure, history of cerebrovascular disease, renal insufficiency, and diabetes mellitus. † According to the American Heart Association/American College of Cardiology classification: high risk = aortic; intermediate risk = abdominal; ear, nose, throat; neurologic; orthopedic; pulmonary; renal transplant; urologic; vascular, excluding aortic and carotid; low risk = breast; carotid; dental; endocrine; eye; gynecology; reconstructive. Within the intermediate risk group, patients undergoing orthopedic or urologic surgery had significantly lower risk than patients undergoing other types of surgery. Therefore, we labeled orthopedic and urologic procedures as low-intermediate risk, and the remaining procedures as intermediate-high risk.

## DISCUSSION

Cardiovascular mortality still is a major burden in patients undergoing non-cardiac surgery. In the investigated cohort, about 7 of every 1000 procedures in men and 3 of every 1000 procedures in women resulted in fatal in-hospital cardiovascular complications. In contrast, anesthesia-related mortality occurs only in approximately 1 of 250 000 procedures[16]. Interestingly, patients who underwent postmortem examination were considerably more often classified as cardiovascular death than were patients in whom no such examination was performed, suggesting that the incidence and effect of cardiovascular complications after non-cardiac surgery may be underestimated in clinical practice.

The Lee index (or revised Goldman index) is considered the best currently available cardiac risk prediction index in non-cardiac surgery because it was developed on contemporary, prospectively gathered clinical data from unselected patients who underwent a wide spectrum of procedures and were followed systematically postoperatively, including standardized visits and cardiac biomarkers, for a range of clinically relevant cardiac outcomes[17,18]. In our study, the Lee index was adapted for an administrative database and its use extended to a different goal––the use of administrative data specifically to predict perioperative cardiovascular mortality. However, in agreement with another investigation[19], our data also suggest that the Lee index is probably suboptimal for identifying patients with greater cardiac risk, perhaps because it excluded emergency operations and perhaps because the type of surgery, which is one of the main determinants of adverse cardiovascular outcome[13], was considered in only 2 subtypes: high risk, including intraperitoneal, intrathoracic and suprainguinal vascular procedures; and all remaining nonlaparascopic procedures, mainly including orthopedic, abdominal, and other vascular procedures. We found that a more subtle classification, as suggested by the American Heart Association/American College of Cardiology guideline committee[13], resulted, at least retrospectively, in a substantially better risk discrimination. We realize that the Lee index was developed for the prediction of prospectively detected "major cardiac complications" (which included myocardial infarction, cardiogenic pulmonary edema, cardiac arrest, and cardiac death) and not for the prediction of cardiovascular death only. It is unknown whether the C statistics would have been more favorable if we had used the same endpoint as Lee and colleagues, but some believe it may be easier to predict the incidence of death than to predict a broader range of clinical outcomes[20]. In addition, from the perspective of assessing quality of care using administrative databases, cardiovascular mortality is certainly a relevant endpoint.

The American Heart Association/American College of Cardiology guidelines identify advanced age as a minor predictor of cardiovascular risk[13]. In our study, as in essentially every study of perioperative risk, cardiovascular mortality increased progressively with age[3-11]. Indeed, elderly patients might often have asymptomatic coronary disease, which places them at increased risk of perioperative cardiovascular complications. The key question has been whether age itself is an independent predictor or whether its importance is subsumed by its strong relation with other measurable evidence of the severity of disease or of comorbid conditions. Our finding of the major importance of age per se might be because our approach to assessing risk factors was by means of the medical history as coded according to the ICD-9 system and subsequently entered in an electronic database by administrative personnel based on written information provided by health-care professionals. These employees are specifically instructed to avoid inappropriate over-diagnosis; as a result, key medical conditions might have been overlooked, and, consequently, the relative contribution of these factors to cardiovascular death might have been underestimated, thereby also increasing the apparent independent contribution of age itself[21]. In addition, we restricted our analyses to patients who underwent surgery. No information was included from patients who were screened but who 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.

The identification of patients at risk of perioperative cardiovascular complications has improved considerably in recent years. Beta-blockers reduce complication rates for some categories of patients, such as those undergoing major vascular surgery[22-24], and statins may be useful as well[25]. By comparison, routine coronary revascularization is not beneficial[26]. The development and implementation of such strategies for the entire spectrum of surgical patients remains an important challenge for contemporary medicine[27]. In that regard, it is noteworthy that the incidence of fatal perioperative cardiovascular complications at our center did not decline during the 10-year study period.

### Conclusion

This single center study, which involved over 100 000 subjects, demonstrated that perioperative cardiovascular mortality is a major burden in patients undergoing non-cardiac surgery. Little progress has been achieved in reducing cardiovascular mortality during the years of the study. The adapted Lee index had an admirable performance to predict cardiovascular mortality, but its simple classification of procedures as high risk versus not high risk seems suboptimal. Our analysis is limited by the fact that our data are derived from an administrative database, the retrospective nature of the data, the ICD-9 coding of clinical characteristics, and our evaluation of cardiovascular death rather than a broader range of clinical complications. Our approach seems most applicable to situations in which administrative data are to be used to assess outcomes and to compare outcomes in different hospitals or regions. Furthermore, prospective studies are warranted to confirm our findings.

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# Chapter 6

## The influence of aging on the prognostic value of the revised cardiac risk index for postoperative cardiac complications in vascular surgery patients

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## ABSTRACT

**Background:** The Lee-risk index (Lee-index) was developed to predict major adverse perioperative cardiac events (MACE). However, age is not included as a risk factor. The aim was to assess the value of the Lee-index in vascular surgery patients among different age categories.

**Methods:** Of 2 642 patients cardiovascular risk factors were noted to calculate the Lee-index. Patients were divided into four age categories; ≤ 55 (n = 396), 56–65 (n = 650), 66–75 (n = 1 058) and >75 years (n = 538). Outcome measures were postoperative MACE (cardiac death, MI, coronary revascularization and heart failure). The performance of the Lee-index was determined using C-statistics within the four age groups.

**Results:** The incidence of MACE was 10.9%, for Lee-index 1, 2 and ≥ 3; 6%, 13% and 20%, respectively. However, the prognostic value differed among age groups. The predictive value for MACE was highest among patients under 55 year (0.76 vs. 0.62 of patients aged > 75). The prediction of MACE improved in elderly (aged > 75) after adjusting the Lee-index with age, revised risk of operation (low, low-intermediate, high-intermediate and high-risk procedures) and hypertension (0.62 to 0.69).

**Conclusion:** The prognostic value of the Lee-index is reduced in elderly vascular surgery patients, adjustment with age, risk of surgical procedure, and hypertension improves the Lee-index significantly.

## INTRODUCTION

Peripheral atherosclerotic disease (PAD) is becoming an increasingly important health issue in the Western society[1-3]. A clear increase of PAD is observed in elderly subjects. In The Rotterdam Study the prevalence of PAD increases from 6.6% in patients aged 55–59 years to 52% in patients aged >85 years[4]. As life expectancy improves, the prevalence of PAD is on the increase leading to 16 000 hospital admissions annually in the Netherlands, 6% of all admissions due to cardiovascular diseases[5]. Postoperative outcome is related to the presence and extent of coronary artery disease as well as the regulation of risk factors for coronary artery disease such as diabetes mellitus, hyperlipidaemia, and hypertension[1,2,4,6]. Commonly, patients are screened prior to surgery using the Revised Cardiac Risk Index, which includes ischemic heart disease, heart failure, cerebrovascular disease, insulin dependent diabetes mellitus, renal dysfunction, and high-risk surgery[7]. However, this risk index may have a potential limitation for preoperative cardiac risk assessment in vascular surgery patients as age is not included and only 21% of the original study population underwent vascular surgery. In this study we evaluated the prognostic value of the Revised Cardiac Risk Index and determined if the accuracy could be improved by the addition of different age categories and additional risk factors.

## METHODS

### Study design and patient selection

Between January 1993 and June 2006, 2 730 open non-cardiac vascular surgical procedures were performed in patients above 18 years old at Erasmus MC, Rotterdam, the Netherlands. Patients were divided into four categories according to their age: ≤ 55, 56–65, 66–75 and >75 years respectively. We excluded 88 procedures that were conducted within 30 days after the index procedure. The postoperative outcome of the remaining 2 642 procedures, performed in 2 298 different patients, was analyzed. Over the 13-year observation study, 250 patients had multiple surgical procedures. The procedure and not the patient was the unit of analysis because this approach is consistent with clinical practice, wherein the risk of perioperative complications is assessed in relation to a specific procedure. The Medical Ethics Committee of the Erasmus MC was informed about the study protocol, and per institutional practice no official approval was requested.

### Revised Cardiac Risk Index factors

The Revised Cardiac Risk Index (Lee-index) assigns 1 point to each of the following 6 characteristics: high-risk surgery, ischemic heart disease, history of heart failure, cerebrovascular disease, renal insufficiency and insulin dependent diabetes mellitus. Ischemic heart disease was defined as a history of MI or positive stress test, current complaint of ischemic chest pain, or use of nitrate therapy, or Q waves on the electrocardiogram, but patients with a history of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) were included only if they had current complaints of chest pain presumed to be due to ischemia; heart failure was defined as a history of heart failure, pulmonary edema, or paroxysmal nocturnal dyspnea, or a chest radiograph showing pulmonary vascular redistribution; renal insufficiency was a creatinine level > 177 umol/L; high-risk surgery as AAA, r-AAA and LLR procedures; and cerebrovascular disease was defined as a history of a stroke or transient ischemic attack. Notably, due to the high surgical risk of LLR, AAA and r-AAA surgery, by definition no Lee-index of 0 points was reported in these patients. This resulted in three categories according to the number of Lee risk index points: 1, 2 and ≥ 3.

### Other risk factors

Other baseline risk factors recorded of all patients were age, gender, hypertension (defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg and/or use of anti-hypertensive medication), chronic obstructive pulmonary disease (COPD) according to symptoms and pulmonary function tests (i.e. forced expiratory volume in 1 second <70% of maximal age and gender predictive value), body mass index, smoking status, hypercholesterolemia (total cholesterol of >5.2 mmol/L) and medication (including statins, diuretics, angiotensin-converting-enzyme inhibitors, calcium antagonists, nitrates, beta-blockers, aspirin and anti-coagulants). All prescription and over-the-counter medications were noted on the day of admission.

### Procedures

All patients underwent open vascular surgery, respectively: carotid endarterectomy (CEA), elective infrarenal abdominal aortic surgery (AAA), acute infrarenal AAA surgery (r-AAA) and lower limb arterial reconstruction procedures (LLR).

### Clinical follow-up and end points

Perioperative clinical information was retrieved from an electronic database of patients maintained in our hospital. From the municipal civil registries, we obtained the survival status. The follow-up was complete in 98.2%. The primary outcomes were major adverse cardiac event (MACE) and all-cause mortality, occurring within 30 days after surgery. The secondary outcome was all-cause mortality during long-term follow-up. MACE within 30-days after surgery, was defined as cardiac death (which was defined as any death with a cardiac complication as the primary or secondary cause, including deaths following myocardial infarction, cardiac arrhythmia and heart failure), myocardial infarction or coronary revascularization (PCI or CABG). Sudden death in a previously stable patient was considered as cardiac death. Myocardial infarction was defined as the presence of 2 out of the following 3 criteria: (1) typical chest-pain complaints, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists >24 hours, and (3) a positive troponin T, i.e. >0.10 ng/ml (>0.1 ug/L), or peak creatinine phosphokinase -MB >8% of an elevated total creatinine phosphokinase with characteristic rise and fall. Heart failure was defined according the New York Heart Association classification. In addition, the causes of death occurring within 30 days after surgery were grouped into three different categories: (1) cerebro-cardiovascular death (CCVD), (2) non-cerebrocardiovascular death (non-CCVD) and (3) unknown cause of death. Cerebro-cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and included deaths following myocardial infarction (MI), serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebro vascular accident (CVA) or transient ischemic attack (TIA)), surgery-related fatal bleeding complications and others. Non-CCVD was defined as any death with a principal non-cerebro-cardiovascular cause, including infection, malignancy, respiratory insufficiency and others. The cause of death was ascertained by reviewing medical records, the computerized hospital database, autopsy reports, or by contacting the referring physician or general practitioner.

### Statistical analysis

Continuous data are described as mean values and its standard deviation (± SD), and dichotomous data are described as percentage frequencies. The chi-square test was used for categorical variables and the analysis of variance (ANOVA) was used for continuous variables. Univariable logistic regression analysis was used to evaluate the relation between the Lee-index and MACE for each age category. Multivariable logistic analysis was performed to evaluate whether the predictive power

of the Lee-index could be improved by adding age, hypertension and more detailed information on the type of surgery (low risk (CEA), low-intermediate risk (LLR), high-intermediate risk (AAA) and high risk (r-AAA)). The performance of the risk model was determined by the C-statistics and its resulting area under the receiver operating characteristics (ROC) curve (AUC), which indicates how well a model rank orders patients with respect to their outcome (where 0.5 indicates no predictive value and 1.0 indicates perfect performance). Kaplan-Meier survival analysis was used to compare survival of patients, according to the three Lee-index categories. To test for differences between the resulting curves, the log-rank test was used. A p value of <0.05 was considered to be significant. All computations were performed with SPSS software version 12.0.1 (SPSS Inc., Chicago, Illinois, USA), running under Windows 2000 Professional.

## RESULTS

### Patient characteristics

A total of 2 642 procedures were performed (21% CEA, 8% r-AAA, 34% AAA and 38% LLR). The mean age was 66 ± 11 years and 75% of the patients were men. Of these patients, 396 (15%) were ≤ 55, 650 (25%) were 56–65, 1 058 (40%) were 66–75 and 538 (20%) were > 75 years. Men were 0.97 years older than were females (p=0.052). With increase of age, higher incidences of hypertension, COPD, ischemic heart disease and r-AAA and AAA surgery were observed (TABLE 6.1). No patients were reported with a Lee-index score of 0, as all patients with CEA had a positive history of cerebrovascular disease and/or presence of another risk factor used in the Lee risk index. The majority of patients had a score of 1 point (52%), followed by 30% and 18%, respectively 2 and ≥ 3 points (TABLE 6.2).

### Primary end-point

A total of 287 (10.9%) patients had a major adverse cardiac event, for Lee-index 1, 2 and ≥ 3 respectively 6.2%, 13.2% and 20.5%. Increasing rates of MACE were found with increased age, with a slight drop of incidences within patients aged >75 years. Within each age category, the Lee-index was significantly associated with incidences of MACE. A correlation of all-cause mortality and Lee-index was found in all patients (p=0.03). However, no correlation of the Lee-index and all-cause mortality was found within each age category. Cerebro-cardiovascular events (116 (76%)) were the major cause of death which included: MI 19%, heart failure 10%, cardiac arrhythmia 10%, stroke 6%, fatal bleeding 26% and others 5%.

The non-cerebro-cardiovascular (36 (24%)) events included: infection 14%, malignancy 0%, respiratory insufficient 6% and others 4%. No patient had an unknown cause of death. In total, 58 (39%) patients died because of cardiac complications within 30 days after surgery.

In univariate analysis, the Lee-index was associated with an increased risk of MACE as its individual components (TABLE 6.3). The prospective C-statistic for the prediction of MACE was 0.65. The predictive value of the Lee-index was significantly superior in patients aged ≤ 55 years compared to patients aged >75 years (area under the curve 0.76 vs. 0.62, $p < 0.01$). When more detailed information, including type of surgery (low, low-intermediate, high-intermediate and high risk of surgery), age (≤ 55, age 56–65, age 66–75 and >75 years) and history of hypertension, was added to the model, the overall C-statistics improved to 0.71. Importantly, after the introduction of these additional risk factors no difference in the C-statistics was observed between each age category ≤ 55, age 56–65, age 66–75 and >75 years), respectively 0.71, 0.71, 0.69 and 0.69. The prediction of MACE in elderly patients improved from 0.62 to 0.69 ($p = 0.02$).

**TABLE 6.1** Baseline characteristics of all patients undergoing major vascular surgery, grouped into four age categories.

| | All 2 642 (100%) | Age ≤ 55 396 (15%) | Age 56 - 65 650 (25%) | Age 66 - 75 1 058 (40%) | Age > 75 538 (20%) | P-value |
|---|---|---|---|---|---|---|
| **Demographics** | | | | | | |
| Mean age (± SD) | 66 (± 11) | 47 (± 8) | 61 (± 3) | 70 (± 3) | 79 (± 4) | <0.001 |
| Male (%) | 75 | 68 | 79 | 77 | 74 | <0.001 |
| **Revised Cardiac Risk Index factors (%)** | | | | | | |
| Ischemic heart disease | 30 | 25 | 31 | 29 | 32 | 0.05 |
| Heart failure | 5 | 6 | 5 | 5 | 7 | 0.5 |
| High-risk surgery | 79 | 79 | 77 | 77 | 87 | <0.001 |
| Abdominal aortic surgery | 34 | 30 | 32 | 36 | 36 | 0.06 |
| Acute aortic surgery | 8 | 3 | 5 | 9 | 13 | <0.001 |
| Lower limb reconstruction | 37 | 47 | 40 | 32 | 39 | <0.001 |
| Renal insufficiency | 6 | 7 | 5 | 6 | 5 | 0.4 |
| Insulin dependent diabetes mellitus | 15 | 17 | 12 | 14 | 17 | 0.08 |
| Cerebrovascular disease | 31 | 27 | 34 | 34 | 25 | <0.001 |
| **Other risk factors (%)** | | | | | | |
| COPD* | 18 | 11 | 15 | 21 | 23 | <0.001 |
| Current smoker | 24 | 25 | 27 | 23 | 22 | 0.2 |
| Hypercholesterolemia | 18 | 25 | 19 | 16 | 13 | <0.001 |
| Body mass index (± SD) | 25.1 (± 5) | 25.4 (± 5) | 25.3 (± 6) | 24.9 (± 4) | 24.7 (± 3) | 0.02 |
| Hypertension | 46 | 39 | 44 | 47 | 48 | 0.02 |
| **Medication use (%)** | | | | | | |
| Statins | 26 | 31 | 31 | 26 | 16 | <0.001 |
| Diuretics | 18 | 13 | 15 | 19 | 23 | <0.001 |
| ACE-inhibitors∓ | 31 | 28 | 34 | 31 | 33 | 0.2 |
| Calcium antagonists | 34 | 33 | 33 | 35 | 31 | 0.4 |
| Nitrates | 19 | 15 | 19 | 19 | 21 | 0.2 |
| Beta-blockers | 33 | 31 | 35 | 35 | 31 | 0.3 |
| Aspirin | 40 | 37 | 40 | 42 | 40 | 0.3 |
| Anti-coagulation | 20 | 18 | 22 | 20 | 18 | 0.4 |

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



Important differences in incidence of MACE were observed in relation to type of surgery. Overall incidences of MACE according to low-risk (CEA), low-intermediate (LLR), high-intermediate (AAA) and high-risk (r-AAA) surgery were 2.4%, 11.6%, 12.3% and 24.0%, respectively ($p < 0.001$) (FIGURE 6.1). Within each type of surgery, the Lee-index was significantly associated with risk of MACE.

When we perform our analysis applied only to patients having a single procedure (n = 2 298, 66 ± 11 years, 75% were men), our results remained the same. For example, incidences of hypertension were 38%, 43%, 46% and 47% for age category ≤ 55, 56–65, 66–75 and > 75 years respectively ($p = 0.03$). The prospective C-statistic for the prediction of MACE was also 0.65 (0.76, 0.66, 0.64 and 0.62 for each age category (≤ 55, age 56–65, age 66–75 and > 75 years)). After the introduction of our additional risk factors no difference in the C-statistics was observed between each age category, respectively 0.74, 0.73, 0.71 and 0.71. The multivariate analysis showed the same results as presented in TABLE 6.3. Because of these findings, we concluded that the influence of patients with multiple procedures on the overall results does not have an important impact on our results.

**Table 6.2** Incidences of major adverse cardiac events and all-cause mortality, according to the Revised Cardiac Risk score.

| | All | Lee-index 1 | Lee-index 2 | Lee-index ≥3 | P-value | AUC | AUC* |
|---|---|---|---|---|---|---|---|
| All | | | | | | | |
| Incidences – no. (%) | 2 642 (100) | 1 371 (52) | 802 (30) | 469 (18) | | | |
| All-cause death – no. (%) | 152 (5.8) | 63 (4.6) | 55 (6.9) | 34 (7.2) | 0.03 | | |
| MACE – no. (%) | 287 (10.9) | 85 (6.2) | 106 (13.2) | 96 (20.5) | < 0.001 | 0.65 | 0.71 |
| Age ≤ 55 | | | | | | | |
| Incidences – no. (%) | 396 (100) | 234 (59) | 94 (24) | 68 (17) | | | |
| All-cause death – no. (%) | 10 (2.5) | 5 (2.1) | 3 (3.2) | 2 (2.9) | 0.84 | | |
| MACE – no. (%) | 17 (4.3) | 3 (1.3) | 5 (5.3) | 9 (13.2) | < 0.001 | 0.76 | 0.71 |
| Age 56 – 65 | | | | | | | |
| Incidences – no. (%) | 650 (100) | 346 (53) | 200 (31) | 104 (16) | | | |
| All-cause death – no. (%) | 22 (3.4) | 10 (2.9) | 7 (3.5) | 5 (4.8) | 0.63 | | |
| MACE – no. (%) | 60 (9.2) | 21 (6.1) | 17 (8.5) | 22 (21.2) | < 0.001 | 0.64 | 0.71 |
| Age 66 – 75 | | | | | | | |
| Incidences – no. (%) | 1 058 (100) | 543 (51) | 335 (32) | 180 (17) | | | |
| All-cause death – no. (%) | 68 (6.4) | 30 (5.5) | 23 (6.9) | 15 (8.3) | 0.38 | | |
| MACE – no. (%) | 144 (13.6) | 43 (7.9) | 59 (17.3) | 43 (23.9) | <0.001 | 0.64 | 0.69 |
| Age > 75 | | | | | | | |
| Incidences – no. (%) | 538 (100) | 248 (46) | 173 (32) | 117 (22) | | | |
| All-cause death – no. (%) | 52 (9.7) | 18 (7.3) | 22 (12.7) | 12 (10.3) | 0.17 | | |
| MACE – no. (%) | 66 (12.3) | 18 (7.3) | 26 (15.0) | 22 (18.8) | 0.003 | 0.62 | 0.69 |

AUC = Area Under the Curve; MACE = major adverse cardiac event; * Adjusted for type of surgery (low, low-intermediate, high-intermediate and high risk of surgery), age (≤ 55, 56 – 65, 66 – 75 and > 75 years) and history of hypertension

**Table 6.3** Unadjusted and adjusted predictors of estimate risk of major adverse cardiac events.

| | Unadjusted HR, (95% CI) | Adjusted HR*, (95% CI) |
|---|---|---|
| Lee-index 1 (reference) | 1.0 | 1.0 |
| Lee-index 2 | 2.30 (1.71 – 3.11) | 1.94 (1.37 – 2.73) |
| Lee-index ≥ 3 | 3.89 (2.85 – 5.33) | 2.92 (1.92 – 4.44) |
| High-risk surgery | 6.17 (3.51 – 10.85) | 6.97 (3.68 – 13.22) |
| Diabetes mellitus | 1.84 (1.36 – 2.48) | 1.51 (1.11 – 2.06) |
| Cerebrovascular disease | 1.76 (1.26 – 2.45) | 1.53 (1.09 – 2.14) |
| Ischemic heart disease | 2.31 (1.80 – 2.97) | 1.70 (1.30 – 2.22) |
| Heart failure | 2.43 (1.60 – 3.68) | 1.31 (0.84 – 2.06) |
| Renal insufficiency | 2.24 (1.64 – 3.05) | 1.71 (1.24 – 2.36) |
| Age ≤ 55 years (reference) | 1.0 | 1.0 |
| Age 56 – 65 years | 2.27 (1.30 – 3.94) | 2.44 (1.34 – 4.42) |
| Age 66 – 75 years | 3.51 (2.10 – 5.89) | 3.49 (1.99 – 6.10) |
| Age > 75 years | 3.11 (1.80 – 5.40) | 2.56 (1.41 – 4.65) |
| Low-risk surgery (reference) | 1.0 | 1.0 |
| Low-intermediate risk | 5.36 (2.99 – 9.60) | 4.04 (2.17 – 7.54) |
| High-intermediate risk | 5.76 (3.21 – 10.34) | 4.14 (2.23 – 7.68) |
| High-risk | 12.95 (6.84 – 24.52) | 10.45 (5.22 – 20.95) |
| History of hypertension | 2.15 (1.67 – 2.77) | 1.70 (1.25 – 2.31) |

HR= hazard ration; CI= confidence interval; *Adjusted for the four age categories (≤ 55, 56-65, 66-75 and > 75 years), risk of surgery (low, low-intermediate, high-intermediate and high risk), hypertension, year of operation, chronic obstructive pulmonary dysfunction, hypercholesterolemia, smoking status, body mass index, gender and cardiovascular medication

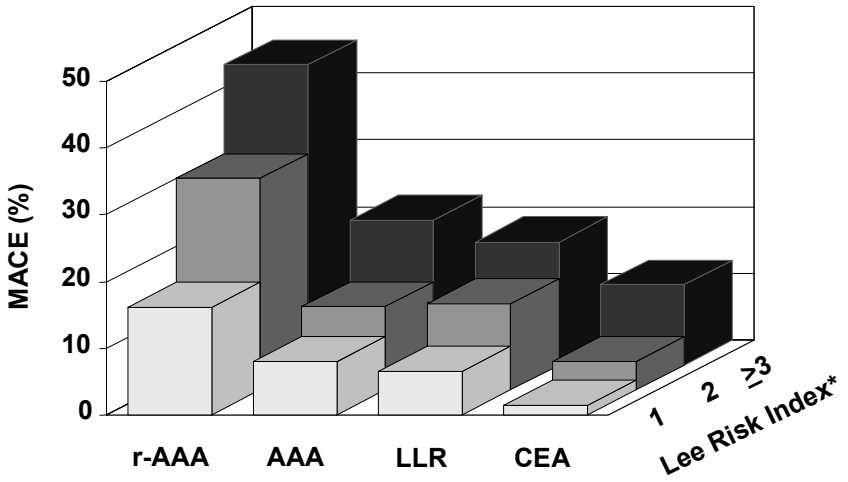


**FIGURE 6.1** Incidences of major cardiac events, according to type of operation and the Revised Cardiac Risk score. MACE = major adverse cardiac events; r-AAA = acute infrarenal AAA surgery; AAA = elective infrarenal abdominal aortic surgery; LLR = lower limb arterial reconstruction procedures; CEA = carotid endarterectomy, *Lee-index that assigns one point to each of the following characteristics: ischemic heart disease, history of heart failure, high-risk surgery, history of cerebrovascular disease, renal insufficiency and diabetes mellitus.



### Secondary end-point

Although the Lee-index was originally developed to predict perioperative cardiac complications, a clear association was found between the Lee-index and all-cause mortality during follow-up (FIGURE 6.2). A total of 1 454 (55%) patients died during a mean period of 6.4 ± 3.9 years. Annual mortality rates of patients with a Lee-index score of 1, 2 and ≥ 3 were 5.2%/year, 6.4%/year and 7.3%/year respectively ($p < 0.001$). In multivariate analysis, adjusting for the four age categories, risk of surgery (low, low-intermediate, high-intermediate and high risk), year of operation, chronic obstructive pulmonary dysfunction, hypercholesterolemia, smoking status, body mass index, gender, hypertension and cardiovascular medication, the risk of all-cause mortality was 1.45 (95% CI: 1.28–1.65) for Lee-index 2 and 1.90 (95% CI: 1.63–2.22) for Lee-index ≥ 3, compared with Lee-index 1. When analysis was performed for patients with a single procedure, the risk of all-cause mortality was 2.01 (95% CI: 1.37–2.94) for Lee-index 2 and 3.11 (95% CI: 1.94–4.97) for Lee-index ≥ 3, compared to Lee-index 1.

## DISCUSSION

The main finding of our study is that the prognostic value of the Revised Cardiac Risk Index (Lee-index) is reduced in the very elderly patients (>75 years) undergoing vascular surgery. The Lee-index was introduced to assess perioperative cardiac risk among a large number of patients. Risk factors included are high-risk surgery, ischemic heart disease, history of heart failure, cerebrovascular disease, renal insufficiency and insulin dependent diabetes mellitus. Importantly, age was not included in the index. In addition, only a low number of vascular surgery patients were included. Our study showed that if additional information was added to the Lee-index (e.g. age, a more detailed classification of type of vascular surgery and history of hypertension), the accuracy of the Lee-index to predict postoperative MACE improves significantly in vascular surgery patients, among the entire strata of age.

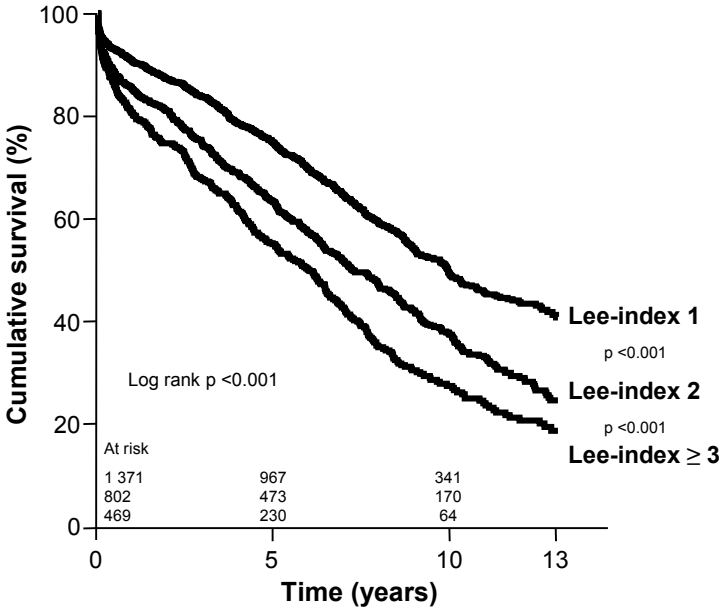


**FIGURE 6.2** All cause long-term mortality in 2,642 patients who underwent major vascular surgery, according to the Revised Cardiac Risk score.
Lee-index that assigns one point to each of the following characteristics: ischemic heart disease, history of heart failure, high-risk surgery, history of cerebrovascular disease, renal insufficiency and diabetes mellitus.

The Lee-index is a modification of the original Goldman risk index[8], developed in the 1990s and validated in numerous clinical studies and is currently considered the best available risk model. Although the Lee-index was developed using clinical data of 4 315 consecutive patients undergoing non-cardiac surgery, the model has shortcomings for vascular surgery patients. Of all patients, only 21% underwent vascular surgery and all procedures were considered as high-risk. However, postoperative morbidity and mortality varied considerably among different vascular surgical procedures[9-11]. In order to improve the predictive value of the Lee-index, we specified the type of vascular surgery into four categories; low, low-intermediate, high-intermediate and high-risk.

However, the main limitation of the Lee-index is that age is not included. The number of patients referred for vascular surgery is increasing with a substantial number of septo- and octogenarians. The average age of AAA surgery increased from 69 to 72 years during 1980–2000[12]. In addition, this aging population presents with complex co-morbidity associated with increased postoperative mortality rates.

Several risk indices have been developed to stratify vascular surgery patients based on age and clinical cardiac risk factors. In 1994, Samy et al. developed a scoring system in 500 patients scheduled for abdominal aortic aneurysm surgery for the prediction of postoperative mortality; the Glasgow aneurysm score[13]. This score included myocardial disease, cerebrovascular disease, renal dysfunction and age as a continuous variable as risk factors. Age was an independent risk factor for postoperative mortality ($p = 0.02$). Steyerberg et al. constructed the Leiden Risk Model in 246 patients undergoing abdominal aortic aneurysm surgery and included age per decade (<60, 60–70 and >70 years) as a

risk factor[14]. Age had only a moderate predictive value for all-cause perioperative mortality (OR 1.9; 95% CI: 0.9–4.2). In addition, L'Italien et al. developed a risk model among 1 081 patients undergoing different vascular surgical procedures, with an overall predictive value for cardiac death and non-fatal myocardial infarction of 0.74 (C-statistic)[15]. They included advanced age (>70 years) as a dichotomous risk factor. The limitations of these studies are the low number of patients included, none of the studies had MACE as their end-point and the focus is predominantly on aortic surgery.

Preoperative cardiovascular risk stratification has been an area of intense interest for identifying patients at higher cardiac risk. Patients classified as high risk can be refrained for surgery or should be considered to undergo less invasive surgery (like endovascular procedures). Additional cardio protective therapy in elderly like beta-blockers and statins[16-18] has improved in recent years. In addition to the immediate postoperative outcome, prognostic indices should be considered to assess long-term prognosis, as patients should live long enough to enjoy the benefits of surgery. As shown in the follow-up of patients undergoing major vascular surgery with different cardiac risk index scores, annual mortality rates increased by each risk factor added, ranging from 5.2%/year in patients with 1 risk factor, to 6.4%/year and 7.3%/year for 2 and ≥ 3 risk factors respectively. This indicates that the prognosis is related to underlying cardiovascular disease. Postoperative surveillance of patients among the high-risk scores with aggressive anti-ischemic therapy is indicated to improve long-term outcome.

A major limitation of our study is the retrospective analysis of prospectively collected data. Changes in the perioperative management have evolved markedly over time and were not taken into account in our analysis. These include multiple factors ranging from preoperative management, such as drug therapy, anesthesiological and surgical techniques to intensive post-surgical care management. We tried to adjust for this confounding by adding the year of operation to our multivariate analysis.



In conclusion, this revision of the Lee-index, now including age, risk of surgery and hypertension, clearly stratifies vascular surgery patients into low, intermediate and high risk. In addition, this model provides long-term prognostic value.

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# Chapter 7

## Preoperative cardiac testing before major vascular surgery

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## INTRODUCTION

Patients undergoing non-cardiac vascular surgery are at significant risk of perioperative cardiac complications[1,2]. Though recent developments in anesthesiological and surgical techniques, e.g. locoregional anesthesia and endovascular treatment modalities, have improved postoperative cardiac outcome considerably, perioperative cardiac complications remain a significant problem.

Myocardial infarction (MI) accounts for 10% to 40% of perioperative fatalities, and is considered to be the major determinant of postoperative mortality in non-cardiac vascular surgery[3-5]. This increased risk of perioperative cardiac complications is a function of both the patient population at risk and the surgical procedure. Importantly, non-cardiac vascular surgery patients frequently have underlying symptomatic or asymptomatic coronary artery disease (CAD). A landmark study by Hertzer et al showed that 61% of 1000 patients undergoing non-cardiac vascular surgery had at least one significant coronary artery stenosis (≥50%)[6].

Patients for vascular surgery should have an extensive preoperative workup for perioperative cardiovascular risk. The primary goal of treatment is to reduce cardiovascular complications around the vascular surgical procedure. Evidently, the long-term cardiovascular event risk will also decrease[7].

This review will describe the current status of preoperative workup for patients undergoing non-cardiac vascular surgery, including noninvasive cardiac testing for myocardial ischemia, a major determinant of perioperative outcome.

## PERIOPERATIVE MYOCARDIAL INFARCTION

Myocardial infarction is known to be the major cause of morbidity and mortality in non-cardiac vascular surgery patients. The highest incidence of perioperative MI (PMI) is within the first 3 days after surgery (± 5%)[2]. The prevalence of acute coronary syndrome with symptomatic or asymptomatic perioperative myocardial ischemia assessed by serum troponin I or T in major vascular surgery patients is even 15% to 25%[8-9].

The pathophysiology of PMI is not entirely clear compared to MIs occurring in the nonoperative setting. Coronary plaque rupture leading to occlusive coronary thrombosis is suggested as an important causal mechanism, like in MIs occurring in the nonoperative setting. Surgery itself is a significant stress factor leading to an increased incidence of plaque rupture. Factors provoking physiologic stress during surgery include anesthetic agents, response to surgically induced hypotension, anemia, and postoperative pain. Two retrospective studies investigated the coronary pathology of fatal PMI. Dawood et al.[10] performed histopathologic analyses of coronary arteries in 42 patients with a fatal PMI within the first 30 days after surgery. Evidence of plaque rupture was found in only 55% of the patients. In more than half of the patients, the investigators were unsuccessful at predicting the site of infarction based on the severity of the underlying coronary artery stenosis. These findings were confirmed by Cohen and Aretz, who analyzed the coronary pathology of 26 patients with PMI[11]. In only 12 of these patients (46%) plaque rupture was identified as the causative mechanism of PMI.

Perioperative MI may also be caused by a sustained myocardial oxygen supply/demand imbalance due to prolonged hemodynamic stress. Surgery-related factors such as increased heart rate, elevated blood pressure, pain, and the use of sympathomimetic drugs may further increase myocardial oxygen

demand. In addition, surgery may cause a decrease in oxygen supply as the result of hypotension, vasospasm, anemia, and hypoxia.

Plaque rupture and sustained myocardial oxygen supply/demand imbalance probably contribute equally to the occurrence of PMI. As already noted, the location of a plaque rupture is impossible to predict with commonly used techniques. However, the extent of significant coronary atherosclerosis can be defined with cardiac stress testing. These two pathophysiological mechanisms imply that multiple strategies are required to reduce perioperative cardiac risk. In this respect, beta-blockers were suggested to prevent MI by reducing the mechanical and hemodynamic stress on vulnerable plaques, and by preventing prolonged, stress-induced ischemia[12].

## CARDIAC RISK STRATIFICATION

Adequate preoperative cardiac risk assessment is essential for identifying high-risk patients for perioperative cardiac events. Several risk indices were developed to stratify vascular surgical patients, based on clinical cardiac risk factors. The cardiac risk index of Goldman et al.[13] in 1977 was the first multifactorial model specifically for perioperative cardiac complications to be widely used. This risk index was developed in a non-cardiac surgical population. The authors identified nine independent risk factors correlated with postoperative serious or fatal cardiac complications: (1) preoperative third heart sound or jugular venous distention; (2) MI in the preceding 6 months; (3) >5 premature ventricular contractions per minute documented at any time before operation; (4) rhythms other than sinus rhythm or the presence of premature atrial contractions on preoperative electrocardiogram (ECG); (5) age >70 years; (6) an intraperitoneal, intrathoracic, or aortic operation; (7) emergency operation; (8) important valvular aortic stenosis; and (9) poor general medical condition. This index was modified by Detsky et al. in 1986[14], who added the presence of angina and a remote history of MI to the original model of Goldman et al.[13] They used a Bayesian approach involving pretest probabilities, and presented the modified cardiac risk index in a simple normogram.



The Glasgow aneurysm score, described in 1994, was one of the first cardiac risk scores only intended for vascular surgical procedures[15]. In a retrospective study of 500 randomly chosen patients scheduled for open abdominal aortic aneurysm repair, potential preoperative risk factors were related to postoperative in-hospital mortality. One year later, the Leiden Risk Model for perioperative mortality in patients with an abdominal aortic aneurysm was developed by Steyerberg et al.[16] This clinical prediction rule was based on several risk factors obtained from the literature, and validated in a cohort of 246 patients undergoing open abdominal aortic aneurysm repair.

In 1996, L'Italien et al. developed and validated a Bayesian model for preoperative cardiac risk assessment in a total of 1081 consecutive patients undergoing elective major vascular surgery[17]. This study had a combined endpoint of nonfatal MI or cardiac death. Using 567 patients as a derivation cohort, the following risk factors were identified as predictors of adverse postoperative outcome: myocardial infarction, congestive heart failure, angina pectoris, prior coronary revascularization, diabetes mellitus, and age >70 years. Importantly, the validation cohort (514 patients) exhibited a prognostic accuracy of 74%. Patients classified as low-risk, intermediate-risk, and high-risk had cardiac event rates of 3%, 8%, and 18%, respectively.

In 1999, Lee et al.[18] developed the largest and currently most widely used model of risk assessment, the Revised Cardiac Risk Index. This index identifies six predictors of major cardiac complications: (1)

high-risk type of surgery, (2) history of ischemic heart disease, (3) history of congestive heart failure, (4) history of cerebrovascular disease, (5) preoperative treatment with insulin, and (6) preoperative serum creatinine >2.0 mg/dL. Based on the presence of none, 1, 2, or ≥3 predictors, the rate of major cardiac complications in the validation cohort (n = 1422) was estimated to be 0.4%, 0.9%, 7%, and 11%, respectively.

The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE) I Trial identified comparable independent clinical risk factors associated with major vascular surgery: a history of myocardial infarction, angina, congestive heart failure, diabetes, renal dysfunction, cerebrovascular events, and age >70 years[19]. Recently, Kertai et al. developed a Bayesian model for the prediction of all-cause perioperative mortality in 1537 patients undergoing all types of open vascular surgery[20]. Risk factors associated with postoperative all-cause death included ischemic heart disease, congestive heart failure, cerebrovascular events, hypertension, renal dysfunction, chronic pulmonary disease, and type of vascular surgery, i.e. ruptured aneurysm abdominal aorta (AAA), elective AAA, lower extremity, and carotid vascular surgery. The final logistic regression model with nine independent predictors (including beta-blocker and statin use) of perioperative mortality was used to create a variable-weight index, the customized probability index, where scores were assigned based on parameter estimates of individual predictors. The sum of scores of surgical risk (0-46 points), medical history (0-67 points), and cardioprotective medication (statins -10 points and beta-blockers -15 points) was calculated for an overall cardiac risk.

## NONINVASIVE TESTING

Once the assessment of risk factors indicates an increased cardiac perioperative risk, or if there is a suspicion of CAD upon examination, further cardiac testing is warranted. According to the current guidelines of the American College of Cardiology/American Heart Association[21], preoperative cardiac exercise or pharmacologic stress testing is recommended for (1) patients with an intermediate pretest probability of CAD, (2) patients undergoing initial evaluation for suspected or proven CAD, (3) subjects with a significant change in clinical status, (4) demonstration of proof of myocardial ischemia before coronary revascularization, (5) evaluation of adequacy of medical treatment, and (6) prognostic assessment after an acute coronary syndrome.

One of the main issues in preoperative cardiac risk assessment is to identify those patients who should undergo additional stress testing before surgery. The randomized, multicenter DECREASE II Study assessed the value of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart-rate control[22]. In total, 1476 vascular surgical patients were divided into three risk groups based on the risk score of Boersma et al.[19] All 770 intermediate-risk patients were randomly assigned to preoperative cardiac stress-testing or no testing. Importantly, all patients in the DECREASE II Study received beta-blocker therapy, irrespective of stress-test results, aiming at tight heart-rate control, i.e. a heart rate of 60 to 65 beats per minute. This study demonstrated no differences in cardiac death and MI at 30 days between patients assigned to no testing versus cardiac stress testing (1.8% versus 2.3%; odds ratio [OR], 0.78; 95% confidence interval [CI], 0.28 to 2.1). Also, 2-year outcomes were comparable in intermediate-risk patients with and without testing, i.e. 4.3% versus 3.1%, respectively. These results indicate that intermediate-risk patients undergoing major vascular surgery are at a relatively low perioperative risk and do not benefit from preoperative cardiac testing when receiving beta-blocker therapy with tight heart-rate control.

For those patients who require cardiac testing, several noninvasive and physiological (and nonphysiological) stress tests are available for the evaluation of perioperative risk. Nonphysiological stress tests are especially recommended to detect preoperative myocardial ischemia in asymptomatic vascular surgery patients.

### Rest Electrocardiography

Different studies associated abnormal ECG findings with perioperative cardiac complications[13,14,23]. In a large prospective study by Lee et al.[18] involving 4315 patients undergoing major non-cardiac surgery, a history of ischemic heart disease was one of the six independent predictors of major cardiac complications. Pathological Q-waves, as an electrocardiographic sign of MI in the past, were found in 17% of patients, with a 2.4-fold increased risk of perioperative events. A recent retrospective study confirmed the prognostic value of routine preoperative electrocardiography in 22,457 non-cardiac operations[24]. Patients with abnormal ECG findings had a higher incidence of 30-day cardiovascular death compared with patients with a normal ECG (1.8% versus 0.3%; adjusted OR, 3.4; 95% CI, 2.4 to 4.5). In addition, it was demonstrated that a preoperative ECG is also predictive for long-term outcome, independent of clinical findings and perioperative ischemia, in CAD patients undergoing major non-cardiac surgery[25].

### ST-segment Holter

The use of ambulant 24-hour ST-segment registration for evaluation of perioperative cardiac risk was first described by Raby et al.[26] They reported a sensitivity of 75% and a specificity of 83% for the prediction of a combined endpoint of cardiac death and nonfatal MI. A large meta-analysis showed lower values, comprising eight studies with a total of 893 patients, with a weighted sensitivity of 52% (95% CI, 21% to 84%) and a specificity of 70% (95% CI, 57% to 83%)[27]. The advantages of ST-segment Holter include its low cost and wide availability.



### Exercise Electrocardiogram

The most commonly used physiologic stress test for detecting myocardial ischemia uses a treadmill or cycle ergometer. Among its advantages, this test provides an estimate of functional capacity, and hemodynamic response, and detects myocardial ischemia through ST-segment changes. The accuracy of an exercise ECG varies widely among studies. A meta-analysis by Kertai et al.[27] for the detection of myocardial ischemia with treadmill testing in vascular surgery patients showed a rather low sensitivity (74%; 95% CI, 60% to 88%) and specificity (69%; 95% CI, 60% to 78%), comparable to daily clinical practice. However, important limitations in patients with peripheral vascular disease involve their frequently limited exercise capacity. Furthermore, preexisting ST-segment deviations, especially in the precordial leads V5 and V6 at the rest ECG, make a reliable ST-segment analysis more difficult[28].

### Stress Echocardiography

Because most patients with peripheral vascular disease are unable to exercise maximally, stress echocardiography with pharmacologic stressors (such as dobutamine) is a good alternative. Although vasodilators (e.g., dipyridamole or adenosine) may have advantages for the assessment of myocardial perfusion, dobutamine is the preferred pharmacological stressor when the test is based on an assessment of regional wall-motion abnormalities[29]. Dobutamine is a synthetic catecholamine with predominantly β1-receptor-stimulating properties, resulting in a strong positive inotropic effect and modest chronotropic effect on the heart. During the stress test, dobutamine is intravenously administered. A graded dobutamine infusion starting at 5 μg/kg/min, and increasing at 3-minute intervals to 10, 20, 30, and 40 μg/kg/min, is the standard for dobutamine stress echocardiography

(DSE). During dobutamine infusion, contractility and heart rate increase, leading to increased myocardial oxygen demand. Myocardial ischemia leading to systolic contractile dysfunction, detectable by echocardiography, occurs in regions supplied by hemodynamically significant stenotic coronary arteries.

Tissue harmonic imaging is advised for stress echocardiography. This special imaging setting reduces near-field artifacts, improves resolution, enhances myocardial signals, and is superior to fundamental imaging for endocardial border visualization. The improvement in endocardial visualization is further enhanced by the use of contrast agents for left-ventricular (LV) opacification. Contrast agents increase the number of interpretable LV wall segments. These recent developments exhibit decreased interobserver variability, and have improved the sensitivity of stress echocardiography[30].

Many reports demonstrated that DSE predicts perioperative events in patients undergoing vascular surgery[31-34]. The negative predictive value of dobutamine stress tests is high, although the positive predictive value is much lower.

Kertai et al. reported a weighted sensitivity of 85% (95% CI, 74% to 97%) and a specificity of 70% (95% CI, 62% to 69%) for DSE in 850 patients from eight studies.[27] A recent meta-analysis by Beattie et al analyzed the predictive value of pharmacological stress testing compared with myocardial perfusion scintigraphy[35]. This report included 25 studies (3373 patients) of mainly dobutamine as well as dipyridamole stress echocardiography. The likelihood ratio of a perioperative event with a positive stress echocardiography was 4.09 (95% CI, 3.21 to 6.56).

### Myocardial Perfusion Scintigraphy

Myocardial perfusion scintigraphy (MPS) is a widely used technique in the preoperative risk assessment of patients undergoing vascular surgery. The technique involves intravenous administration of a small quantity of a radioactive tracer. The detection of CAD is based on a difference in blood-flow distribution through the LV myocardium. These differences in perfusion can be explained by insufficient coronary blood flow based on coronary stenosis. Nowadays, technetium-99m-labeled radiopharmaceutical is the most widely used tracer. Myocardial perfusion scintigraphy is used in combination with exercise or pharmacologic stress testing to diagnose the presence of CAD. If there is a decrease or loss in regional perfusion after maximal vasodilatation with, for example, adenosine, as seen in hemodynamically significant CAD or in transmural MI, a reduced radiopharmaceutical signal is observed. Stress and rest MPS are compared for reversible abnormalities. A positive MPS is associated with an increased risk of perioperative and postoperative cardiac complications.

This method of noninvasive testing has been extensively studied, and was included in several meta-analyses[27,35-37]. Boucher et al. were among the first to report on using MPS for preoperative cardiac risk assessment[36]. They performed preoperative dipyridamole-thallium imaging in 48 patients scheduled for peripheral vascular surgery. Half of the patients with thallium redistribution had cardiac events, whereas no events occurred in the 32 patients with a normal scan or with nonreversible defects only ($p < 0.001$).

Studies indicate that MPS is highly sensitive for the prediction of cardiac complications, but its specificity was reported as less satisfactory. A meta-analysis by Etchells et al.[37] investigated the prognostic value of semiquantitative dipyridamole MPS for perioperative cardiac risk in patients undergoing non-cardiac vascular surgery. They included nine studies, involving a total of 1179 vascular surgery patients, with a 7% cardiac complication rate. One of the most important findings in this study was

that reversible ischemia in <20% of the myocardial segments did not change the likelihood of perioperative complications. Patients with more extensive reversible defects were at increased risk: 20 to 29% reversibility (likelihood ratio [LR] 1.6; 95% CI 1.0 to 2.6), 30 to 39% reversibility (LR 2.9; 95% CI 1.6 to 5.1), 20 to 9% reversibility (LR 1.6; 95% CI 1.0 to 2.6), 40% to 49% reversibility (LR 2.9; 95% CI 1.4 to 6.2) and ≥50% or more reversibility (LR 11; 95% CI 5.8 to 20). These reversible defects in >20% of myocardial segments were only seen in 23% of all patients.

Another meta-analysis which assessed the prognostic value of six diagnostic tests reported a sensitivity of 83% (95% CI, 77% to 89%) and a much lower specificity of 47% (95% CI, 41% to 57%) for MPS[27]. More recently, Beattie et al.[35] performed a meta-analytic comparison, including in total 39 thallium-imaging studies involving vascular surgery patients were included, and resulted in a summary likelihood ratio of 1.83 (95% CI, 1.57 to 2.13).

### Which Test to Choose?

There is no large direct comparison of these techniques in perioperative risk assessment in the same patient population. However, several meta-analyses compared different techniques with respect to sensitivity and specificity. An early comparison of dipyridamole perfusion imaging and DSE was performed by Shaw et al.[34] The recent meta-analysis by Kertai et al. compared six different diagnostic tests for diagnostic accuracy to predict perioperative cardiac risk in patients undergoing major vascular surgery[27]. Eventually, 58 studies met the inclusion criteria, with a total of 8119 patients. A positive trend in favor of DSE for better diagnosis compared with other tests was indicated. However, this was only statistically significant compared with MPS. Beattie et al. conducted a meta-analysis of 68 studies comparing thallium MPS with stress echocardiography in 10,049 non-cardiac surgery patients[35]. The authors concluded that stress echocardiography was preferable for predicting postoperative events because of its better negative predicative characteristics.



Nevertheless, because the tests have comparable accuracy, there is no definite answer to the question of which test to choose. The choice of test should be based on the center's experience and short-term availability. Accurate assessment of the ischemic burden is important in predicting perioperative and postoperative risk.

## PERIOPERATIVE MANAGEMENT

In general, two strategies have been used in an attempt to reduce the incidence of PMIs and other cardiac complications: preoperative coronary revascularization, and prophylactic pharmacological treatment. In recent years, more attention has been focused on the role of pharmacological treatment, whereas controversy continues over the appropriate management of patients diagnosed preoperatively with significant coronary artery disease. With respect to prophylactic coronary revascularization, American College of Cardiology/American Heart Association guidelines recommend revascularization only for subgroups of high-risk patients with unstable cardiac symptoms or with likely long-term benefits of coronary artery revascularization[21]. However, these current guideline recommendations are based on studies not designed to answer the research question of prophylactic revascularization[38,39]. Recently, the randomized Coronary Artery Revascularization Prophylaxis (CARP) Trial demonstrated that there is no reduction in the number of perioperative or postoperative MIs, deaths, lengths of hospital stay, or improved long-term outcomes in patients who undergo preoperative coronary revascularization compared with patients who receive optimized medical therapy[40]. Yet it must be noted that the majority of patients in the CARP Trial had only one-vessel or two-vessel

disease, with preserved LV function. Optimal preoperative medical treatment, especially with tight heart rate control, is essential for decreasing perioperative risk. The aim of the recent randomized pilot study DECREASE V was to assess the feasibility of prophylactic coronary revascularization in patients with preoperative, extensive, stress-induced ischemia[41]. Patients with ≥3 risk factors, and who had extensive stress-induced ischemia using DSE, were randomly assigned to prophylactic revascularization or pharmaceutical treatment. Revascularization did not improve 30-day or 1-year outcomes. The incidence of the composite endpoint of all-cause 30-day mortality and MI for patients with preoperative revascularization or medical treatment was 43% versus 33%, respectively (OR, 1.4; 95% CI, 0.7 to 2.8) and at 1 year, 49% versus 44% (OR, 1.2; 95% CI, 0.7 to 2.3).

These findings of both CARP and DECREASE V support the current guidelines of the American College of Cardiology and American Heart Association for perioperative management in high-risk patients, to reserve revascularization only for cardiac unstable patients. In high-risk patients scheduled for major non-cardiac vascular surgery, prophylactic revascularization might be switched to postoperative revascularization, preventing the delay of surgery.

It must be noted that preoperative revascularization can even be harmful for the patient because of periprocedural complications during revascularization and postponement of the non-cardiac procedure. Importantly, the cumulative risk of prophylactic coronary revascularization and non-cardiac surgery needs to be weighed against the risk of non-cardiac surgery alone and the immediate benefits of prophylactic coronary revascularization.

Besides coronary revascularization, an extensive preoperative cardiac evaluation with noninvasive cardiac testing might improve outcomes by inducing optimal medical management in the perioperative periods. Perioperative beta-blockers and statins have, in this respect, shown a significant benefit in decreasing perioperative cardiac mortality and morbidity[42-46]. Because of the increasing evidence of the beneficial effects of beta-blockers in the perioperative period, the guidelines on perioperative beta-blocker therapy were recently updated[47].

## CONCLUSIONS

Preoperative risk assessment with a noninvasive stress test (MPS or DSE) is necessary only in high-risk patients without unnecessary delay for vascular surgery. High-risk patients can easily be selected through the risk score index. Prophylactic revascularization should only be performed in those with unstable coronary artery disease. The optimal perioperative medical treatment, especially tight heart-rate control, is essential for decreasing perioperative and postoperative cardiac risk.

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# Chapter 8

## Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control?

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## ABSTRACT

**Background:** Treatment guidelines of the American College of Cardiology/American Heart Association recommend cardiac testing in these patients to identify subjects at increased risk. This policy delays surgery, even though test results might be redundant and beta-blockers with tight heart rate (HR) control provide sufficient myocardial protection. Furthermore, the benefit of revascularization in high-risk patients is ill-defined. The purpose of this study was to assess the value of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight HR control scheduled for major vascular surgery.

**Methods:** All 1,476 screened patients were stratified into low-risk (0 risk factors), intermediate-risk (1 to 2 risk factors), and high-risk (≥ 3 risk factors). All patients received beta-blockers. The 770 intermediate-risk patients were randomly assigned to cardiac stress-testing (n = 386) or no testing. Test results influenced management. In patients with ischemia, physicians aimed to control HR below the ischemic threshold. Those with extensive stress-induced ischemia were considered for revascularization. The primary end point was cardiac death or myocardial infarction at 30-days after surgery.

**Results:** Testing showed no ischemia in 287 patients (74%); limited ischemia in 65 patients (17%), and extensive ischemia in 34 patients (8.8%). Of 34 patients with extensive ischemia, revascularization before surgery was feasible in 12 patients (35%). Patients assigned to no testing had similar incidence of the primary endpoint as those assigned to testing (1.8% vs. 2.3%; odds ratio [OR] 0.78; 95% confidence interval [CI] 0.28 to 2.1; p = 0.62). The strategy of no testing brought surgery almost 3 weeks forward. Regardless of allocated strategy, patients with a HR <65 beats/min had lower risk than the remaining patients (1.3% vs. 5.2%; OR 0.24; 95% CI 0.09 to 0.66; p = 0.003).

**Conclusions:** Cardiac testing can safely be omitted in intermediate-risk patients, provided that beta-blockers aiming at tight HR control are prescribed.

## INTRODUCTION

According to the guidelines of the American College of Cardiology /American Heart Association ( ACC/AHA), all patients scheduled for major vascular surgery who have clinical features associated with increased cardiac risk should undergo noninvasive cardiac stress-testing[1]. Perioperative beta-blocker therapy is recommended for patients with inducible ischemia undergoing major vascular surgery. The guidelines also recommend coronary angiography for patients with high-risk noninvasive test results and myocardial revascularization in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved. However, noninvasive testing might delay surgery and run the risk of aortic aneurysmal rupture or exacerbation of critical limb ischemia. Furthermore, a recent randomized, controlled trial of preoperative myocardial revascularization in vascular surgery patients showed no improvement in perioperative or long-term outcome associated with prophylactic revascularization[2].

In a previous retrospective observational study of 1,351 patients undergoing major vascular surgery, we found that counting clinical risk factors effectively stratified vascular surgery patients into low-risk (0 risk factors), intermediate-risk (1 to 2 risk factors), and high-risk (≥ 3 risk factors) categories[3]. Among patients receiving beta-blockers, perioperative cardiac event rates were 0% and 0.9% in low- and intermediate-risk patients, respectively. Of all intermediate-risk patients studied, only a minority (2%) experienced extensive stress-induced myocardial ischemia[3]. These data do not support the routine use of preoperative noninvasive testing in intermediate-risk patients, who constitute more than 50% of the major vascular surgery population, provided that perioperative beta-blockade is employed.

We therefore undertook the second multi-center DECREASE-II (Dutch Echocardiographic Cardiac Risk Evaluation) study to prospectively assess the value of cardiac testing according to the ACC/AHA guidelines in intermediate-risk patients receiving beta-blocker therapy with tight heart rate (HR) control scheduled for major vascular surgery.

## METHODS

### Study protocol

Between 2000 and 2005, we enrolled 1,476 patients undergoing elective open abdominal aortic or infrainguinal arterial reconstruction at 5 participating centers. Patients were screened for the following cardiac risk factors: age over 70 years, angina pectoris, prior myocardial infarction (MI) on the basis of history or a finding of pathologic Q waves on electrocardiography, compensated congestive heart failure or a history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction (serum creatinine >160 µmol/l), and prior stroke or transient ischemic attack.

On the basis of previous study results, patients were divided into 3 groups: 0 risk factors (low-risk), 1 or 2 risk factors (intermediate-risk), ≥ 3 risk factors (high-risk)[3]. Low-risk patients were referred for surgery with beta-blocker therapy without additional testing. Intermediate-risk patients were randomly (1:1) assigned to preoperative cardiac stress-testing or no testing. Cardiac testing was performed by dobutamine echocardiography or dobutamine or dipyridamole perfusion scintigraphy, as previously described[4,5]. Test results were scored by the extent of stress-induced ischemia with a 16-segment model in dobutamine echocardiography and a 6-wall model in stress perfusion scintigraphy. In addition during dobutamine echocardiography, the HR at which ischemia occurred (i.e. ischemic HR threshold) was noted. Limited ischemia was defined by the presence of 1 to 4 ischemic segments

or 1 to 2 ischemic walls, whereas extensive ischemia was defined by ≥ 5 ischemic segments or ≥ 3 ischemic walls. Patients without ischemia as well as those with limited ischemia were referred for surgery with beta-blocker therapy. In patients with extensive ischemia, test results were discussed with the treating physicians and only in those patients in whom the index surgical procedure could be delayed was coronary angiography performed and revascularization considered after the angiography data were obtained. The type of coronary revascularization, bypass surgery or percutaneous coronary intervention, was decided by the treating physicians on the basis of coronary anatomy and the possible delay of the index surgical procedure. High-risk patients were referred for additional cardiac testing. All patients provided written informed consent, and the study was approved by the Erasmus Medical Center medical ethics committee and local research ethics committees.

### Beta-blocker therapy

Perioperative beta-blocker therapy was installed in all patients. Patients receiving chronic beta-blocker therapy continued their medication. Patients without beta-blockers started with bisoprolol 2.5 mg once/day at the screening visit. Beta-blocker dose was adjusted in all patients at admission to the hospital and on the day before surgery to achieve a resting HR of 60 to 65 beats/min. The same dose of beta-blockers was continued postoperatively except in patients who were unable to take medication orally or by nasogastric tube postoperatively. In these patients, the HR was monitored continuously in the intensive care unit or hourly at the ward, and intravenous metoprolol was administered at a dose sufficient to keep the HR between 60 and 65 beats/min. The HR and blood pressure were measured immediately before each scheduled dose of beta-blockers. Beta-blockers were withheld if the HR was under 50 beats/min or the systolic blood pressure was under 100 mmHg. After discharge, patients continued beta-blocker therapy and dose adjustments were carried out during outpatient visits to achieve a resting HR of 60 to 65 beats/min.



### Perioperative management

Anesthetic management, monitoring, surgical technique, and other aspects of perioperative management were at the discretion of the attending physician. Results of preoperative testing and coronary revascularization were discussed with the attending physicians. In patients with limited or extensive ischemia, HR and hemodynamic management during surgery was implemented to control HR below the ischemic threshold and otherwise below 65 beats/min. Anticoagulant and antiplatelet therapy were continued for a period of at least 4 weeks after percutaneous coronary intervention and continued during surgery. Intraoperative ischemia was treated at the discretion of attending physicians, and additional beta-blockers were permitted.

### End point definition

All patients were monitored for cardiac events during hospital stay after surgery. Twelve-lead electrocardiography and serum troponin-T level was determined 1, 3, 7, and 30 days after surgery. Additional tests were performed at the discretion of the attending physician. Outpatient follow-up was performed at 30 days if a patient had been discharged from the hospital. At the outpatient clinic all patients were screened at 3-month intervals for cardiac events by clinical history, troponin-T measurements, and 12-lead electrocardiography recording. All data were collected by the participating centers and evaluated in a blinded fashion by members of the adverse-events committee. The median follow-up was 2.0 years (25th and 75th percentile: 0.8 and 3.1, respectively).

The primary end point was a composite of cardiac death and nonfatal MI at 30 days after surgery. Cardiac death was defined as a death caused by acute MI, significant cardiac arrhythmias, or refractory congestive heart failure or as a death occurring suddenly without another explanation. A nonfatal MI

was defined by both a positive troponin-T level and a finding of new Q waves lasting more than 0.03 s on the electrocardiogram. We also report the incidence of the composite end point during long-term follow-up. A nonfatal MI during follow-up was defined by new Q waves lasting more than 0.03 s on the electrocardiogram with or without positive troponin-T level.

### Sample size

The primary objective of this trial was to demonstrate that the strategy of no testing is non-inferior to the strategy of cardiac testing in intermediate-risk patients. In a previous study we noted a 5% incidence of perioperative cardiac death or nonfatal MI in intermediate-risk patients[3]. We judged that the strategy of no testing is non-inferior to testing if the difference in primary end point is not more than 4%. On the basis of these assumptions, a total of 734 patients are needed to demonstrate non-inferiority with an alpha level of 5% and a power of 80%.

### Statistical analysis

Continuous data are presented as median values and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical and surgical characteristics between patients allocated to no testing or testing were evaluated by chi-square tests. Differences in the incidence of the primary end point were evaluated by a chi-square test. The incidence of cardiac events over time was further examined by the Kaplan-Meier method, whereas a log-rank test was applied to evaluate differences between the allocated treatment strategies. Analyses were performed according to the intention to treat principle. All statistical tests were 2-sided and a p value $< 0.05$ was considered significant.

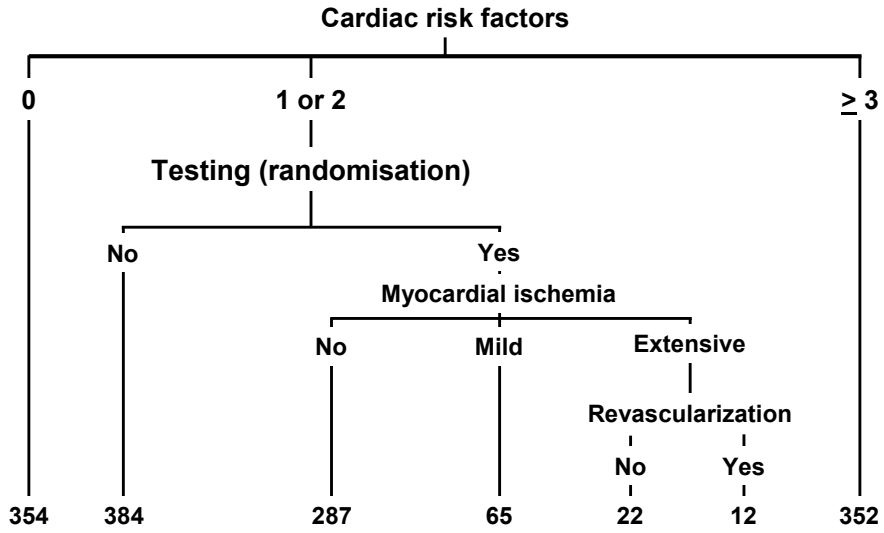


**Figure 8.1** Flow chart of the study.
Cardiac risk factors included: age over 70 years, angina pectoris, prior myocardial infarction on the basis of history or a finding of pathologic Q waves on electrocardiography, compensated congestive heart failure or a history of congestive heart failure, current treatment for diabetes mellitus, renal dysfunction (serum creatinine >160 µmol/l), and prior stroke or transient ischemic attack. Patients with 1 or 2 cardiac risk factors were randomly (1:1) assigned to cardiac testing or no testing. Test results were classified as no ischemia, limited ischemia, and extensive ischemia. Patients with extensive ischemia were considered for coronary revascularization.

## RESULTS

### Characteristics of patients

A total of 1,476 patients were enrolled and screened for cardiac risk factors, and 354 patients (24%), 770 patients (52%), and 352 patients (23%) were classified as low-, intermediate- and high-risk, respectively (FIGURE 8.1). A total of 386 intermediate-risk patients were assigned to cardiac testing and 384 patients were assigned to no testing. There were no differences in the presence of ischemic heart disease (i.e., previous MI and angina pectoris) between the 2 groups (TABLE 8.1). Testing showed no ischemia in 287 patients (74%); limited ischemia in 65 patients (17%), and extensive ischemia in 34 patients (8.8%). No serious side effects occurred during stress-testing. Stress-induced ischemia during dobutamine echocardiography was noted in 90 patients. The median HR at which ischemia occurred was 112 beats/min (range 92 to 120 beats/min). Of 34 patients with extensive stress-induced ischemia, revascularization before surgery was considered feasible by the treating physicians in 12 patients (35%), percutaneous intervention in 10 patients, and bypass surgery in 2 patients. Coronary angiography showed 2-vessel disease in 5 patients (42%) and 3-vessel disease in 6 patients (50%). Complete revascularization was achieved in 6 patients (50%).

The median duration of screening to operation was 53 days (range 13 to 121 days) in patients assigned to testing and 34 days (range 7 to 88 days) in the no-testing group ($p < 0.001$). The HR decreased from a median of 70 beats/min at the screening visit to 60 beats/min before operation and was similar in both groups (FIGURE 8.2).

### Perioperative cardiac events

The incidence of the 30-day end point in low-, intermediate-, and high-risk patients was 0.3%, 2.2%, and 8.5%, respectively ($p < 0.001$) (TABLE 8.2). No difference in 30-day outcome was observed in



**TABLE 8.1** Baseline characteristics.

| | | Patients with 1 or 2 cardiac risk factors* | |
|---|---|---|---|
| | All Patients | Testing | No Testing |
| No. of patients | 1,467 | 386 | 384 |
| Age (yrs) | 67.0 (59.5, 73.8) | 67.3 (60.9, 73.9) | 68.0 (60.9, 73.5) |
| Men (%) | 73.3 | 77.5 | 72.1 |
| History of diabetes (%) | 21.8 | 22.3 | 21.9 |
| History of angina pectoris (%) | 55.1 | 67.6 | 63.8 |
| History of myocardial infarction (%) | 27.0 | 18.7 | 15.9 |
| History of congestive heart failure (%) | 11.5 | 3.9 | 3.7 |
| History of cerebrovascular accident (%) | 19.1 | 16.1 | 16.7 |
| History of renal failure (%) | 8.5 | 4.9 | 6.0 |
| Statin use (%) | 42.1 | 42.8 | 42.2 |
| ACE inhibitor use (%) | 32.6 | 31.6 | 33.1 |
| Aspirin use (%) | 45.3 | 47.2 | 44.5 |
| Type of surgery | | | |
| Thoraco-abdominal (%) | 4.9 | 5.2 | 4.4 |
| Tube graft (%) | 12.6 | 15.0 | 10.7 |
| Bifurcated graft (%) | 38.1 | 38.9 | 34.1 |
| Femoro-popliteal (%) | 44.4 | 40.9 | 50.8 |

ACE = angiotensin-converting enzyme. *Cardiac risk factors include: age ≥70 yrs, angina pectoris, myocardial infarction, congestive heart failure, cerebrovascular accident, diabetes mellitus, and renal failure[3].

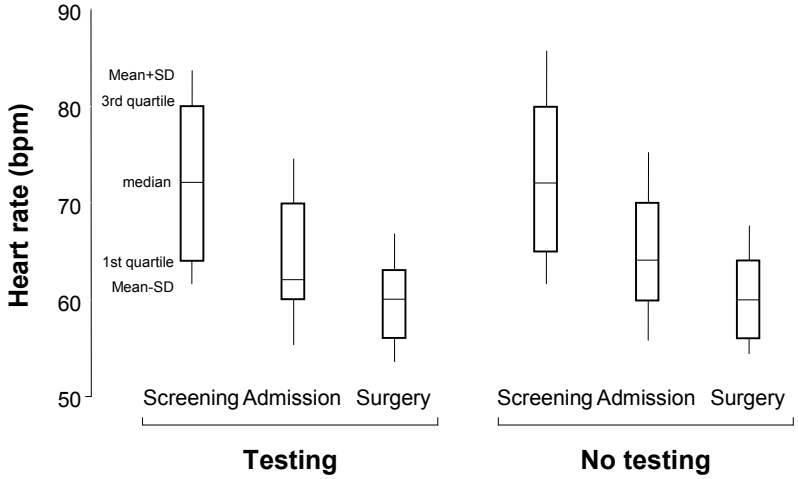


**FIGURE 8.2** Heart rate at the screening visit, at the day of hospital admission, and immediately before surgery in patients allocated to cardiac testing (left) or no testing (right).
Heart rate values are presented as beats/min (bpm).

intermediate-risk patients with and without testing, (2.3% vs. 1.8%; odds ratio [OR] 0.78, 95% confidence interval [CI] 0.28 to 2.1) (TABLE 8.2). The upper limit of the 95% CI of the absolute risk difference in favor of cardiac testing was 1.2%, indicating non-inferiority of the no-testing strategy according to our pre-specified criteria. The incidence of the primary end point in patients without, limited, and extensive ischemia was 0%, 6.2%, and 14.7%, respectively ($p < 0.001$). In intermediate-risk patients with extensive ischemia, revascularization did not improve 30-day outcome (25.0% vs. 9.1% events; OR 3.3, 95% CI 0.5 to 24; $p = 0.32$). One patient died after successful revascularization before surgery because of a ruptured aortic aneurysm.

**TABLE 8.2** Patient outcome at 30 days after surgery.

| | No. of Patients | All-Cause Death (%) | p-value | Cardiovascular Death (%) | p-value | MI (%) | Cardiovascular Death or MI (%) | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|---|
| All patients | 1,476 | 51 (3.5) | | 27 (1.8) | | 39 (2.6) | 48 (3.3) | | |
| Cardiac risk factors | | | 0.002 | | <0.001 | | | | <0.001 |
| 0 | 354 | 6 (1.7) | | 1 (0.3) | | 0 (0) | 1 (0.3) | 1 | |
| 1 or 2 | 770 | 23 (3.0) | | 8 (1.0) | | 13 (1.7) | 17 (2.2) | 8.0 (1.1, 161) | |
| ≥3 | 352 | 22 (6.3) | | 18 (5.1) | | 26 (7.4) | 30 (8.5) | 33 (4.8, ∞) | |
| Patients with 1 or 2 cardiac risk factors | | | 0.14 | | 0.29 | | | | 0.62 |
| Allocated to testing | 386 | 15 (3.9) | | 6 (1.6) | | 7 (1.8) | 9 (2.3) | 1 | |
| Allocated to no testing | 384 | 8 (2.1) | | 2 (0.5) | | 5 (1.3) | 7 (1.8) | 0.78 (0.28, 2.1) | |
| Patients with 1 or 2 cardiac risk factors allocated to testing | | | <0.001 | | <0.001 | | | | <0.001 |
| No ischemia | 287 | 6 (2.1) | | 0 (0) | | 0 (0) | 0 (0) | 1 | |
| 1–4 ischemic segments | 65 | 3 (4.6) | | 2 (3.1) | | 4 (6.2) | 4 (6.2) | 42 (2.2, ∞)* | |
| ≥5 ischemic segments | 34 | 6 (17.7) | | 4 (11.8) | | 3 (8.8) | 5 (14.7) | 107 (5.8, ∞)* | |

CI = confidence interval; MI = myocardial infarction. These estimators use a correction of 0.5 in the cell that contains a zero.

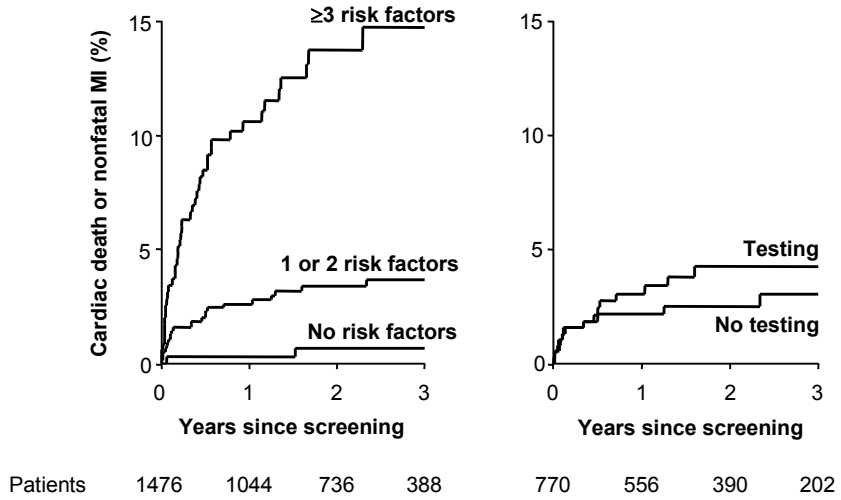


**FIGURE 8.3** Incidence of cardiac death or myocardial infarction (MI) during 3-year follow-up according to the number of cardiac risk factors (left) and allocated strategy in patients with 1 or 2 cardiac risk factors only (right).
The incidence of cardiac death or MI was associated with the number of cardiac risk factors at screening (log-rank $p < 0.001$). There was no significant difference in the long-term incidence of cardiac events between patients allocated to cardiac testing or no testing (log-rank $p = 0.30$).



### Late cardiac events

The incidence of the 3-year end point in low-, intermediate-, and high-risk patients was 0.7%, 3.7%, and 14.8%, respectively. No difference in 2-year outcome was observed in intermediate-risk patients with and without testing (4.3% vs. 3.1%; $p = 0.30$) (FIGURE 8.3).

### HR control

The incidence of the 30-day end point showed a significant correlation with HR control. The study aimed at a HR between 60 and 65 beats/min before surgery, and the median HR was 60 beats/min. The HR was below 50 beats/min in 1.7% of the intermediate-risk patients and more than 65 beats/min in 16.5% (no difference between allocated groups). Patients with a HR <65 beats/min had lower incidence of the primary end point than the remaining patients (1.3% vs. 5.2%; OR 0.24, 95% CI 0.09 to 0.66; $p = 0.003$). The incidence of the primary end point increased by a factor 1.5 (95% CI 1.1 to 2.0; $p = 0.006$) for each 5 beats/min heart-rate increase (FIGURE 8.4).

## DISCUSSION

In this randomized, multicenter study, we found that cardiac testing of intermediate-risk patients before major vascular surgery, as recommended by the guidelines of the ACC/AHA, provided no benefit in patients receiving beta-blocker therapy with tight HR control[1]. Cardiac test results influenced patients' management. The treating physicians were aware of the presence of stress-induced myocardial ischemia as well as the HR at which ischemia occurred (i.e. ischemic threshold). Physicians were encouraged to control HR below the ischemic threshold. Furthermore, in a selected number of patients with extensive stress-induced ischemia, preoperative coronary revascularization was performed. According to the present guidelines, this is thought to be the optimal strategy. However,

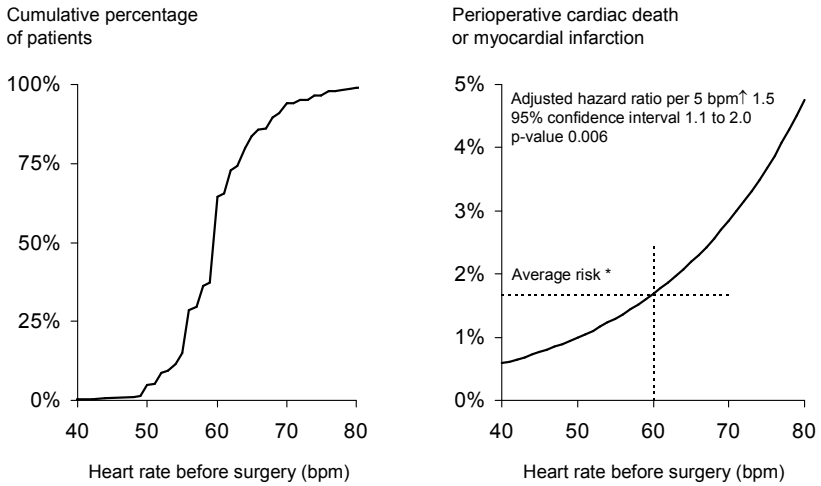


**FIGURE 8.4** Cumulative distribution of the heart rate before surgery (left) and the relation between heart rate and perioperative cardiovascular events (right).
For this analysis we included patients with 1 to 2 risk factors. The hazard ratio was adjusted for clinical risk factors. bpm = beats/min.

interestingly, compared with the no-testing population, a reverse trend in perioperative outcome was observed. An absolute increase in perioperative cardiac death or MI of more than 1.2% in patients assigned to no testing can be excluded with 95% certainty. Importantly, the strategy of no testing brought the operation almost 3 weeks forward.

Although testing identified a minority of intermediate-risk patients with an increased risk of perioperative cardiac death or MI, we considered the overall cardiac event rate of 2.2% in this population as sufficiently low to preclude testing.

Preoperative risk stratification with simple clinical cardiac risk markers effectively identified patients at low-, intermediate-, and high-risk with a perioperative cardiac event rate of 0.3%, 2.2%, and 8.5%, respectively. The absence of the aforementioned cardiac risk factors identified a population of truly low risk, even in the presence of peripheral atherosclerotic disease. During long-term follow-up a similar trend was observed; the incidence of late cardiac death and MI in low-, intermediate-, and high-risk patients was 0.7%, 3.7%, and 14.8%, respectively ($p < 0.001$).

Beta-blocker therapy has become an essential part of the medical treatment of patients with acute coronary syndromes, also a major cause of perioperative adverse outcome. Two randomized trials showed that perioperative beta-blocker therapy was associated with an improved outcome in high-risk surgical patients[6,7]. A recent large retrospective observational study, evaluating the effect from 663,635 surgical procedures confirmed the benefit of beta-blocker in those with increased risk[8]. These promising results were questioned by a recent meta-analysis of 8 randomized clinical trials evaluating a total number of 1,152 patients. This meta-analysis showed only a nominal statistically significant effect of beta-blockers for the composite end point of 30-day cardiovascular mortality, nonfatal MI, and nonfatal cardiac arrest (relative risk 0.44; 95% CI 0.20 to 0.97)[9]. Two more recently completed studies failed to show a favorable effect of beta-blockers. In the POBBLE (Perioperative Beta-Blockade) trial metoprolol failed to improve 30-day cardiovascular outcome in 97 low-risk

vascular surgery patients; those with a history of ischemic heart disease were excluded[10]. The DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, involving 921 patients with diabetes undergoing non-cardiac surgery, failed to show that metoprolol significantly reduced the risk of death and cardiac complications after a median follow-up of 18 months[11].

A potential factor that might explain these conflicting study outcomes is a difference in dosing and HR control. Beta-blockers reduce HR and myocardial contractility and, subsequently, myocardial oxygen demand. To exert the optimal beneficial effect, dose adjustments for HR control are important. In a small randomized study, the HR threshold at which ischemia occurred was assessed with ambulatory electrocardiographic monitoring in 26 patients[12]. These patients were randomized to either tight HR control (i.e. 20% less than the ischemic threshold but >60 beats/min) or normal, non-adjusted beta-blocker therapy. Tight HR control was associated with a significant reduction of perioperative ischemia in 7.7% versus 92%. We confirmed these findings, because tight HR control was clearly associated with an improved outcome. We believe that for a proper interpretation of the perioperative cardiac protective effect of beta-blockers, the effect on HR control needs to be taken into account. This might be a potential limitation for clinical trials using a study design with blinded randomization and fixed beta-blocker doses.

*Study limitations*

The assessment of the HR at which ischemia occurred during stress-testing was only feasible in patients evaluated by dobutamine echocardiography. In patients evaluated by nuclear imaging only, the presence and extent of ischemia could be assessed. The effect of coronary revascularization in intermediate-risk patients with extensive stress-induced ischemia cannot be assessed, owing to the insufficient number of patients studied.



## Conclusions

In conclusion, we found that 30-day and long-term cardiac death and MI rate in intermediate-risk patients undergoing abdominal aortic or infrainguinal arterial reconstruction surgery was sufficiently low to preclude preoperative testing for coronary artery disease.

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# Chapter 9

## The influence of aneurysm size on perioperative cardiac outcome in elective open infrarenal aortic aneurysm repair

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## ABSTRACT

**Background:** Abdominal aortic aneurysm (AAA) size and growth has been found to be associated with local generation of inflammation markers such as interleukin-6. Inflammation also seems to play a pivotal role in perioperative adverse cardiac events. We hypothesized that patients with a large AAA are at increased risk for cardiac events.

**Methods:** Consecutive patients who underwent a CTA scan prior to open elective infrarenal AAA repair between March 2000 and December 2005 at 3 hospitals were analyzed. All patients were screened for clinical risk factors (age, gender, angina pectoris, myocardial infarction, heart failure, diabetes, stroke, renal failure, chronic obstructive pulmonary disease), and cardioprotective medication. Postoperatively data on troponin release, CK/CK-MB, and ECG were routinely collected. The main outcome measure was the combined endpoint of 30-day cardiovascular death and non-fatal MI. Multivariate Cox regression analysis was used to evaluate the influence of AAA size on postoperative cardiac outcome.

**Results:** A total of 500 patients were included in this study. Their mean age was 70 ± 9.3 years, and 431 (86%) were male. Thirty-one (6.2%) patients suffered from perioperative cardiovascular complications, including 15 (3.0%) cardiovascular deaths and 16 (3.2%) nonfatal MIs. After correction for other risk factors, including age, Revised Cardiac Risk Index, medication use, duration of surgery, and intraoperative blood loss, AAA size was independently associated with perioperative nonfatal MI and cardiovascular death (3.2% increase in risk for each millimeter added, 95% CI 1.1% to 6.2%, p=0.007).

**Conclusion:** A larger AAA size is independently associated with an increased incidence of perioperative cardiovascular complications after elective infrarenal AAA repair.

## INTRODUCTION

Abdominal aortic aneurysm (AAA) occurs frequently in the elderly population, i.e. a prevalence of 5-7% in males between 65 and 74 years, increasing to over 10% in males over 74 years of age[1-3]. The overall mortality from ruptured AAA remains high, i.e. up to 75%, and preventive elective repair of large AAAs appears to be the best option[4]. However, perioperative cardiac complications of elective AAA repair remain a significant problem despite recent perioperative advancements such as cardio-protective medication and improved anesthesiological and surgical care[5,6].

The pathophysiology of these perioperative adverse cardiac events is not entirely clear. Coronary plaque instability because of inflammation leading to thrombosis and myocardial infarction is a major cause of perioperative cardiac events similar to myocardial infarctions occurring in the non-operative setting[7]. At least two studies evaluating the pathophysiology of perioperative MI using non-invasive tests, coronary angiography, and autopsy results showed that coronary plaque rupture and thrombus formation occurred in around 50% of all fatal cases, while a sustained mismatch of oxygen supply and demand was responsible for the remaining half[8,9].

It has been shown that AAAs might be an important source of circulating inflammatory markers, e.g. Interleukin-6 (IL-6), serum amyloid A, C-reactive protein, and high sensitive C-reactive protein. These inflammatory markers are also positively related to the abdominal aortic size[10-13]. As was recently shown the concentration of inflammatory markers such as IL-6 and high sensitive C-reactive protein is predictive for adverse cardiac events in patients with peripheral arterial disease[14]. Furthermore it has also been shown by Brady et al. that AAA size is predictive for long-term cardiovascular mortality[15].

Since AAA size and growth seems to be related to the concentration of circulating (pro-) inflammatory markers and to long-term cardiac outcome we hypothesized that patients with a large AAA might be more prone to adverse perioperative cardiac events after AAA repair than patients with small AAAs. To evaluate this hypothesis we conducted the present study.

## METHODS

### Patient population

The study population was composed of patients who underwent a CTA scan prior to elective open infrarenal abdominal aortic aneurysm repair between January 2000 and January 2005 at one of three hospitals, i.e. Erasmus University Medical Center in Rotterdam, Albert Schweitzer Hospital in Dordrecht, and Reinier de Graaf Hospital in Delft, the Netherlands. Patients were retrospectively identified by screening of surgical medical charts. A CTA scan of the AAA prior to surgical repair to measure the maximum diameter of the AAA was required to be included in this analysis. All CTA scans were scored, including maximum diameter, by the attending radiologist. In a weekly meeting of radiologists and vascular surgeons the measurements of the AAAs were reviewed and if necessary adjusted after consensus was reached. To obtain a more homogenous study population patients with an inflammatory or mycotic aneurysm were excluded from analysis. All operation reports were screened to make sure only patients requiring infrarenal aortic cross clamping were included in the analysis. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center.

### Perioperative cardiac risk assessment

All patients were screened for cardiac risk factors, including age, hypertension (i.e. medical therapy to control hypertension), history of or presence of angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure (i.e. a serum creatinine of >2.0 mg/dL), diabetes mellitus. Smoking status (never, current, or former) and the presence of chronic obstructive pulmonary disease (COPD) was noted as well. A patient was classified as having COPD at the preoperative screening visit according to symptoms and pulmonary function test (i.e. FEV1 <70% of maximal age and gender predictive value). Heart failure was scored according to the notes of the preoperative screening visits as well. All prescription and over-the-counter medications were noted on the day of admission and were classified as follows: statins, beta-blockers, platelet aggregation inhibitors, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics, and nitrates. Patients unable to take medication orally perioperatively were switched to intravenous formula. If no intravenous formula was available, i.e. statins and angiotensin converting enzyme inhibitors, oral medication was restarted as soon as possible after surgery. In all patients duration of surgery and intraoperative blood loss were noted.

### Outcome

The main outcome measure was the combined endpoint of 30-day cardiovascular death and non-fatal myocardial infarction. Secondary, 30-day all-cause mortality was analyzed. Cardiovascular death was defined as any death with a cardiovascular cause, including those deaths following a cardiac procedure, cardiac arrest, myocardial infarction, pulmonary embolus, stroke, or sudden deaths not ascribed to other causes. Myocardial infarction was defined as the presence of 2 out of the following 3 criteria: (1) Characteristic ischemic symptoms lasting > 20 minutes, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists > 24 hours, and (3) a positive troponin T, i.e. >0.10 ng/ml, or peak creatinine phosphokinase -MB >8% of an elevated total creatinine phosphokinase with characteristic rise and fall[16]. To assess cardiac complications during the postoperative period blood and plasma samples for cardiac troponin T, creatinine phosphokinase levels, creatinine phosphokinase -MB levels, and electrocardiography were collected.



### Statistical analysis

Continuous variables were described as mean value (range), and categorical variables as percent frequencies. Linear regression analysis was used to explore the relation between aneurysm size and duration of surgery and blood loss. Kaplan-Meier survival curves were constructed to assess perioperative cardiovascular event-free and overall survival. The association of AAA size, cardiovascular risk factors and medication use with perioperative cardiovascular complications and all-cause death was assessed via multivariate Cox regression analysis. All covariables associated with perioperative cardiac complications or all-cause mortality ($p < 0.20$ in univariate analysis) were included in the multivariate model. 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 perioperative composite endpoint, we used the Revised Cardiac Risk Index[16]. The Revised Cardiac Risk Index identifies 6 predictors (high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, insulin dependent diabetes mellitus, and renal failure) of major cardiac complications. Based on the presence of 0, 1, 2, or 3 or more of these predictors, the rate of major cardiac complications was estimated to be 0.4%, 0.9%, 7%, and 11%, respectively in the original study by Lee et al. resulting in an excellent area under the curve (AUC) of 0.81. Receiver operating characteristic curve analysis was performed to calculate AUC values. The performance of risk models can be determined by the AUC, which indicates

how well a model rank orders patients with respect to their outcomes, where 0.5 indicates no predictive value and 1.0 indicates perfect performance[17]. The limit of statistical significance was set at p = 0.05 (two sided). All analysis was performed using the statistical software SPSS for Windows 12.1 (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

### Patient characteristics

A total of 500 patients with an infrarenal AAA were included in the study. The majority of patients were males (86%) and the mean age was 70 ± 9.3 years. The overall median maximum AAA diameter was 56 mm (range 42 to 110 mm). According to the Revised Cardiac Risk index classification almost half of the patients (41%) had 1 risk factor, i.e. high-risk type of surgery, whereas respectively 33% and 26% had 2, and 3 or more risk factors. Baseline clinical characteristics and medication use are presented in TABLE 9.1. The median duration of surgery was 216 minutes and median blood loss

**TABLE 9.1** Baseline characteristics, surgery, and medication use during hospitalization of all patients and in patients with or without perioperative events.

| | All patients (N=500) | Patients without events (N=469) | Patients with events (N=31) |
|---|---|---|---|
| Men – no. (%) | 431 (86) | 404 (86) | 27 (87) |
| Age – mean (SD) | 70 (9.3) | 70.3 (60 – 89) | 73.5 (64 – 89) |
| Median AAA size – mm (range) | 56 (42 – 110) | 56 (42 – 110) | 66 (47 – 95) |
| Median duration of surgery – min (range) | 216 (120 – 535) | 216 (120 – 500) | 210 (140 – 535) |
| Median blood loss – ml (range) | 2100 (400 –18000) | 2100 (400 – 18000) | 3100 (2000 - 6500) |
| | | | |
| Previous Angina Pectoris – no. (%) | 110 (22) | 101 (22) | 9 (29) |
| Previous myocardial infarction – no. (%) | 163 (33) | 150 (32) | 13 (42) |
| Previous heart failure – no. (%) | 26 (5) | 24 (5) | 2 (7) |
| CVA or TIA – no. (%) | 77 (15) | 72 (15) | 5 (16) |
| Diabetes Mellitus – no. (%) | 48 (10) | 45 (10) | 3 (10) |
| Renal failure – no. (%) | 28 (6) | 24 (5) | 4 (13) |
| Systemic hypertension – no. (%) | 207 (42) | 197 (43) | 10 (33) |
| COPD – no. (%) | 127 (25) | 115 (25) | 12 (39) |
| | | | |
| Revised Cardiac Risk Index | | | |
| 1 risk factor – no. (%) | 203 (41) | 195 (42) | 8 (26) |
| 2 risk factors – no. (%) | 165 (33) | 154 (33) | 11 (36) |
| 3 or more risk factors – no. (%) | 132 (26) | 120 (26) | 12 (39) |
| | | | |
| Platelet aggregation inhibitors – no. (%) | 178 (36) | 170 (36) | 8 (26) |
| ACE-inhibitors – no. (%) | 152 (31) | 144 (31) | 8 (26) |
| Diuretics – no. (%) | 84 (17) | 80 (17) | 4 (13) |
| Nitrates – no. (%) | 66 (13) | 60 (13) | 6 (19) |
| Beta-blockers – no. (%) | 364 (73) | 349 (74) | 15 (48) |
| Statins – no. (%) | 202 (40) | 196 (42) | 6 (19) |
| Calcium-antagonists – no. (%) | 157 (31) | 147 (32) | 10 (32) |

MI = myocardial infarction; CVA = Cerebrovascular event; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; ACE = angiotensin-converting enzyme

during surgery was 2100 ml. Neither duration of surgery (p = 0.78) nor blood loss during surgery (p = 0.13) was related to AAA size.

### Perioperative cardiovascular outcome

Perioperative cardiac events occurred in 31 (6.2%) patients. These events included cardiovascular death (n=15) and non-fatal MI (n=16). In univariate analysis age, AAA diameter, and Revised Cardiac Risk Index were associated with worse outcome, whereas beta-blocker therapy and statin therapy were both associated with a reduced incidence of perioperative adverse cardiac events (TABLE 9.2). In multivariate analysis AAA size was associated with an increased incidence of perioperative cardiac events (3.4% increase in risk for each millimeter added, 95% CI 1.1 % - 6.2%, p = 0.007). Furthermore age and a higher score of the Revised Cardiac Risk Index were associated with an increased risk of perioperative cardiac events (TABLE 9.2). ROC analysis showed an area-under-the-curve (AUC) of 0.60 for the Revised Cardiac Risk Index alone, but this AUC improved to 0.69 if AAA size was added to the model (p = 0.001). If age was added to the model as well, the AUC further improved to 0.75 (p = 0.003). Beta-blocker therapy and statin therapy on the other hand were both associated with a reduced incidence of perioperative cardiac events in multivariate analysis (Hazard ratio 0.31, 95% CI 0.15-0.63, and Hazard ratio 0.40, 95% CI 0.16–0.95 respectively).

**TABLE 9.2** Perioperative cardiac death and nonfatal myocardial infarction.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P-value | adjusted OR | 95% CI | P-value |
| Men | 1.09 | 0.38 – 3.12 | 0.87 | | | |
| Age (per year increase) | 1.09 | 1.04 – 1.14 | 0.001 | 1.07 | 1.02 – 1.12 | 0.01 |
| AAA diameter (per mm increase) | 1.04 | 1.02 – 1.06 | 0.001 | 1.03 | 1.01 – 1.06 | 0.007 |
| Intraoperative blood loss (per 500 ml increase) | 1.06 | 0.92 – 1.22 | 0.41 | | | |
| Duration of surgery (per 10 minutes increase) | 1.02 | 0.97 – 1.07 | 0.43 | | | |
| Systemic hypertension | 0.68 | 0.32 – 1.46 | 0.68 | | | |
| Chronic obstructive pulmonary disease | 1.91 | 0.93 – 3.93 | 0.08 | 1.81 | 0.85 – 3.89 | 0.13 |
| | | | | | | |
| Revised Cardiac Risk Index | | | | | | |
| 1 risk factor | 1 | | | 1 | | |
| 2 risk factors | 1.73 | 0.70 - 4.30 | 0.24 | 2.30 | 0.92 - 5.76 | 0.07 |
| 3 or more risk factors | 2.35 | 0.96 – 5.75 | 0.06 | 3.55 | 1.40 – 8.99 | 0.008 |
| | | | | | | |
| Medication use | | | | | | |
| Platelet aggregation inhibitors | 0.62 | 0.28 – 1.40 | 0.25 | | | |
| ACE-inhibitors | 0.79 | 0.36 – 1.78 | 0.58 | | | |
| Diuretics | 0.73 | 0.26 – 2.10 | 0.56 | | | |
| Nitrates | 1.58 | 0.65 – 3.86 | 0.31 | | | |
| Beta-blockers | 0.34 | 0.17 – 0.69 | 0.003 | 0.31 | 0.15 – 0.63 | 0.01 |
| Statins | 0.35 | 0.14 – 0.85 | 0.02 | 0.40 | 0.16 – 0.95 | 0.04 |
| Calcium-antagonists | 1.04 | 0.49 - 2.20 | 0.92 | | | |

AAA = abdominal aortic aneurysm; COPD = chronic obstructive pulmonary disease; ACE = angiotensin converting enzyme; Odds ratio (OR), 95% confidence intervals (CI) and p-values in univariate analysis by means of the Log-rank test and multivariate analysis by means of Cox regression analysis

**TABLE 9.3** Perioperative all-cause mortality.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P-value | adjusted OR | 95% CI | P-value |
| Men | 1.39 | 0.42 – 4.58 | 0.59 | | | |
| Age (per year increase) | 1.10 | 1.04 – 1.15 | 0.001 | 1.09 | 1.03 – 1.15 | 0.005 |
| AAA diameter (per mm increase) | 1.02 | 0.99 – 1.05 | 0.08 | 1.02 | 0.98 – 1.05 | 0.35 |
| Intraoperative blood loss (per 500 ml increase) | 1.14 | 1.01 – 1.28 | 0.04 | 1.07 | 1.01 – 1.17 | 0.04 |
| Duration of surgery (per 10 minutes increase) | 1.02 | 0.97 – 1.08 | 0.39 | | | |
| Systemic hypertension | 1.51 | 0.71 – 3.21 | 0.28 | | | |
| Chronic obstructive pulmonary disease | 1.83 | 0.86 – 3.87 | 0.12 | 1.50 | 0.63 – 3.58 | 0.36 |
| | | | | | | |
| Revised Cardiac Risk Index | | | | | | |
| 1 risk factor | 1 | | | 1 | | |
| 2 risk factors | 2.79 | 0.97 – 8.02 | 0.06 | 3.28 | 1.11 – 9.72 | 0.03 |
| 3 or more risk factors | 4.16 | 1.48 – 11.66 | 0.007 | 4.88 | 1.62 – 14.67 | 0.005 |
| | | | | | | |
| Medication use | | | | | | |
| Platelet aggregation inhibitors | 0.82 | 0.37 – 1.79 | 0.61 | | | |
| ACE-inhibitors | 0.73 | 0.31 – 1.70 | 0.46 | | | |
| Diuretics | 1.96 | 0.87 – 4.43 | 0.11 | 2.10 | 0.79 – 5.61 | 0.14 |
| Nitrates | 1.06 | 0.37 – 3.04 | 0.91 | | | |
| Beta-blockers | 0.29 | 0.14 – 0.61 | 0.001 | 0.21 | 0.10 – 0.45 | <0.001 |
| Statins | 0.30 | 0.12 – 0.79 | 0.02 | 0.26 | 0.11 – 0.76 | 0.01 |
| Calcium-antagonists | 2.08 | 1.01 – 4.32 | 0.05 | 2.10 | 0.89 – 4.82 | 0.09 |

AAA = abdominal aortic aneurysm; COPD = chronic obstructive pulmonary disease; ACE = angiotensin converting enzyme; Odds ratio (OR), 95% confidence intervals (CI) and p-values in univariate analysis by means of the Log-rank test and multivariate analysis by means of Cox regression analysis

### Perioperative all-cause mortality

In total 29 (5.8%) patients died during the first 30 days after AAA repair. Of these 15 (52%) were caused by cardiovascular complications, 4 (14%) by respiratory complications, 6 (21%) by multi-organ failure, and 4 (14%) by other complications. The results of univariate analysis are shown in TABLE 9.3. The size of AAA was not significantly associated with perioperative all-cause death ($p = 0.08$) in univariate analysis. In multivariate analysis (TABLE 9.3) AAA size was also not associated with an increase or reduction in perioperative all-cause mortality (adjusted Odds ratio for every mm increase in size 1.02, 95% CI 0.98–1.05, $p = 0.35$). Two or more clinical risk factors and increased age were associated with an increased incidence of 30-day mortality in multivariate analysis. Beta-blocker therapy and statin therapy on the other hand were associated an approximate 4-fold relative risk reduction (TABLE 9.3).

## DISCUSSION

This study showed an association between AAA size and perioperative cardiovascular complications after elective infrarenal AAA repair irrespective of other known factors influencing perioperative cardiovascular outcome. This study also showed a beneficial effect of both statin therapy and beta-blocker therapy in patients undergoing open AAA repair.

The overall 30-day mortality rate of 5.8% is in line with other studies on open infrarenal AAA repair[18]. As has been reported in previous studies approximately half of all perioperative deaths after AAA repair are attributable to cardiovascular complications, an observation that was confirmed in our study. The 6.2% perioperative overall cardiac event rate of our study emphasizes the high cardiac risk for patients undergoing vascular surgery. This high cardiac risk is explained by the high prevalence of (a-) symptomatic coronary artery disease in AAA patients. As was shown by Hertzer et al. in a study involving 1000 vascular surgical patients undergoing coronary angiography, over 60% of patients with an AAA have some form of coronary artery disease[19]. As these lesions may cause a myocardial supply / demand imbalance due to prolonged tachycardia and increased myocardial contractility[20], they are thought to be responsible for approximately half of all postoperative myocardial infarctions. This hypothesis has been confirmed in at least two studies using non-invasive tests, coronary angiography, and autopsy results[8,9]. The other 50% of myocardial infarctions might be caused by sudden rupture of so-called vulnerable coronary plaques. Surgery imposes extra myocardial workload, resulting in mechanical stress, stress-induced inflammation and possibly spasms. This can cause vulnerable plaques to become unstable, leading to the cascade of plaque rupture, thrombus formation, myocardial ischemia, myocardial infarction, and eventually death. Naghavi and colleagues, in their extensive review on vulnerable plaques, reported that inflammation is one of the major criteria in the definition of vulnerable plaques[7,21]. It is generally well accepted that inflammation is of imminent importance in the whole process. Therefore, most research has been focused on inflammation of coronary plaques as the ultimate trigger for vulnerable plaque rupture. This interest in inflammatory components has been justified in several population-based studies in which a positive relationship between inflammation markers and the occurrence of cardiovascular events was found[22].



In recent studies the presence of an abdominal aortic aneurysm was found to be positively related to circulating inflammatory markers. These inflammatory markers include IL-1 beta, IL-6, TNF-alpha, IFN-gamma, CRP, and high-sensitive CRP[10-13,23]. Importantly, both Jones et al. and Rhode et al. found a positive correlation between circulating IL-6 levels and AAA size[10]. Vainas et al. found a similar correlation between high-sensitive CRP and AAA size. Importantly, they also found CRP mRNA in AAA tissue[11]. Based on these observations it might be hypothesized that aneurysmal tissue produces inflammatory markers. In other words, patients with an AAA have a higher level of circulating inflammatory markers, and patients with a large AAA have a higher level of circulating inflammatory markers than patients with small AAAs. However, a different hypothesis might also be true; patients with an elevated inflammatory status may be more prone to AAA development and growth than patients with a normal inflammatory status. Subsequently patients with an elevated inflammatory status have a faster growing, larger AAA. Which hypothesis is true remains unknown and further research in this area is required.

In large prospective population based studies it was shown that circulating levels of high-sensitive C-reactive protein and IL-6 are related to long-term cardiac outcome. In a study by Ridker et al. IL-6 was a good predictor for myocardial infarction during a 6-year follow-up in 440 patients[24]. Also elevated high-sensitive C-reactive protein levels nowadays, supported by several clinical studies, are considered to be associated with long-term adverse cardiac events.

Since patients with large AAAs seem to have an elevated inflammatory status compared to patients with small AAAs it might be hypothesized that patients with a large AAA are more prone to vulnerable plaque rupture than patients with a small AAA (FIGURE 9.1). This hypothesis was confirmed by Brady et al. in a group of 2305 patients; AAA size was associated with a 34% increased risk for cardiovascular long-term mortality for every 0.8 cm added to AAA size[15].

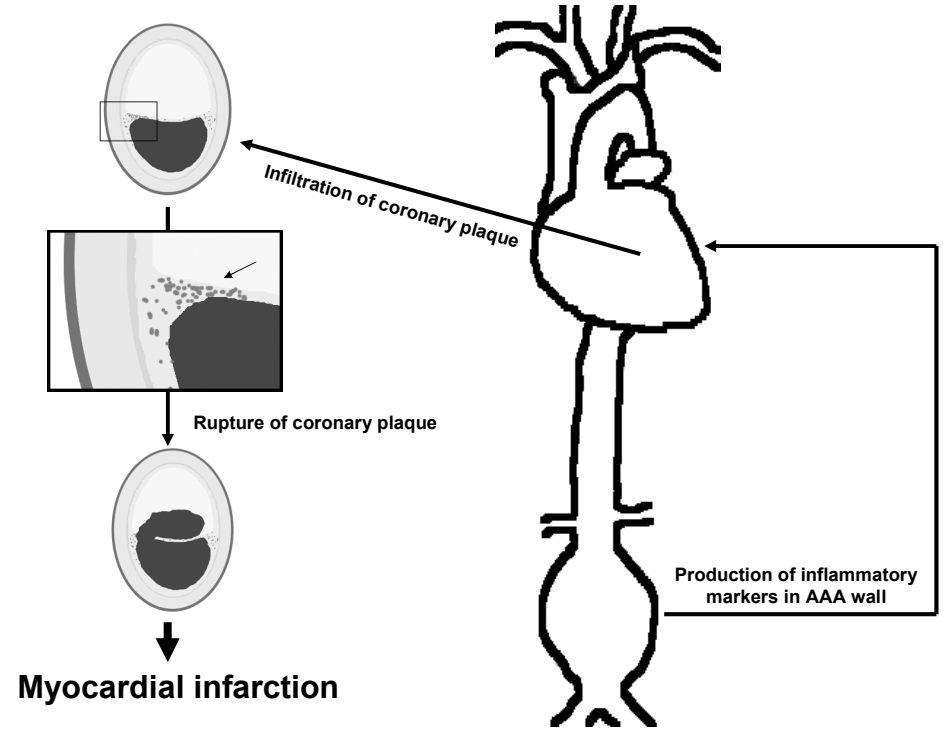


**Figure 9.1** From abdominal aortic aneurysm (AAA) to myocardial infarction in patients undergoing AAA repair.

The outcome of the UK Small Aneurysm Trial did not show a relation between AAA size and perioperative all-cause 30-day mortality[25]. Our study confirmed this observation. No association between AAA size and perioperative all-cause mortality was found. Unfortunately the UK Small Aneurysm Trial did not reported on cardiac death. It would be interesting to evaluate recent prospective trials on infrarenal abdominal aneurysm repair such as the UK Small Aneurysm Trial, the DREAM trial[26] and EVAR-1 trial[27] for the relationship between AAA size and postoperative cardiac outcome.

This study has several limitations due to its retrospective nature. Autopsy was performed in only a minority of patients that died and thus misclassification of cause of death might have occurred. Also, there was no prespecified protocol for the measurement of the maximum abdominal aortic diameter and the measurement of this diameter was done on the basis of institutional common practice. Furthermore no information on the inflammatory state of our study population, e.g. IL-6 and hsCRP levels, was available.

In conclusion, this study shows a clear association between AAA size and postoperative cardiac outcome, irrespective of other known risk factors. Future studies on the influence of AAA size on perioperative outcome should, if possible, also include the patients' inflammatory status.

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# Chapter 10

## Plasma N-Terminal Pro-B-Type Natriuretic Peptide as a predictor of perioperative and long-term outcome after vascular surgery

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## ABSTRACT

**Objective:** N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted by the heart in response to ventricular wall stress and has prognostic value in patients with heart failure, coronary artery disease and heart valve abnormalities. Postoperative and long-term outcome is also related to these risk factors. This study was conducted to assess the additional prognostic value of NT-proBNP levels as a simple objective risk marker for postoperative cardiac events among vascular surgery patients.

**Methods:** In 400 vascular surgery patients a detailed cardiac history (angina, myocardial infarction, age > 70 years, diabetes, renal failure, stroke, heart failure), resting echocardiography and NT-proBNP levels were obtained. Postoperative troponin-T and ECG were obtained on day 1, 3, 7, 30 and whenever clinically indicated. Patients were followed every 6 months at the outpatient clinic. Study endpoints were perioperative cardiac events, i.e. composite of cardiac death, myocardial infarction, and troponin release, and long-term all-cause mortality. Multivariable regression analyses were used to assess the additional value of NT-proBNP, and the optimal cut-off value was assessed by ROC curve analysis.

**Results:** Postoperative troponin T release occurred in 79 (20%) patients. Using cardiac risk factors only, patients were classified as low (0 risk factors), intermediate (1-2) and high (≥ 3) cardiac risk (event rate 7%, 15%, and 37% respectively). Median NT-proBNP level was 206 pg/ml (interquartile range 80-548). The risk of postoperative cardiac events was augmented with increasing NT-proBNP, irrespective of underlying cardiac risk factors and type of vascular surgery. In addition to cardiac risk factors only (C-index 0.66) or cardiac risk factors and site and type of surgery (C-index 0.81), NT-proBNP was an excellent tool for further risk stratification (C-index 0.86) with an optimal cut-off value of 350 pg/ml. In multivariate analysis NT-proBNP > 350 pg/ml remained significantly associated with perioperative cardiac events (OR 4.7, 95% CI 2.1-10.5, $p < 0.001$). NT-proBNP > 350 pg/ml was also associated with an independent 1.9-fold (95% CI 1.1-3.2) increased risk for long-term mortality during a median follow-up of 2.4 years.

**Conclusion:** NT-proBNP is an independent prognostic marker for postoperative cardiac events and long-term mortality in patients undergoing different types of vascular surgery and might be used for preoperative cardiac risk stratification.

## INTRODUCTION

Cardiovascular complications are a major cause for morbidity and mortality in patients undergoing non-cardiac vascular surgery. The incidence of perioperative myocardial infarction in major non-cardiac vascular surgery is around 4 to 5% and the prevalence of symptomatic or asymptomatic perioperative myocardial damage as assessed by serum troponin I or serum troponin T is even 15 to 25%[1,2]. Also long-term outcome of vascular patients after surgery is severely compromised by their cardiac status. As was recently shown, cardiovascular deaths account for up to 50% of long-term mortality in this group of patients[3].

Identification of patients at increased cardiac risk is of critical importance. In a previous observational study of 1,351 patients undergoing major vascular surgery, we found that counting clinical risk factors effectively stratified vascular surgery patients into low-risk (0 risk factors), intermediate-risk (1 to 2 risk factors), and high-risk (≥ 3 risk factors) categories[4]. In vascular surgery patients clinical evaluation alone may underestimate cardiac risk as symptoms of coronary artery disease might be obscured by peripheral arterial disease symptoms such as intermittent claudication. As was shown cardiac stress testing significantly improves preoperative risk stratification in vascular surgical patients[4]. However, cardiac stress testing is costly, requires highly trained personnel and is time consuming.

Recently, it has been suggested that N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) might be a useful laboratory measurement to improve preoperative cardiac risk stratification in addition to clinical evaluation[5-7]. This laboratory measurement is simple, avoids the extra costs and time of cardiac stress testing and is easy to interpret. Previously, several studies at our institution were performed evaluating the predictive value of NT-proBNP. However, the studied groups were relatively small and the maximum median follow-up was only 14 months. Therefore, the aim of the current study was to evaluate the usefulness of NT-pro-BNP in risk stratification, for both perioperative and long term outcome, of an unselected group of patients undergoing non-cardiac vascular surgery.

## METHODS

### Patients

The study population consisted of 400 patients undergoing elective surgery during the period January 2005 to November 2006. Patients undergoing abdominal aortic aneurysm repair, peripheral bypass surgery and carotid surgery were included in the analysis. These patients were identified in a prospectively maintained database of all patients undergoing vascular surgery at this institution. The study was approved by the Medical Ethics Committee of Erasmus MC.

Prior to surgery, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure >140/90 mmHg, or medical therapy to control hypertension), diabetes mellitus (fasting glucose level >7.0 mmol/L, or medication to control diabetes), and renal failure (serum creatinine level ≥ 2.0 mg/dL). The presence of coronary artery disease was indicated by a previous myocardial infarction, previous coronary intervention, or present stable angina pectoris. Other cardiovascular risk factors scored in all patients included a history of CVA or TIA, age over 70 years, chronic heart failure, and chronic obstructive pulmonary disease (defined as a FEV1 < 70% of age and gender predictive value or medication use).

At our institution troponin T levels are routinely measured in patients undergoing major vascular surgery on postoperative day 1, 3, 7, 30 and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Routinely ECGs were recorded preoperatively and on day 1, 3, 7, and 30 after surgery. Troponin T level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany).

### Measurement of plasma NT–pro-BNP

A median of 27 days (interquartile range 3–83 days) prior to the surgical procedure NT-proBNP level was measured. The samples were centrifuged, and plasma was frozen at –80°C until assay. NT–pro-BNP was measured with an electrochemoluminescence immunoassay kit (Elecsys 2010, Roche Diagnostics GmbH, Mannheim, Germany). The method is a "sandwich"-type quantitative immunoassay based on polyclonal antibodies against epitopes in the N-terminal part of pro-BNP. The lower detection limit was 5 pg/ml. Intra-assay coefficients of variance at 271 and 6,436 pg/ml were 1.9% and 0.9%, respectively. Assays were performed by a laboratory technician blinded to the patients' clinical data.

### Outcome measures

Perioperative endpoints were myocardial damage, defined by elevated troponin T levels, non-fatal myocardial infarction and cardiovascular death within 30 days after surgery. The long-term endpoint was all-cause mortality. Myocardial infarction was defined as the presence of 2 out of the following 3 criteria: (1) Characteristic ischemic symptoms lasting > 20 minutes, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists > 24 hours, and (3) a positive troponin T, i.e. >0.10 ng/ml, or peak CK-MB >8% of an elevated total creatinine phosphokinase with characteristic rise and fall[8]. Cardiovascular death was defined as any death with a cardiovascular cause, including those deaths following a cardiac procedure, cardiac arrest, myocardial infarction, pulmonary embolus, stroke, or sudden deaths not ascribed to other causes. Survival status was ascertained by contacting the civil service registry.



### Statistical analysis

Continuous data with a normal distribution are expressed as means and were compared using Student's t test. Continuous data with a significant skewed distribution are expressed as medians and were compared using the Mann-Whitney U-statistic test. Categorical data are presented as percentage frequencies, and differences between proportions were compared using the chi-square test. Univariate logistic regression analysis was used to evaluate the association of baseline characteristics and NT–pro-BNP values with postoperative outcome. Furthermore, the association of cardiovascular risk factors, site and type of surgery and NT-proBNP levels with perioperative cardiovascular complications and all-cause death as well as long-term mortality was assessed via multivariate Cox regression analysis including interaction terms. All covariables associated with perioperative cardiac complications or all-cause mortality ($p < 0.20$ in univariate analysis) were included in the multivariate model. 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 perioperative and long-term endpoint, we used the cardiac risk score as described by Boersma et al.[4] This cardiac risk score identifies 7 predictors (age > 70 years, history of myocardial infarction, congestive heart failure, angina pectoris, cerebrovascular disease, diabetes mellitus, and renal failure) of major cardiac complications. Based on these risk factors patients can be categorized as low risk (no risk factors), intermediate risk (1 or 2 risk factors) and high risk (≥ 3 risk factors). Receiver operating characteristic curve analysis was performed to calculate AUC values and the optimal NT-proBNP cut-off value for both perioperative

cardiac events and long-term mortality. The performance of risk models can be determined by the AUC, which indicates how well a model rank orders patients with respect to their outcomes, where 0.5 indicates no predictive value and 1.0 indicates perfect performance. The limit of statistical significance was set at p = 0.05 (two-sided). All analysis was performed using the statistical software SPSS for Windows 12.1 (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

### Patient characteristics

A total of 400 patients undergoing abdominal aortic aneurysm repair (n=159), lower limb arterial reconstructions (n=130) or carotid artery surgery (n=111) were included in the study. Endovascular procedures comprised 30% of the studied surgical procedures; 68 endovascular aneurysm repair and 52 carotid artery stenting. The majority of patients were males (76%) and the mean age was 67.5 ± 10.6 years. According to cardiac risk score by Boersma et al. 14% of patients had low cardiac risk, 60% intermediate cardiac risk and 26% high cardiac risk. Baseline clinical characteristics are presented in TABLE 10.1.

The median NT-proBNP level was 206 pg/ml, interquartile range 80–548 pg/ml. Median levels of NT-proBNP increased with preoperative cardiac risk according to clinical risk factors[4]; low risk 95 pg/ml,

**TABLE 10.1** Baseline characteristics.

| | All patients (N =400) |
|---|---|
| Men – no. (%) | 305 (76) |
| Age – mean ± SD | 67.5 ± 11 |
| Risk factors | |
| Previous angina pectoris – no. (%) | 101 (25) |
| Previous myocardial infarction – no. (%) | 118 (30) |
| Previous heart failure – no. (%) | 18 (5) |
| Previous CABG or PTCA – no. (%) | 91 (23) |
| CVA or TIA – no. (%) | 156 (9) |
| Diabetes Mellitus – no. (%) | 88 (23) |
| Renal failure – no. (%) | 33 (8) |
| Systemic hypertension – no. (%) | 189 (47) |
| COPD – no. (%) | 140 (35) |
| Clinical cardiac risk | |
| Low – no. (%) | 54 (14) |
| Intermediate – no. (%) | 241 (60) |
| High – no. (%) | 105 (26) |
| Site of surgery | |
| Carotid artery – no. (%) | 111 (28) |
| Abdominal aortic – no. (%) | 159 (40) |
| Lower extremity – no. (%) | 130 (32) |
| Type of surgery | |
| Endovascular treatment – no. (%) | 120 (30) |
| Open surgery – no. (%) | 280 (70) |

CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; CVA = cerebrovascular accident; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

**TABLE 10.2** Association between risk factors and median NT-proBNP levels (pg/ml).

| | Yes | No | P-value |
|---|---|---|---|
| Men | 204 | 213 | 0.49 |
| Age (per year increase) | | | 0.18 |
| **Risk factors** | | | |
| Previous angina pectoris | 326 | 170 | 0.04 |
| Previous myocardial infarction | 329 | 162 | 0.006 |
| Previous heart failure | 1064 | 192 | <0.001 |
| CVA or TIA | 182 | 210 | 0.17 |
| Diabetes Mellitus | 211 | 198 | 0.27 |
| Renal failure | 1484 | 180 | <0.001 |
| **Clinical cardiac risk** | | | |
| Low | 95 | | Reference |
| Intermediate | 184 | | 0.11 |
| High | 440 | | 0.01 |
| **Site of surgery** | | | |
| Carotid artery | 119 | | Reference |
| Abdominal aortic | 226 | | 0.09 |
| Lower extremity | 283 | | 0.004 |
| **Type of surgery** | | | |
| Endovascular treatment | 188 | | 0.71 |
| Open surgery | 213 | | |

CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; CVA = cerebrovascular accident; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease



intermediate risk 184 pg/ml, and high risk 440 pg/ml. Patients undergoing aortic aneurysm repair or lower extremity arterial reconstructions had a significantly higher median NT-proBNP level compared to patients scheduled for carotid artery surgery; respectively 226 pg/ml, 283 pg/ml, and 119 pg/ml. Other variables associated with NT-proBNP are shown in TABLE 10.2.

## Perioperative outcome

A total of 79 patients (20%) experienced troponin release, indicative for myocardial ischemia. Of these 19 (5%) patients had also either ischemic symptoms or ECG changes suggestive for infarction and were thus classified as patients with myocardial infarction. At total of 12 (3.0%) patients died within 30 days after surgery of which 8 (2.0%) died due to a cardiovascular cause.

Patients undergoing aortic aneurysm repair or lower extremity arterial revascularization had a significantly higher incidence of myocardial damage as compared to patients undergoing carotid artery surgery (30%, 21% and 4% respectively, $p < 0.001$). Also preoperative risk score based on clinical risk factors alone was a good predictor for postoperative myocardial damage; the incidence of myocardial ischemia was 7% for patients deemed to be at low risk, 15% for patients at intermediate risk, and 37% for patients at high risk ($p < 0.001$). Tertiles of NT-proBNP were also strong predictors of perioperative events, in particular patients in the highest tertile had a high risk for perioperative events; lowest tertile 6%, intermediate tertile 12% and highest tertile 42% ($p < 0.001$) (FIGURE 10.1A and 10.1B). Other univariate predictors of perioperative cardiac events are shown in TABLE 10.3.

Using ROC curve analysis an optimal cut-off value for NT-proBNP for the prediction of perioperative cardiac events was established, i.e. 350 pg/ml (FIGURE 10.2). Using this cut-off value, in univariate

**TABLE 10.3** Predictors of perioperative cardiac damage.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | **P-value** | **OR** | **95% CI** | **P-value** |
| Clinical risk score | | | | | | |
| Low cardiac risk | 1 | - | | 1 | - | |
| Intermediate cardiac risk | 3.2 | 0.95 – 10.8 | 0.06 | 4.5 | 0.94 – 21.7 | 0.06 |
| High cardiac risk | 7.0 | 2.32 – 20.9 | 0.001 | 14.9 | 2.9 – 34.3 | <0.001 |
| Site of surgery | | | | | | |
| Carotid | 1 | - | | 1 | - | |
| Lower extremity | 7.5 | 2.53 – 22.3 | <0.001 | 4.3 | 1.1 – 17.4 | 0.04 |
| Abdominal aortic | 10.9 | 3.80 – 31.5 | <0.001 | 12.8 | 3.4 – 48.0 | <0.001 |
| Type of surgery | | | | | | |
| Open | 1 | - | | 1 | - | |
| Endovascular | 0.3 | 0.12 – 0.52 | <0.001 | 0.11 | 0.04 – 0.30 | <0.001 |
| NT-proBNP | | | | | | |
| ≤ 350 pg/l | 1 | - | | 1 | - | |
| > 350 pg/l | 7.0 | 3.97 – 12.3 | <0.001 | 4.7 | 2.1 – 10.5 | <0.001 |
| Male | 2.1 | 1.04 – 4.13 | 0.04 | 1.65 | 0.57 – 4.8 | 0.36 |
| COPD | 2.8 | 1.62 – 4.56 | <0.001 | 1.4 | 0.60 – 3.4 | 0.42 |

Odds ratio (OR), 95% confidence intervals (CI) and p-values in univariate analysis by means of the Log-rank test and multivariate analysis by means of logistic regression analysis; COPD = Chronic Obstructive Pulmonary Disease

analysis patients with levels of NT-proBNP above this value were at 7-fold increased risk for perioperative cardiac events (95% CI 4.0–12.3) (FIGURE 10.3). Also in multivariate analysis, using interaction terms and adjusting for clinical cardiac risk factors, site and type of surgery, patients with a NT-proBNP level > 350 pg/ml were at a significant 4.7 fold increased risk (95% CI 2.1–10.5, p<0.001). Importantly, also when adding the different clinical risk factors separately in the multivariate model, i.e. not as a clinical risk index, an elevated NT-proBNP remained independently associated with an increased risk for perioperative myocardial damage (adjusted OR 5.8; 95% CI 2.9–11.8).

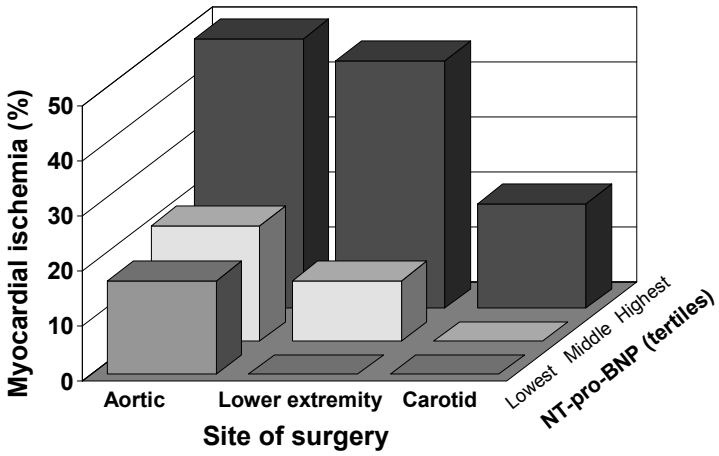


**FIGURE 10.1A** Preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in tertiles and the relation with site of surgery and perioperative myocardial damage.

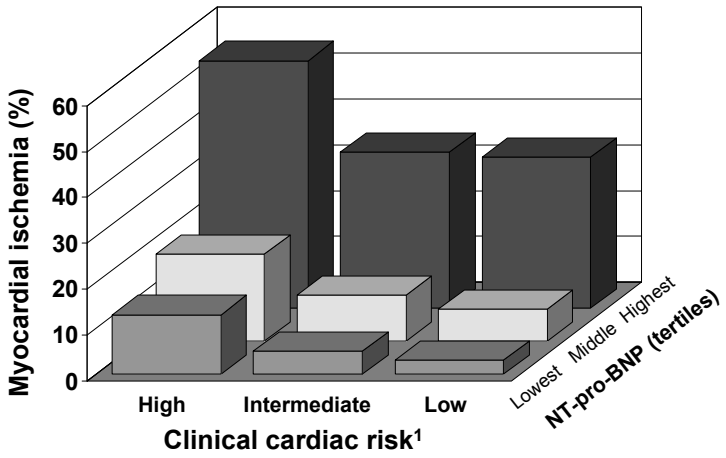


**FIGURE 10.1B** Preoperative NT-proBNP levels in tertiles and the relation with clinical cardiac risk and perioperative myocardial damage.
NT-proBNP tertiles in pg/mL: Lowest, 5-119; middle, 122-383; highest, >383.

ROC analysis showed an area-under-the-curve (AUC) of 0.66 for the clinical cardiac risk score alone, but this AUC improved to 0.81 if site and type of surgery were added to the model. If NT-proBNP (cut-off 350 pg/ml) was added to the model as well, the AUC further improved to 0.86.



## Long-term survival

During a median follow-up of 29 months (interquartile range 20–36 months) 58 patients died. In univariate analysis patients considered to be at low risk according to the risk score by Boersma indeed had a better survival compared to those at intermediate or high risk (HR 4.4, 95% CI 1.1–18.2, and HR 7.8, 95% CI 1.9–32.9 respectively, TABLE 10.4). Also, patients undergoing carotid artery procedures

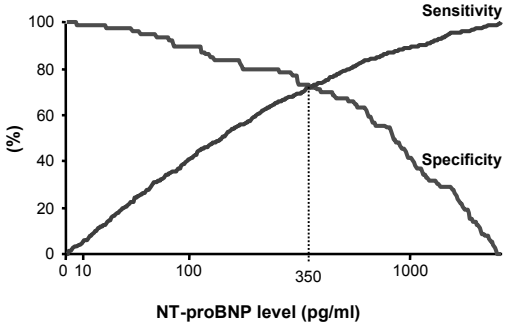


**FIGURE 10.2** Assessment of the optimal cutoff value (i.e. 350 pg/mL) of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for the prediction of perioperative myocardial damage.

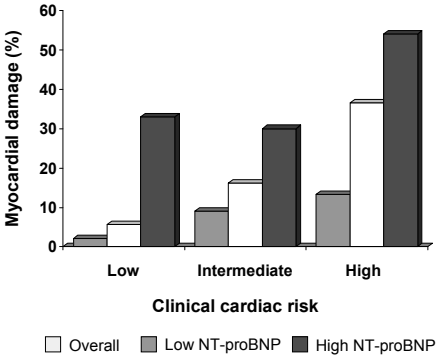


**FIGURE 10.3** Value of N-terminal pro-B-type natriuretic peptide (NT-proBNP), divided in low (<350 pg/mL, light bars) and high (>350 pg/mL, dark bars), for perioperative cardiac risk assessment in addition to a clinical cardiac risk score.

**TABLE 10.4** Predictors of long-term mortality.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | **P-value** | **HR** | **95% CI** | **P-value** |
| Clinical risk score | | | | | | |
| Low cardiac risk | 1 | - | | 1 | - | |
| Intermediate cardiac risk | 4.4 | 1.05 – 18.2 | 0.042 | 5.0 | 1.2 – 21.1 | 0.03 |
| High cardiac risk | 7.8 | 1.85 – 32.8 | 0.005 | 7.8 | 1.8 – 34.5 | 0.007 |
| Site of surgery | | | | | | |
| Carotid | 1 | - | | 1 | - | |
| Lower extremity | 7.0 | 2.48 – 19.8 | <0.001 | 6.7 | 2.2 – 19.8 | 0.001 |
| Abdominal aortic | 4.7 | 1.66 – 13.5 | 0.004 | 4.4 | 1.5 -12.5 | 0.007 |
| Type of surgery | | | | | | |
| Open | 1 | - | | 1 | - | |
| Endovascular | 0.6 | 0.34 – 1.1 | 0.09 | 0.8 | 0.4 – 1.6 | 0.58 |
| NT-proBNP | | | | | | |
| ≤ 350 pg/l | 1 | - | | 1 | - | |
| > 350 pg/l | 3.2 | 1.93 – 5.3 | <0.001 | 1.9 | 1.1 – 3.2 | 0.02 |
| Male | 1.68 | 0.85 – 3.3 | 0.13 | 1.6 | 0.8 – 3.2 | 0.17 |
| Hypertension | 0.91 | 0.56 – 1.5 | 0.71 | | | |
| COPD | 1.33 | 0.81 – 2.2 | 0.26 | | | |

Hazard ratio (HR), 95% confidence intervals (CI) and p-values in univariate analysis by means of the Log-rank test and multivariate analysis by means of Cox regression analysis; COPD = Chronic Obstructive Pulmonary Disease

were at 4-6 fold lower risk compared to patients who underwent abdominal aortic or peripheral bypass surgery.

Similar to the perioperative setting, using ROC curve analysis an optimal cut-off value for NT-proBNP for the prediction of long-term survival was established. Interestingly the optimal value was similar to that in the perioperative setting, i.e. 350 pg/ml. Using this cut-off value, in univariate analysis patients with levels of NT-proBNP above this value were at 3-fold increased risk for long-term mortality (95% CI 1.9–5.3). Also in multivariate analysis, adjusting for clinical risk factors, site and type of surgery patients with a NT-proBNP level > 350 pg/ml were at a significant 1.9 fold increased risk (95% CI 1.1–3.2) for all-cause mortality.

## DISCUSSION

The current study shows that NT-proBNP is a highly promising tool for perioperative and long-term cardiac risk stratification in patients undergoing vascular surgery.

The reasons why NT-proBNP seems to be so effective in perioperative risk stratification are multifactorial and are related to the cause of NT-proBNP release. Previous studies revealed that ventricular wall stress modulates BNP gene expression in cardiomyocytes[9]. Factors that induce ventricular wall stress are numerous and several are known to be related to outcome in patients undergoing vascular surgery. In cardiology literature NT-proBNP had emerged as an independent predictor of clinical outcome in patients with heart failure[10-12]. Several studies have shown that heart failure also is a strong predictor for both perioperative and long-term cardiac outcome in patients scheduled for vascular surgery[4,13]. Another important factor related to both NT-proBNP level and postoperative outcome

is the presence of coronary artery disease detected during non-invasive stress testing. Importantly there is a close correlation between the level of NT-proBNP and the presence and extent of stress inducible myocardial ischemia non-invasive stress testing. In the PROMPT- TIMI 35 study Sabatine et al. described a population of 112 patients undergoing nuclear perfusion imaging[14]. In patients with mild or moderate stress inducible myocardial ischemia median levels of NT-proBNP were higher compared to patients without stress inducible myocardial ischemia (158 an 302 pg/ml versus 109 pg/ml respectively). Since stress inducible myocardial ischemia is a strong predictor of postoperative cardiac events it is not surprising that in the present study patients with high NT-proBNP were at increased risk for perioperative events.

Besides heart failure and myocardial ischemia there are several other factors, both cardiac and non-cardiac, that might influence NT-proBNP levels and postoperative outcome such as aortic valve stenosis, renal dysfunction, left ventricular hypertrophy, pulmonary hypertension, COPD and BMI[15,16].

The results of the registry of the DECREASE I trial showed that non-invasive stress testing indeed has important additional prognostic implications on top of clinical cardiac risk factors only in patients undergoing vascular surgery[4]. However, as shown in the randomized DECREASE II trial, in patients on tight heart rate control preoperative non-invasive stress testing in patients at intermediate cardiac risk, i.e. 1 or 2 clinical risk factors, has no additional value and postpones the surgical procedure unnecessary[17]. However, also in patients with 1 or 2 risk factors only, there is a small group of approximately 10% with extensive stress inducible myocardial ischemia with severe prognostic implications[17]. Though not cost-effective to detect these patients with non-invasive stress testing, a relative simple and cheap NT-proBNP measurement might guide us to this small, but very high-risk, proportion of patients. On the other hand in patients deemed to be at high cardiac risk based on clinical risk factors, i.e. ≥ 3 risk factors, approximately 60% does not have stress inducible myocardial ischemia[4]. Theoretically these patients undergo unnecessary extensive cardiac evaluation. The current study showed that NT-proBNP levels, divided in low (< 350 pg/ml) and high (> 350 pg/ml), effectively stratifies patients into low and high risk independent of the clinical cardiac risk score. Hence NT-proBNP might be useful as an initial screening tool to identify those that require more extensive preoperative cardiac work-up.



The findings of the current study are in line with previous studies at other institutions. Yeh et al. reported on a group of 190 patients undergoing elective non-cardiac surgery requiring general anesthesia. They found an optimal cut-off value of 450 pg/ml for adverse perioperative cardiac events. Several other studies have been performed using BNP instead of NT-proBNP. Importantly the results also consistently showed a predictive value of BNP similar to the studies with NT-proBNP[5,6,18]. In the present study it was confirmed that not only in relatively high risk patients undergoing high risk vascular surgery NT-proBNP might be a useful screening tool but also in a general population of vascular surgery patients undergoing all types of vascular procedures.

In this respect it is noteworthy that among patients scheduled for carotid artery surgery only those with a NT-proBNP above 350 pg/ml experienced cardiac troponin T release, suggestive for myocardial necrosis. In general carotid procedures are associated with a substantial lower cardiac risk as compared to lower extremity arterial reconstructions and AAA repair. Therefore noninvasive stress testing in this group of patients is usually not performed. However with the short-term results of the SAPPHIRE trial[19] in mind, identification of patients at increased cardiac risk is preferable, also in this patient population, to make a balanced decision to treat patients either with carotid endarterectomy or carotid stenting. NT-proBNP might be useful for the identification of these patients.

It should be noted that the current available studies on the use of NT-proBNP are relatively small and the potential pitfalls of NT-proBNP, such as the influence of renal function, COPD and BMI must be clarified. Recently we described the impact of renal function on the usefulness of NT-proBNP. In particular in patients with severe renal dysfunction, i.e. GFR < 30 ml/min, the reliability of NT-proBNP as a screening marker was questioned[20].

Furthermore, the positive finding in this study in favor of NT-proBNP as a preoperative risk marker should not be overestimated. One must realize that NT-proBNP covers only parts of the pathways of perioperative myocardial infarctions. Although the pathophysiology of perioperative myocardial infarction is not entirely clear, plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is implicated in a similar manner to that causing MI in the non-operative setting. Autopsies have shown that coronary plaque rupture and thrombus formation occur in 50% of all fatal MIs, whereas a sustained oxygen supply-demand mismatch is responsible for the other half. Due to the nature of the release of this peptide it might be expected that it will only cover the mechanism of sustained myocardial oxygen demand-supply mismatch adequately. This is also reflected by the sensitivity and specificity of approximately 80% found in the current study. The finding that despite these limitations NT-proBNP still seems to be a good cardiac risk marker might be explained by the presence of both significant stenotic and unstable non-significant stenotic lesions in a diffusely diseased coronary tree.

In conclusion, NT-proBNP is a promising marker in the setting of preoperative cardiac risk stratification. An elevated NT-proBNP should be seen as an alert for a possible increased risk for perioperative events and should trigger the treating physician to find the cause responsible for this elevation. Though the initial results of NT-proBNP as a screening tool for perioperative and long-term cardiac risk assessment in patients undergoing vascular surgery are promising further, larger studies are required to establish the usefulness and limitations more precisely. One of the ongoing studies in this respect is the DECREASE VI study (ISRCTN 48518771) in which 1800 patients will participate and is scheduled to be completed in 2010.

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# Part II

## Perioperative Risk Reduction

# Chapter 11

## Fluvastatin and bisoprolol for the reduction of perioperative cardiac mortality and morbidity in high-risk patients undergoing non-cardiac surgery: rationale and design of the DECREASE-IV study

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*Am Heart J. 2004;148(6):1047-52.*

## INTRODUCTION

About 3.8% of the population of the Netherlands will undergo non-cardiac surgery annually[1]. Patients undergoing major non-cardiac surgery are at significant risk of cardiovascular morbidity and mortality. Although the perioperative event rate has declined over the past 30 years, 30-day cardiovascular mortality in major non-cardiac surgery remains as high as 3% to 6%[2,3]. Myocardial infarction (MI) is the most frequent fatal complication in this respect, accounting for 10-40% of postoperative fatalities[4,5]. Although the understanding of the pathophysiology is not entirely clear, evidence exists that coronary plaque rupture, which leads to thrombus formation and subsequent vessel occlusion, is the predominant causative mechanism behind such complications, similar to MIs occurring in the nonoperative setting[6-9]. However, a MI may also be induced by perioperative myocardial oxygen demand / supply mismatch[10]. Factors involved include surgical stress, tachycardia, hypertension, and pain. It should be noticed that these factors might also be directly involved in the process of coronary plaque instability and subsequent rupture. The incidence of vasospasm, anemia, and hypoxia may worsen these conditions further.

Plaque instability and oxygen demand / supply mismatch leading to myocardial infarction might be positively influenced by drugs acting on these mechanisms. To assess the effect of pharmaceutical strategies (beta-blockers, statins or both) to prevent perioperative cardiac complications, a large prospective, randomized trial has been set up: the DECREASE-IV study.

### Preoperative cardiovascular risk assessment

Numerous investigators have described the relationship between patient characteristics and the risk of adverse cardiovascular outcome[10-17]. The multivariable cardiovascular risk indices developed by Goldman, Detsky and Eagle are most frequently quoted in perioperative care management[10,14,17]. Nowadays, the clinical importance of perioperative cardiovascular complications is well recognized. However, most studies evaluating cardiovascular risk in a general surgical population date from the 1970s and 1980s. These 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[12,17]. Consequently, important risk factors may have been missed, due to a lack of statistical power. More recent studies have focused mainly on patients undergoing specific types of surgery, such as thoracic, orthopedic, or vascular[15,18,19]. Furthermore, there have been significant advances in perioperative care in the last decades. For instance, the identification of patients at risk using perfusion scintigraphy or stress echo has become widely available. The impact of these developments on the incidence and lethality of cardiovascular complications and the predictive value of established cardiac risk factors is yet unknown.

### Implications of perioperative cardiovascular risk reduction

Perioperative cardiovascular risk reduction could potentially save many lives. In the Netherlands with 16 million inhabitants for example, every year approximately 800.000 non-cardiac surgical procedures are performed. In the last decade the number of postoperative deaths in the Netherlands was stable at around 15,200 annually[1]. Considering that approximately one third of postoperative fatalities are ascribed to cardiac complications, yearly 5,000 surgical patients die of perioperative cardiac complications in the Netherlands. Hence, a 10% reduction in perioperative cardiac mortality will save approximately 500 lives annually (FIGURE 11.1).

However, studies that successfully aimed at cardiovascular risk identification were not succeeded by trials that focused at systematic risk reduction. Hence, effective cardioprotective treatment strategies

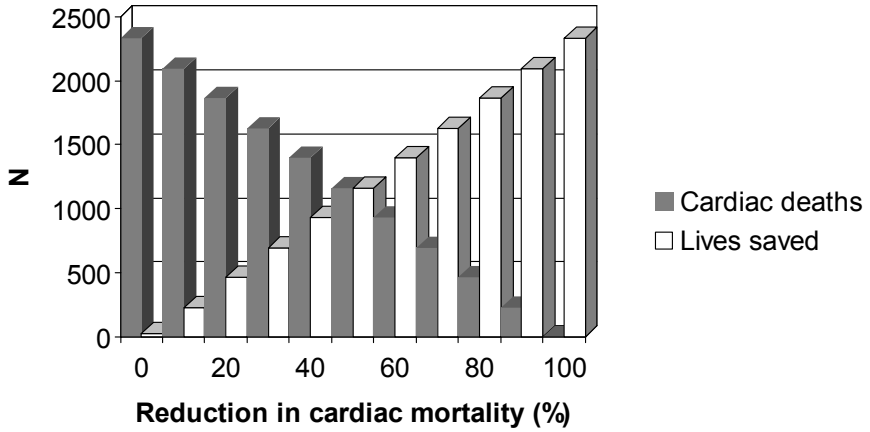


**FIGURE 11.1** Lives saved per year in the Netherlands by reducing the perioperative cardiac risk.

remain undefined for substantial portions of the non-cardiac surgery population. Especially, the optimal cardiovascular risk reduction strategy in patients with moderate to high risk (i.e. risk of cardiovascular mortality more than 1%) is yet unknown. Ideally, cardiac risk factors should identify those patients who experience an increased risk of perioperative myocardial ischemia. In previous studies[15,19-22], it is suggested that for patients at low or intermediate risk (i.e. two or less risk factors), effective systemic pharmacological protection reduces perioperative cardiovascular risk to an acceptable level. Patients at high risk should undergo exercise or pharmacological testing to exclude extensive myocardial ischemia. If a patient at high risk has no or only mild ischemia during stress testing, pharmacological protection is probably sufficient. On the other hand, patients with excessive myocardial ischemia suggestive of left main or three-vessel disease should probably undergo coronary revascularization before being operated.



### Perioperative risk reduction by beta-blockers

Beta-blockers form a class of agents with great cardioprotective potential. Beta-blockers will decrease myocardial oxygen demand by reduction of heart rate and myocardial contractility[23,24]. Furthermore, beta-blockers reduce the adrenergic activity, which results in reduced levels of free fatty acid, thus causing a shift in the myocardial metabolism towards glucose uptake[25].

Several studies addressed the relation between beta-blocker use and perioperative myocardial ischemia. Stone and co-authors studied the effect of low-dose beta-blockers (labetolol, atenolol, or oxprenolol) in 128 hypertensive patients undergoing non-cardiac surgery[26]. Patients who received beta-blockers had a lower incidence of myocardial ischemia, as diagnosed using continuous 12-lead ECG monitoring, than patients without beta-blocker treatment (2.2% versus 28.0% events; p-value <0.001). Wallace and co-authors confirmed these findings in a data set of 200 patients who either had established CAD, or had increased risk of CAD, according to clinical characteristics and age[27]. The incidence of myocardial ischemia was significantly lower among patients randomized to atenolol as compared to placebo (24% versus 39% events; p-value 0.03).

Mangano and co-authors conducted the first randomized controlled study evaluating the cardioprotective effect of beta-blockers in patients undergoing non-cardiac surgery[28]. Two hundred patients undergoing vascular surgery were randomized to atenolol treatment or placebo. No difference was observed in perioperative mortality between the two treatment arms. However, atenolol was

associated with significant lower mortality during two-year follow-up. The lack of a perioperative cardioprotective effect of atenolol in this study was probably related to the fact that unselected, low risk patients were included. The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE-I) study[29], clearly demonstrated a cardioprotective effect of bisoprolol, a selective beta-blocker, in high-risk patients undergoing major vascular surgery. Bisoprolol was associated with a significant reduction in composite endpoint of cardiovascular death and myocardial infarction during the 30-day perioperative phase (3.3% versus 34.0% events; p-value <0.01).

Although the results are promising, the use of beta-blockers in patients at risk for CAD is not yet common practice. In a recent study, Schmidt et al. showed that in 158 patients undergoing major non-cardiac surgery only 27% of eligible patients did receive beta-blockers[30]. Similar results were shown in a survey of Canadian anesthesiologists[31].

### Perioperative risk reduction by statins

Several investigations have demonstrated that 3-hydroxy-3-methylglutaril coenzyme A reductase inhibitors (statins) have favorable actions on atherosclerosis and vascular properties that go beyond those attributed to cholesterol lowering[32-34]. Statins may attenuate coronary artery plaque inflammation, induce plaque stability in addition to antithrombogenic, antiproliferative and leukocyte-adhesion inhibiting effects [32,35-42]. Due to these properties, statins may help stabilize vulnerable coronary plaques, thereby prevent plaque rupture with subsequent myocardial ischemia and myocardial damage. In a recently conducted case-control study, Poldermans et al. demonstrated that statin use among patients undergoing major vascular surgery was associated with a four-fold risk reduction in perioperative all-cause mortality (multivariably adjusted odds ratio 0.22 and 95% confidence interval 0.10 to 0.47)[43]. This result was consistent in subgroups of patients according to the type of surgery, cardiovascular risk factors, and beta-blocker use. Similarly, Durazzo et al., reported a 68% reduction in the incidence of adverse cardiovascular events during 6-months follow-up among vascular surgery patients who were randomly assigned to atorvastatin compared with placebo (8.3% versus 26.0% events; p-value <0.01)[44]. Recently Lindenauer et al. confirmed these results in another retrospective study. In a study of 780,591 patients undergoing major non-cardiac surgery 9.9% of patients were on statin therapy[45]. Statin therapy was associated with a risk reduction of postoperative death of 40%.

## THE DECREASE-IV TRIAL

*Study population*

Patients who are (1) aged 40 years or older, (2) scheduled for elective non-cardiac surgery and (3) have an estimated risk for cardiovascular death of more than 1%, will be enrolled in the DECREASE-IV trial. Exclusion criteria for this trial are: the use of beta-blockers; a contraindication for beta-blocker use; the use of statins prior to randomization; a contraindication for statin use; unstable coronary heart disease, evidence of 3-vessel disease or left main disease; elevated cholesterol according to the national cholesterol consensus; emergency surgery; inability or unwillingness to provide written informed consent; and previous participation in this same trial.

*Study objectives*

The general objective of the DECREASE-IV trial is to assess the clinical efficacy of beta-blocker therapy, statin therapy and combination therapy with beta-blockers and statins in patients undergoing major non-cardiac surgery.

*Study design*

The overall study design of the DECREASE-IV trial is shown in the flowchart (FIGURE 11.2). During a period of 4 years all patients planned for elective surgery at Erasmus Medical Centre Rotterdam will be screened at the preoperative screening visit according to a newly developed cardiovascular

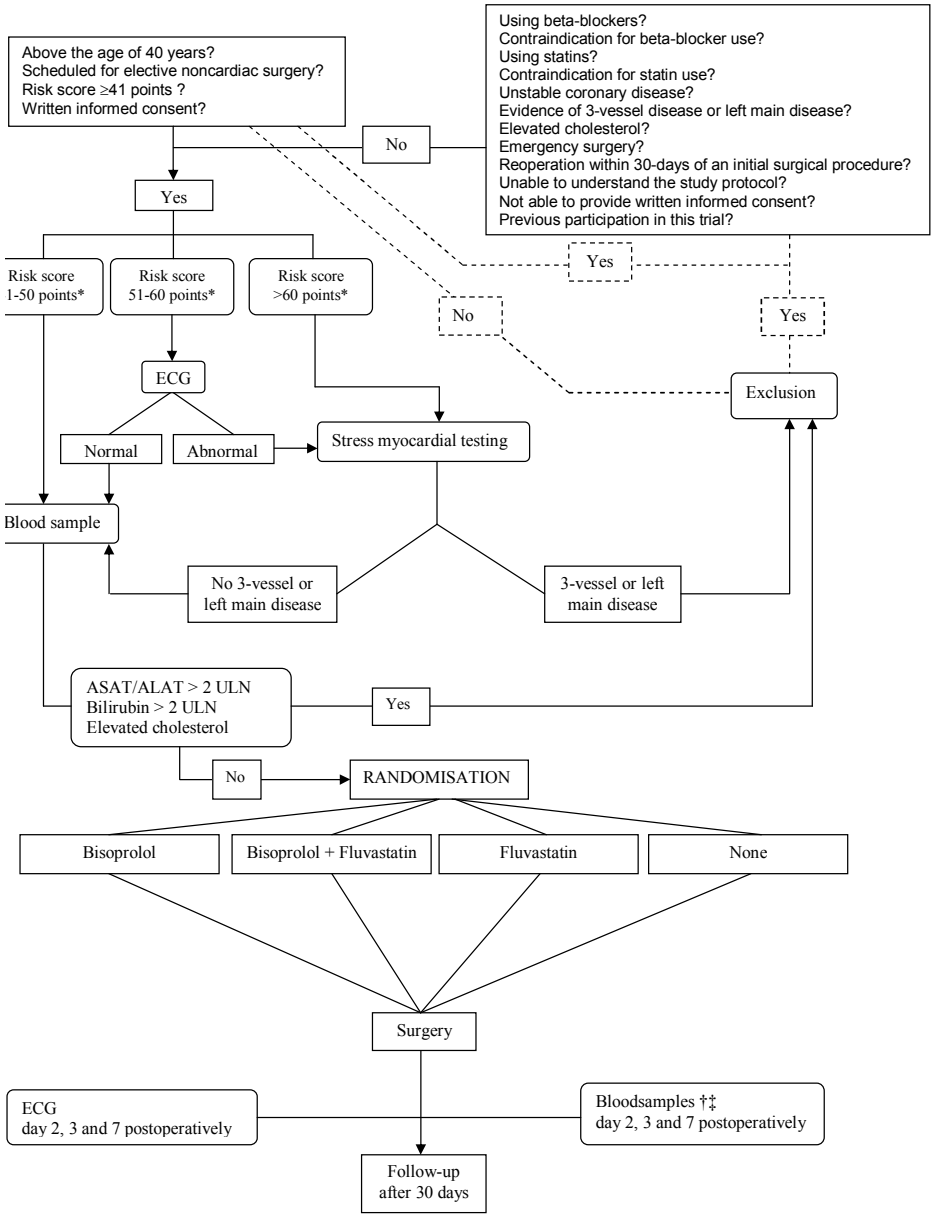


**FIGURE 11.2** Flowchart of the DECREASE-IV trial.
ASAT, Aspartate transaminase; ALAT, alanine aminotransferase; ULN, upper Limit of Normal.*Boersma et al.[46] †Liver enzymes; ‡Heart enzymes.

risk-evaluation scheme[46]. A computerized version of this scheme will be applied, which enables an automated check on all in- and exclusion criteria. According to the outcome of the risk-evaluation scheme, patients with a chance of more than 2% on perioperative cardiovascular death will undergo further cardiac evaluation, including ECG and/or stress myocardial testing. Patients with extensive myocardial ischemia are excluded. Participants will then be randomized according to an open-label, factorial design between (1) beta-blocker therapy (bisoprolol), (2) statin (fluvastatin), (3) combination of beta-blockers and statins (bisoprolol and fluvastatin) and (4) neither beta-blockers nor statins (control group). Study medication is started within 0-30 days prior to surgery and will be continued until 30 days after surgery.

The starting dose of bisoprolol is 2.5 mg orally per day, if resting heart rate >50 bpm. During hospitalization the resting heart rate will be evaluated on a daily basis and the bisoprolol regimen might be modified +/- 1.25 or 2.5 mg per day, i.e. dosages of 1.25, 2.5, 3.75, 5.0, 7.5 and 10 mg, in order to obtain a target heart rate of 50-70 bpm. Patients who are not able to take bisoprolol orally in the perioperative period will receive IV metoprolol until the patient is able to switch back to oral medication. Bisoprolol administration will be temporarily stopped if resting heart rate is < 50 bpm or systolic blood pressure is < 100 mmHg, or a patient is suspected to be in congestive heart failure, bronchospasm or develops first degree AV-block with a PR interval > 0.30 seconds or second or third degree of AV block.

Patients assigned to the statin or combined group will start with fluvastatin 80 XL daily tablets before surgery. To avoid problems with statin intake and low plasma levels shortly after the operation, the "slow-release" statin Fluvastatin 80 XL has been chosen. Patients not able to take fluvastatin orally will take fluvastatin medication by naso-gastric tube. If oral or naso-gastric administration is impossible, fluvastatin medication is skipped, as no IV formulations of statins are available.

To assess perioperative cardiac events, an ECG will be made at days 1, 3 and 7 postoperatively. On these same days blood samples will be taken to assess heart- and liver enzymes. Patients will be evaluated at follow-up visits 30 days and 1 year after surgery.

The primary efficacy objective is to determine the impact of perioperative administration of bisoprolol, fluvastatin and their combination on the incidence of 30-day cardiovascular events, i.e. the composite of cardiac death, and non fatal MI (TABLE 11.1), in moderate and high risk patients undergoing non-cardiac surgery. MI is based on the definition of the consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition

**TABLE 11.1** Definitions of primary end points.

| | |
|---|---|
| Cardiovascular death | Any death with a cardiovascular cause, including those deaths following a cardiac procedure, cardiac arrest, myocardial infarction, pulmonary embolus, stroke, hemorrhage, or deaths due to unknown causes. |
| Non fatal myocardial infarction | Requires 2 of the following:<br>(1) Characteristic ischemic symptoms (i.e. chest pain, shortness of breath, etc) lasting longer than 20 minutes;<br>(2) ECG changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists for at least 24 hours;<br>(3) A positive troponin, i.e. >0.10 ng/ml, or peak CK-MB ≥8% of an elevated total CK with characteristic rise and fall. |

of myocardial infarction[47]. Secondary efficacy objectives of the DECREASE-IV study are to determine the impact of perioperative administration of bisoprolol and/or fluvastatin on (1) the incidence of total mortality, cardiovascular death, and nonfatal myocardial infarction during 1 year follow-up; (2) the length of hospital stay, and length of ICU/CCU stay; (3) the 30-day incidence of clinically significant cardiac arrhythmias and heart failure and the need for coronary revascularization procedures. Furthermore, the DECREASE-IV trial has five safety objectives, namely to determine the impact of the different treatments on: (1) the 30-day congestive heart failure; (2) the 30-day incidence of clinically significant bradycardia; (3) the 30-day incidence of clinically significant hypotension; (4) the 30-day incidence of clinically significant liver dysfunction and (5) the occurrence of myopathy.

*Data analysis*

The incidence of the primary outcome, 30-day cardiovascular events, in the control group is estimated to be 6.0%. A 30% relative risk reduction (odds ratio 0.7) associated with bisoprolol therapy as well as with fluvastatin therapy is anticipated. The combination of bisoprolol and fluvastatin is supposed to result in a 50% relative risk reduction (odds ratio 0.7*0.7=0.49) as compared to control therapy.

Based on these assumptions a sample size of 6 000 patients, with 1 500 patients in each group, is needed to detect the anticipated risk reduction of 30% with a power of 81%, $\alpha$=0.05 (two-sided). The power will be 97% to detect the anticipated 50% risk reduction associated with combination therapy. The intention to treat principle will guide all analyses. Time-to-the first occurrence of one of the components of the primary efficacy endpoint will be presented using the Kaplan-Meier estimator. The rate of occurrence of the primary endpoint between the randomized groups will be compared using the log-rank statistics. Employing the Cox proportional hazards model, the hazard ratio and its associated 95% confidence interval, will derive treatment effect. Univariable and multivariable analysis will be conducted. Secondary endpoints will be tabulated by treatment group. The rate of occurrence of each secondary endpoint will be compared using log-rank statistics. Length of hospital stay and length of IC/CCU stay will be compared using one-way analysis if variance or a non-parametric test. Multivariable Cox proportional hazards regression analyses will be performed to evaluate differential treatment effects with regard to subgroups (e.g. age, gender, duration of statin treatment, heart rate). Safety outcomes will be compared using the log-rank statistic.

The DECREASE-IV trial was designed as an investigator-initiated protocol from the clinical epidemiology unit of the department of cardiology at the Erasmus Medical Centre Rotterdam, the Netherlands. An independent Endpoint Adjudication Committee will meet on a monthly basis to review all patients that are operated during that month. An independent 4-member Data and Safety Monitoring Board has been established and will review unblinded safety data four times yearly and will advise the Steering Committee on continuation or termination of the trial in relation to safety aspects.

*What will the DECREASE-IV trial teach us?*

The DECREASE-IV trial has been designed to teach us critical new insights in the best pharmaceutical prevention of perioperative cardiovascular complications in surgical patients. This issue is of significant importance since cardiovascular complications are the main cause of death among patients undergoing non-cardiac surgery, accounting for an approximate death rate of 3-6% in moderate and high-risk patients. Apart from mortality, cardiovascular caused perioperative complications necessitate a prolonged hospital stay in a substantial number of patients. As a consequence, a positive finding of the DECREASE-IV trial will have a major beneficial effect on perioperative mortality, morbidity and costs. It would provide us a clear indication for the routine use of statins, beta-blockers or a combination of both in the perioperative period.

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# Chapter 12

## Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing non-cardiovascular surgery; a randomized controlled trial (DECREASE-IV)

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## ABSTRACT

**Background:** Beta-blockers and statins reduce perioperative cardiac events in high-risk patients undergoing vascular surgery by restoring the myocardial oxygen supply/demand balance and/or stabilizing coronary plaques. However their effects in intermediate risk patients remained ill-defined. This study evaluated the effectiveness and safety of beta-blockers and statins for the prevention of perioperative cardiovascular events in intermediate-risk patients undergoing non-cardiovascular surgery.

**Methods:** Prior to surgery (median 34 days), 1066 patients were assigned to bisoprolol, fluvastatin, combination treatment or control therapy. Intermediate-risk patients were defined by an estimated risk of perioperative cardiac death and myocardial infarction (MI) of 1-6%, using clinical data and type of surgery. Starting dose of bisoprolol was 2.5 mg daily, titrated to a perioperative heart rate of 50-70 beats per minute. Fluvastatin was prescribed in a fixed dose of 80 mg. The primary endpoint was the composite of 30-day cardiac death and MI.

**Results:** Patients randomized to bisoprolol (N=533) had a lower incidence of the endpoint than those randomized to bisoprolol-control (2.1% vs. 6.0% events; HR 0.34; 95% CI: 0.17-0.67; p=0.002). Patients randomized to fluvastatin experienced a lower incidence of the endpoint than those randomized to fluvastatin-control therapy (3.2% vs. 4.9% events; HR 0.65; 95% CI 0.35-1.10), but statistical significance was not reached (p=0.17).

**Conclusion:** Bisoprolol was associated with a significant reduction of 30-day cardiac complications, while fluvastatin showed a trend for improved outcome.

## INTRODUCTION

Annually approximately 40 million people in the European Union undergo non-cardiac surgery. Cardiac events are a major cause of perioperative morbidity and mortality in these patients, resulting in a mortality rate of 1%[1]. A myocardial infarction (MI) accounts for 10-40% of postoperative fatalities[2]. Both beta-blockers and statins reduce perioperative cardiac events in high-risk patients[3-6]. The pathophysiology of a fatal MI is complex. It can be related to myocardial oxygen demand/supply mismatch, due to perioperative surgical stress, tachycardia, hypertension, and pain[7]. Alternatively, coronary plaque instability and subsequent rupture may lead to infarction[8]. Drugs that influence plaque stability and myocardial oxygen balance may influence the incidence and severity of perioperative MI. Beta-blockers improve myocardial oxygenation by decreasing heart rate and myocardial contractility[9]. Additionally, by reducing mechanical and shear stresses, beta-blockers may also promote coronary plaque stability. Additionally, beta-blockers might have anti-inflammatory effects[10]. Statins aim at coronary plaque stabilization by decreasing lipids, lipid oxidation, inflammation, matrix metalloproteinase and cell death, and increasing tissue inhibitor of metalloproteinase and collagen[11]. Both therapies have been associated with improved outcome in high-risk surgery. However, the vast majority of patients scheduled for surgery are at low- and intermediate-risk. In this population, the effect of perioperative beta-blockers and statins remains undefined. Our primary goal was to assess the effectiveness and safety of beta-blockers, statins and their combination, on the incidence of perioperative cardiac death and myocardial infarction in intermediate-risk surgical patients undergoing non-cardiovascular surgery.

## METHODS

The DECREASE-IV study was a prospective, open-label, multicenter, randomized, controlled trial and was done in accordance with the Declaration of Helsinki. The protocol was approved by all hospital ethics committees. All patients gave written informed consent.

### Study population

The design of DECREASE-IV has been published previously and is registered under number ISRCTN47637497[12]. Briefly, patients aged ≥ 40 years, who were scheduled for elective non-cardiovascular surgery and had an estimated risk for a perioperative cardiovascular event between 1 and 6% were eligible. The risk-estimation was based on clinical characteristics and an electrocardiogram (ECG)[1]. Exclusion criteria for enrolment were: the use of or a contraindication for beta-blocker or statin use; emergency surgery; inability to provide written informed consent; and previous participation in this trial. The exclusion of patients on beta-blocker or statin therapy was based on ethical considerations, being unable to withhold the use of these medications in the presence of an existing indication.

### Treatment

A 2x2 factorial study design was used[13]. After signing informed consent, patients were randomized on a 1:1 ratio to receive beta-blocker therapy (bisoprolol, Merck KGaA, Darmstadt, Germany) or beta-blocker control. Patients were also randomized on a 1:1 ratio to receive statin therapy (fluvastatin XL, Novartis, Basel, Switzerland) or statin control. Hence, there were 4 treatment groups: bisoprolol alone, fluvastatin alone, both, or neither (double control). Randomization was applied by using a computer algorithm, and was stratified according to hospital. Study medication was started immediately after randomization, median 34 days prior to surgery, and continued until 30 days after surgery.

The starting dose of bisoprolol was 2.5 mg orally per day, if resting heart rate was >50 bpm. During hospitalization, resting heart rate was evaluated on a daily basis and drug dose was modified with steps of 1.25 or 2.5 mg per day, up to a maximum dose of 10 mg, aiming at a heart rate of 50-70 bpm. The use of an open-label design was therefore necessary in order to titrate the bisoprolol dose to the therapeutic heart rate. Patients unable to take bisoprolol orally received intravenous metoprolol until the patient was able to switch back to oral medication. Bisoprolol administration was temporarily withheld if any of the following developed: resting heart rate <50 bpm; systolic blood pressure <100 mmHg; heart failure; bronchospasm; PR interval >0.30 s; second or third degree AV block. Fluvastatin was prescribed in a fixed daily dose of 80 mg. The "slow-release" statin fluvastatin 80 XL was chosen, to overcome problems in those patients who could not take statins early after surgery orally. If patients used nasogastric feeding, standard fluvastatin therapy was administered. Perioperatively, patient treatment was left to the attending physician's discretion as needed, with no restrictions imposed.

### Endpoints

The primary efficacy endpoint was a composite of cardiac death and non-fatal MI until 30-days after surgery. MI was defined on the basis of cardiac troponins and ECG-measurements, which were systematically collected on days 1, 3 and 7 postoperatively and whenever clinically indicated. Nonfatal MI required any two of the following: (1) characteristic ischemic symptoms lasting > 20 minutes; (2) ECG changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists for at least 24 hours; (3) a positive troponin T measurement with characteristic rise and fall[14]. All deaths were classified as either cardiovascular or non-cardiovascular. Cardiovascular death is defined as any death with a cardiovascular complication as the primary or secondary cause, and includes deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Non-cardiovascular death is defined as any death with a primary non-cardiovascular cause, including surgery-related bleeding complications, cancer, trauma and infection. Sudden death in a previously stable patient is considered as cardiovascular[15].



Secondary efficacy endpoints included all-cause mortality, cardiac arrhythmias, acute heart failure, and coronary revascularization.

Safety endpoints included stroke, clinically significant bradycardia and hypotension, clinically significant liver dysfunction, i.e. ALAT > 3 times upper limit of normal, CK level more than 10 times upper limit of normal, myopathy, and rhabdomyolysis. All endpoints that occurred since randomization until 30 days after surgery were counted.

### Sample size calculation

The incidence of the primary efficacy endpoint in patients randomized to double control was estimated at 6.0%. We anticipated a 30% relative risk reduction (odds ratio 0.7) associated with bisoprolol as well as fluvastatin therapy. The combination of bisoprolol and fluvastatin was anticipated to result in a 50% relative risk reduction (odds ratio 0.7*0.7=0.49), compared to double control therapy. A total of 6000 patients are needed (1500 per group) to detect the anticipated risk reduction with a power of 81% and a two-sided α of 5%.

In the participating hospitals a total of 10,000 patients undergo elective non-cardiovascular surgery annually. We had anticipated that 2,000 of them would be eligible and provide informed consent, so that patient enrolment would be completed within 3 years. Actual enrolment started in July 2004 and ended in February 2008. The study was terminated early because of slow patient recruitment. During

the study period, roughly 45,000 patients were screened, of whom 6,460 met the inclusion criteria. However, 78% of these otherwise eligible patients were receiving beta-blocker or statin therapy, instead of the anticipated 20%. Of the remaining patients, 355 did not provide informed consent or had previously participated in the study, leaving 1066 patients to be included.

### Data analysis

The time to the first occurrence of the primary efficacy endpoint was determined according to the Kaplan-Meier method, and differences between allocated groups were evaluated by log-rank statistics. The Cox proportional hazards (PH) model was applied to obtain treatment effects on the primary efficacy endpoint, which are presented as hazard ratio's (HR) and 95% confidence intervals (CI). Cox PH models including interaction terms were applied to evaluate the effects of bisoprolol and fluvastatin treatment in each other's presence or absence. Analyses of other endpoints were based on contingency tables and chi-square tests. All analyses were performed according to the intention-to-treat principle. All statistical tests were 2-sided, and a p-value <0.05 was considered significant.

## RESULTS

### Patients

A total of 264 patients were randomized to bisoprolol therapy, 265 to fluvastatin therapy, 269 to combination therapy and 268 patients to double control therapy. Patient characteristics are presented in TABLES 12.1 and 12.2. The key characteristics were as follows: median age 64 years; 60% male; 11% diabetes mellitus; 6% angina pectoris; 5% prior MI; 4% prior stroke. Most common types of surgery were general (39%), urological (19%), orthopedic (16%), and ear-nose-throat (12%). General anesthesia was used in 94%, and 91% of patients were in American Society of Anesthesiologists (ASA) class 1 or 2. The treatment groups did not differ with respect to baseline or operative characteristics (TABLES 12.1 and 12.2).

### Outcome

The median time between starting medication and surgery was 34 (21-53) days, with no differences between treatment groups (TABLE 12.3). Two patients died from non-cardiac complications while awaiting surgery. Twenty-four patients died within 30 days after surgery. Five patients suffered cardiac death and 38 patients had nonfatal MI within 30 days. Thus, 43 (4.0%) patients reached the primary efficacy endpoint of cardiac death or nonfatal MI (TABLE 12.3). Time-to-event curves for the primary end point, by treatment group, are presented in FIGURE 12.1. The incidence of the primary outcome differed significantly between allocated groups, being lowest in the patients randomized to bisoprolol alone (1.9%) and highest in the patients randomized to double control (7.8%).

*Comparison of the 533 patients allocated to bisoprolol therapy with the 533 patients allocated to bisoprolol-control therapy*

Baseline heart rate was similar in patients randomized to bisoprolol and the patients randomized to bisoprolol-control, but preoperative heart rate was significantly lower in patients randomized to bisoprolol (TABLE 12.2), indicating adequate drug compliance. On the day of surgery, the bisoprolol dose was 2.5 mg in 99% of patients and 5.0 mg in 1%. All patients allocated to bisoprolol had a heart rate of < 70 beats per minute prior to surgery. A total of 11 (event rate according to the Kaplan-Meier method 2.1%) patients allocated to bisoprolol therapy reached the primary efficacy endpoint, compared to 32 (6.0%) allocated to bisoprolol-control (FIGURE 12.2). Hence, bisoprolol therapy was associated with a 67% relative reduction in the incidence of cardiac death or MI (HR 0.34; 95% CI:

**TABLE 12.1** Baseline characteristics, medication use and preoperative 12-lead ECG findings per treatment group.

| | Total (N=1066) | Bisoprolol only (N=264) | Fluvastatin only (N=265) | Combination therapy (N=269) | Double control (N=268) |
|---|---|---|---|---|---|
| Baseline characteristics | | | | | |
| Male gender – no. (%) | 639 (60.0) | 160 (60.8) | 163 (61.5) | 163 (60.8) | 153 (57.1) |
| Age, years (*IQR) | 65.4 (57,74) | 66.8 (58,74) | 65.4 (59,73) | 63.8 (56,74) | 65.6 (57,74) |
| Diabetes Mellitus – no. (%) | 115 (10.8) | 29 (11.0) | 32 (12.1) | 30 (11.2) | 24 (9.0) |
| Angina Pectoris – no. (%) | 55 (5.6) | 11 (4.2) | 15 (5.7) | 14 (5.2) | 15 (5.6) |
| Myocardial infarction – no. (%) | 54 (5.1) | 16 (6.1) | 16 (6.0) | 13 (4.8) | 9 (3.4) |
| Chronic heart failure – no. (%) | 8 (0.8) | 3 (1.1) | 3 (1.1) | 2 (0.7) | 0 |
| Stroke – no. (%) | 46 (4.3) | 11 (4.2) | 10 (3.8) | 13 (4.8) | 12 (4.5) |
| Renal failure – no. (%) | 11 (1.0) | 2 (0.8) | 3 (1.1) | 2 (0.7) | 4 (1.5) |
| Medication use | | | | | |
| Diuretics – no. (%) | 102 (9.6) | 24 (9.1) | 20 (7.6) | 29 (10.8) | 29 (10.8) |
| Aspirin – no. (%) | 102 (9.6) | 26 (9.6) | 27 (10.2) | 25 (9.3) | 24 (9.0) |
| Calcium antagonists – no. (%) | 34 (3.2) | 8 (3.0) | 7 (2.6) | 11 (4.1) | 8 (3.0) |
| ACE inhibitors – no. (%) | 96 (9.0) | 23 (8.7) | 26 (9.8) | 23 (8.6) | 24 (9.0) |
| Angiotensin II inhibitors – no. (%) | 58 (5.4) | 11 (4.2) | 16 (6.0) | 15 (5.6) | 16 (6.0) |
| Anticoagulants – no. (%) | 48 (4.5) | 11 (4.2) | 16 (6.0) | 12 (4.5) | 9 (3.4) |
| Antiarrythmics – no. (%) | 9 (0.8) | 1 (0.4) | 2 (0.8) | 4 (1.5) | 2 (0.8) |
| Nitrates – no. (%) | 11 (1.0) | 1 (0.4) | 4 (1.5) | 2 (0.7) | 4 (1.5) |
| Digoxin – no. (%) | 15 (1.4) | 3 (1.1) | 6 (2.3) | 1 (0.4) | 5 (1.9) |
| Oral antidiabetics – no. (%) | 78 (7.3) | 21 (8.0) | 19 (7.2) | 20 (7.4) | 18 (6.7) |
| Insulin – no. (%) | 48 (4.5) | 7 (2.7) | 18 (6.8) | 11 (4.1) | 12 (4.5) |
| Glucocorticoids – no. (%) | 88 (8.3) | 18 (6.8) | 19 (7.2) | 31 (11.5) | 20 (7.5) |
| Preoperative 12-lead ECG findings | | | | | |
| Abnormal ECG – no. (%) | 487 (45.7) | 122 (46.2) | 122 (46.0) | 124 (46.1) | 119 (44.4) |
| Atrial fibrillation – no. (%) | 15 (1.4) | 4 (1.5) | 5 (1.9) | 3 (1.1) | 3 (1.1) |
| Right bundle branch block – no. (%) | 90 (8.4) | 18 (6.8) | 21 (7.9) | 20 (7.4) | 31 (11.6) |
| Left bundle branch block – no. (%) | 74 (6.9) | 18 (6.8) | 19 (7.2) | 22 (8.2) | 15 (5.6) |
| Q-waves – no. (%) | 103 (9.7) | 22 (8.3) | 32 (12.1) | 27 (10.0) | 22 (8.2) |
| Left ventricle hypertrophy – no. (%) | 83 (7.8) | 24 (9.1) | 21 (7.9) | 22 (8.2) | 16 (6.0) |
| Right ventricle hypertrophy – no. (%) | 1 (0.1) | 1 (0.4) | 0 | 0 | 0 |
| Preventricular contractions – no. (%) | 78 (7.3) | 20 (7.6) | 24 (9.1) | 23 (8.6) | 11 (4.1) |

*IQR = interquartile range



0.17-0.67; p = 0.002). There was no evidence of heterogeneity in the beneficial effect of bisoprolol between patients randomized to fluvastatin versus fluvastatin-control (p-value associated with the interaction term 0.26).

Ischemic stroke occurred in 7 (0.7%) patients, of which 4 (0.8%) were randomized to bisoprolol and 3 (0.6%) to bisoprolol-control (p = 0.68). In total, 3 (0.6%) patients randomized to bisoprolol reached one other beta-blocker-related safety endpoint (heart failure clinically significant bradycardia or hypotension), compared to 2 (0.4%) patients randomized to bisoprolol-control (p = 0.65).

**Table 12.2** Surgery details per treatment group.

| | Total (N=1066) | Bisoprolol only (N=264) | Fluvastatin only (N=265) | Combination therapy (N=269) | Double control (N=268) |
|---|---|---|---|---|---|
| Anesthesia | | | | | |
| General – no. (%) | 1001 (93.9) | 249 (94.3) | 246 (92.8) | 253 (94.1) | 253 (94.4) |
| Spinal – no. (%) | 29 (2.7) | 8 (3.0) | 7 (2.6) | 7 (2.6) | 7 (2.6) |
| Local – no. (%) | 36 (3.4) | 7 (2.7) | 12 (4.8) | 9 (3.3) | 8 (3.0) |
| Specialism | | | | | |
| General surgery – no. (%) | 415 (38.9) | 97 (36.9) | 96 (36.2) | 106 (39.4) | 116 (43.3) |
| Urology – no. (%) | 205 (19.3) | 58 (22.1) | 53 (20.0) | 46 (17.1) | 48 (17.9) |
| Orthopedics – no. (%) | 174 (16.3) | 50 (19.0) | 43 (16.2) | 48 (17.8) | 33 (12.3) |
| Ear-nose-throat – no. (%) | 133 (12.4) | 30 (11.4) | 30 (11.3) | 35 (13.0) | 38 (14.2) |
| Gynaecology – no. (%) | 53 (5.0) | 8 (3.0) | 13 (4.9) | 17 (6.2) | 15 (5.6) |
| Plastic surgery – no. (%) | 55 (5.1) | 12 (4.6) | 22 (8.3) | 9 (3.4) | 12 (4.5) |
| Dental surgery – no. (%) | 10 (0.9) | 1 (0.4) | 4 (1.5) | 2 (0.7) | 3 (1.1) |
| Ophthalmology – no. (%) | 10 (0.9) | 4 (1.5) | 3 (1.1) | 1 (0.4) | 2 (0.8) |
| Other – no. (%) | 10 (0.9) | 3 (1.1) | 1 (0.4) | 5 (1.9) | 1 (0.4) |
| *ASA score | | | | | |
| 1 – no. (%) | 392 (36.8) | 95 (36.0) | 96 (36.2) | 105 (39.0) | 96 (35.8) |
| 2 – no. (%) | 573 (53.8) | 144 (54.6) | 140 (52.8) | 140 (52.0) | 149 (55.6) |
| 3 – no. (%) | 101 (9.5) | 25 (9.5) | 29 (11.0) | 24 (8.9) | 23 (8.6) |

*ASA = American Society of Anesthesiologists

**Table 12.3** Treatment information, primary and secondary study end points per treatment group.

| Variable | Total (N=1066) | Bisoprolol only (N=264) | Fluvastatin only (N=265) | Combination therapy (N=269) | Double control (N=268) | p-value |
|---|---|---|---|---|---|---|
| Treatment information | | | | | | |
| Time to surgery, days (IQR*) | 34 (21,53) | 34.5 (22,52) | 36 (22,56) | 35 (20,52) | 34 (20,53) | 0.88 |
| Heart rate at screening, bpm (IQR) | 77 (70,85) | 76.5 (71,84) | 77 (68,85) | 77 (72,85) | 77 (67,87) | 0.60 |
| Heart rate preoperative, bpm (IQR) | 68 (62,76) | 64 (60,68) | 78 (68,84) | 65 (62,68) | 76 (68,84) | <0.001 |
| Heart rate difference, bpm (IQR) | -8 (-14,0) | -12 (-21,-7) | 0 (-7,6) | -12 (-19,-8) | 0 (-8,6) | <0.001 |
| Primary end points | | | | | | |
| Cardiac death or MI (%)† | 43 (4.0) | 5 (1.9) | 11 (4.1) | 6 (2.2) | 21 (7.8) | 0.001 |
| Myocardial infarction (%) | 38 (3.6) | 5 (1.9) | 9 (3.4) | 6 (2.2) | 18 (6.7) | 0.01 |
| 30-day total mortality (%) | 26 (2.4) | 3 (1.1) | 7 (2.6) | 7 (2.6) | 9 (3.4) | 0.41 |
| Cardiac (%) | 5 (0.5) | 0 | 2 (0.8) | 0 | 3 (1.1) | 0.15 |
| Sepsis (%) | 11 (1.0) | 3 (1.1) | 2 (0.8) | 4 (1.5) | 2 (0.7) | 0.80 |
| Other (%) | 10 (0.9) | 0 | 3 (1.1) | 3 (1.1) | 4 (1.5) | 0.31 |
| Secondary end points | | | | | | |
| Hospital stay, days (IQR) | 8 (5,15) | 8.5 (5,14) | 8 (5,15) | 8 (5,14) | 9 (5,15) | 0.71 |
| ‡ICU admittance (%) | 213 (20.0) | 53 (20.1) | 52 (19.6) | 50 (18.6) | 58 (21.6) | 0.85 |
| ‡ICU stay, days (IQR) | 2 (1,6) | 2 (2,5) | 3 (1,11) | 2 (1,4) | 2 (1,4) | 0.68 |
| Arrhythmia (%) | 9 (0.8) | 2 (0.8) | 3 (1.1) | 1 (0.4) | 3 (1.1) | 0.74 |
| Heart failure (%) | 3 (0.3) | 1 (0.4) | 1 (0.4) | 0 | 1 (0.4) | 0.79 |
| Revascularization (%) | 1 (0.1) | 0 | 1 (0.4) | 0 | 0 | 0.39 |

* IQR = interquartile range, † MI = myocardial infarction, ‡ ICU = intensive care unit

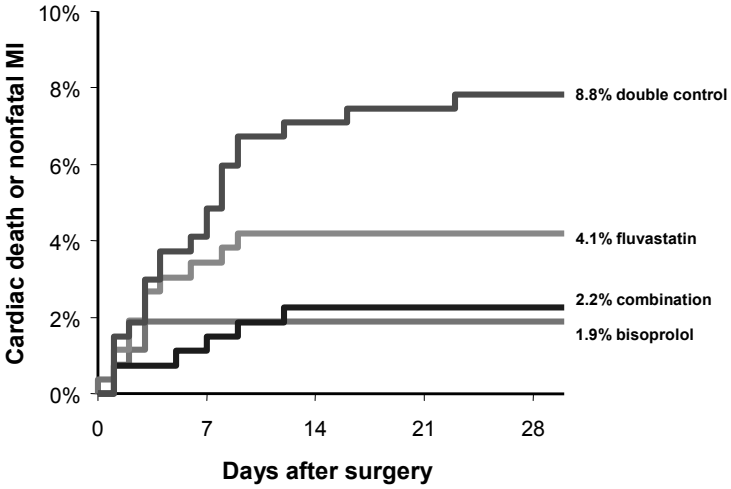


**FIGURE 12.1** Incidence of primary study end point by treatment group.

*Comparison of the 534 patients allocated to fluvastatin therapy with the 532 patients allocated to fluvastatin-control therapy*

A total of 17 (event rate according to the Kaplan-Meier method 3.2%) patients allocated to fluvastatin therapy reached the primary endpoint, compared to 26 (4.9%) allocated to therapy without fluvastatin (FIGURE 12.2). Hence, a reduction in the incidence of the primary endpoint was observed in favor of fluvastatin therapy, but statistical significance was not reached (HR: 0.65; 95% CI: 0.35-1.20; p = 0.17).



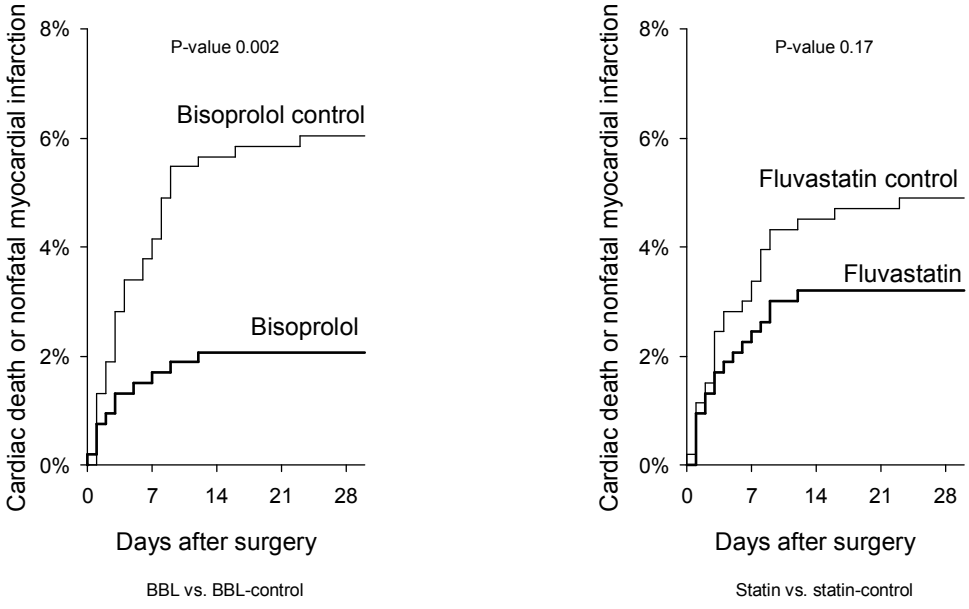


**FIGURE 12.2** Incidence of primary study end point for each individual treatment vs. control.

A stroke occurred in 3 (0.6%) patients who were randomized to fluvastatin therapy and in 4 (0.7%) patients randomized to fluvastatin-control (p = 0.71). In total, 8 (1.5%) patients randomized to fluvastatin therapy had clinically significant liver dysfunction compared to 11 (2.1%) on fluvastatin-control therapy (p = 0.48). No patient experienced myopathy or rhabdomyolysis.

## DISCUSSION

The DECREASE-IV study shows that treatment with bisoprolol, titrated to a perioperative heart rate of 50-70 beats per minute and initiated at a median of 34 days prior to surgery, resulted in a significant reduction of perioperative cardiovascular complications, particularly MI. Only 26 patients need to receive bisoprolol prophylaxis to prevent one perioperative cardiac event. This study was not able to demonstrate a significant reduction in cardiovascular complications by fluvastatin therapy. However, we appreciate that – due to its early termination – DECREASE-IV lacked statistical power to reveal clinically relevant differences in this respect. Slow enrolment occurred due to the fact that 78% of the patients who met the inclusion criteria were on beta-blocker and/or statin therapy, as opposed to the estimated 10% of patients receiving beta-blocker and 10% receiving statin therapy.

*Beta-blocker therapy for perioperative cardiac risk reduction*

Although widely prescribed, there is still considerable debate about the protective effect of beta-blockers, with several studies showing a benefit of perioperative beta-blocker treatment[2-4], while others found no cardioprotective effect[16-18]. The POISE study showed, similar to DECREASE-IV, that beta-blocker therapy reduced the risk of MI but increased the incidence of stroke and overall mortality, a finding that was not confirmed in DECREASE-IV[19]. There are two major design differences between DECREASE-IV and POISE that may explain the differential findings: dose titration and timing of therapy.

It is well-known that initiation time and dose titration influence the effectiveness of perioperative beta-blocker therapy. The effects of acute beta-blockade include a reduction of myocardial oxygen demand. However, a beneficial effect of beta-blockade on coronary plaque stability, related to sustained mechanical and anti-inflammatory effects, might require weeks to develop. Prolonged beta-blockade has been shown to decrease the level of inflammatory cytokines both in the myocardium and the systemic circulation[10,20,21], as well as decreasing the progression of coronary atherosclerosis[22]. Additionally, it seems crucial to continue beta-blockers postoperatively. It has been shown that withdrawal of beta-blocker therapy early after surgery was associated with a 2.7-fold increased risk of 1-year mortality compared to patients not using beta-blockers[23].

In addition to initiation time, dose adjustment for heart rate control is important in beta-blocker therapy[24]. Accordingly, the new ACC/AHA guidelines on perioperative care strongly recommend achieving and maintaining a heart rate of 60-65 beats per minute[25]. The POISE trial initiated metoprolol treatment just before surgery and the maximum recommended therapeutic dose (MRTD) could be achieved within the first day of treatment[19]. In contrast, the DECREASE studies employed a relatively low bisoprolol dose (12.5% of MRTD) that was carefully titrated during approximately 30 days[12,26]. Notably, the POISE trial observed a 1% incidence of stroke in the group randomized to metoprolol compared to 0.5% in the control group. In comparison the incidence of stroke was 0.4% in the DECREASE studies, with no difference between groups.

The outcome of these studies suggest that two different treatment protocols applying beta-blockers are effective in reducing perioperative cardiac complications; one prescribing a high dose immediately prior to surgery, the other a dose titration approach over a prolonged period. However, the cardioprotective effect of the high dose regimen comes at the cost of an increased incidence of side effects, such as stroke.

*Statin therapy for perioperative cardiac risk reduction*

Statins are widely prescribed in patients with or at risk of coronary artery disease (CAD) because of their lipid lowering capacity. Beyond this property, statins may stabilize coronary artery plaque and thereby prevent plaque rupture and subsequent MI in the perioperative period[27].

Multiple clinical trials and large observational studies have demonstrated a beneficial effect of perioperative statin use[5,6,28-30]. The first prospective, randomized controlled, clinical trial evaluating the effects of statin therapy on perioperative cardiovascular complications was performed by Durazzo et al.[6] After six months follow-up, the incidence of cardiovascular events was more than 3-fold higher with placebo than with atorvastatin (26% vs. 8%, p=0.031).

A major concern of statin therapy is the potential for side effects including myopathy and rhabdomyolysis. In a retrospective study, Schouten et al. studied the potential risk of myopathy from perioperative statin therapy[31]. After correcting for cardiac risk factors and clinical risk factors for myopathy, length of surgery remained the only factor independently associated with creatine kinase elevations. Rhabdomyolysis was not observed. Considering that the risk of perioperative cardiovascular complications is far greater than the risk of statin-induced myopathy and rhabdomyolysis, the potential benefits of perioperative statin use seem to outweigh the hazards. However, despite a numerical reduction in cardiac events in patients on fluvastatin therapy, statistical significance was not achieved in this study. Larger randomized controlled trials investigating perioperative statin therapy are indicated.



*Limitations*

A potential limitation of this study was is its open-label design and lack of blinding, with a consequent risk of treatment bias. However, since beta-blocker therapy cannot be titrated to heart rate in a double-blind setting, an open-label design was employed. In addition, the recognizable hemodynamic effects of bisoprolol potentially decrease the effectiveness of a double-blind design. The statin arms of this study were also not blinded, as this would severely complicate the 2 by 2 study design. The study was terminated before the target sample size was achieved, with a resultant decrease in statistical power. This may explain the failure to achieve statistical significance regarding the efficacy of fluvastatin therapy. Therefore, further large, randomized controlled trials of statin therapy are indicated. Finally, our results are applicable only to intermediate-risk patients undergoing non-cardiovascular surgery and are not applicable to the large population of low-risk patients.

*Conclusion*

Although, the identification of patients at risk has improved recently, no widely applicable perioperative cardiovascular risk reduction strategies for intermediate-risk patients have been developed. The current trial demonstrates that bisoprolol treatment, begun one month preoperatively, and titrated to heart rate, significantly reduces the incidence of perioperative cardiac death and MI, without increasing morbidity or non-cardiac mortality. This represents a significant advance in the management of this sizable patient population.

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# Chapter 13

## A meta-analysis of safety and effectiveness of perioperative beta-blocker use for the prevention of cardiac events in different types of non-cardiac surgery

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## ABSTRACT

**Background:** Perioperative beta-blocker therapy has been proposed to improve outcome. However, most of the trials conducted lacked statistical power to evaluate the incidence of hard cardiac events and the relation to the type of surgery. Therefore we conducted a meta-analysis of all randomized controlled trials in which beta-blocker therapy was evaluated.

**Methods:** An electronic search of published reports on Medline was undertaken to identify studies published between January 1980 and November 2004 in English language journals. All studies reported on at least one of three end-points: perioperative myocardial ischemia, perioperative non-fatal MI, and cardiac mortality. Type of surgery, defined as low, intermediate and high risk according to ACC/AHA guidelines, was noted.

**Results:** In total 15 studies were identified, which enrolled 1077 patient. There were no significant differences in baseline clinical characteristics between patients randomized to beta-blocker therapy and control/placebo. Beta-blocker therapy was associated with a 65% reduction in perioperative myocardial ischemia (11.0% versus 25.6%; OR 0.35, 95%CI 0.23-0.54; p<0.001). Furthermore, a 56% reduction in MI (0.5% vs. 3.9%, OR 0.44, 95% CI 0.20-0.97; p=0.04), and a 67% reduction (1.1% vs. 6.1%, OR 0.33, 95% CI 0.17-0.67; p=0.002) in the composite endpoint of cardiac death and non-fatal MI was observed. No statistical evidence was observed for heterogeneity in the treatment effect in subgroups according to type of surgery (p for heterogeneity 0.2).

**Conclusion:** This meta-analysis shows that beta-blocker use in non-cardiac surgical procedures is associated with a significant reduction of perioperative cardiac adverse events.

## INTRODUCTION

It is estimated that annually 4-10% of the population of the United States is scheduled for non-cardiac surgery[1]. Patients undergoing major non-cardiac surgery are at a significant risk of cardiac events due to underlying (a-) symptomatic coronary artery disease (CAD). Although the overall perioperative event rate has declined over the past 30 years, 30-day cardiovascular mortality remains as high as 3% to 5%[2,3]. Myocardial infarction (MI) is the most frequent fatal complication in this respect, accounting for 10-40% of postoperative fatalities[4,5].

The high incidence of perioperative adverse cardiac events has resulted in the development of cardiac risk scores and guidelines, in relation to the risk of specific procedures, to identify patients at risk[6-12]. Based on these models, several clinical trials have been conducted to improve outcome and to study whether cardioprotective medical therapy and/or preoperative coronary revascularization are associated with risk reduction. The results of the recently published CARP-trial showed that preoperative coronary revascularization does not reduce perioperative MI and long-term survival in a group of 510 patients at high risk[13]. The ineffectiveness of preoperative revascularization was partially explained by improved medical therapy, in particular by the wide spread use of perioperative beta-adrenergic blocking agents in approximately 90% of the control group.

The use of beta-blockers has been associated with a reduced risk on the surrogate end point of perioperative myocardial ischemia. However, most of the trials conducted so far lacked the statistical power to evaluate the cardioprotective effect of beta-blockade on the incidence of hard cardiac endpoints, such as myocardial infarction and cardiac death. Also the influence of the risk of specific procedures remains unknown. Therefore we conducted a meta-analysis of all randomized controlled trials in which the effectiveness and safety of perioperative beta-adrenergic blockade on perioperative cardiac events was studied against placebo/control therapy for specific types of surgery.

## METHODS

Although the principles that lie behind a meta-analysis of randomized clinical trials have been described in detail, we will highlight the relevant principles applied herein. Due to the limited sample size and variable risk reductions noted across trials, the synthesis of available evidence may better aid in discerning the weighted evidence on the use of beta-blockers from existing randomized trial data.

### Trial selection

We intended to include all trials reported since January 1980 with the following subject headings: randomization of patients scheduled for elective non-cardiac surgical interventions; and comparison of an adrenergic beta-antagonists (beta-blockers) with placebo or control therapy. To be included in the analysis, studies had to report one or more of three end-points: perioperative (i.e. < 30 days after surgery) myocardial ischemia, perioperative nonfatal MI, or cardiac mortality. Using these selection criteria, a total of 15 randomized clinical trials were identified (n=1,077).

A systematic electronic search of published reports on Medline was undertaken to identify studies published between January 1980 and January 2005 in English language. To identify eligible trials the following Medical Subject Heading (MESH) terms, or a combination of these, were used: adrenergic beta-antagonist, myocardial infarction, myocardial ischemia, mortality, and perioperative care.

Furthermore, we examined the reference lists of identified articles and published recommendations for perioperative cardiac risk management.

### Data management

Pertinent data from the selected studies were extracted independently by two investigators (OS and DP), using standardized spreadsheets. Discrepancies were resolved by consensus and oversight from a 3rd investigator (EB). Information extracted included reference data (first author, journal, institution), publication year, number of patients, mean age, proportion of male patients, type of surgery, type of beta-blocker therapy, duration and dose of beta-blocker therapy, duration of follow-up, history of coronary artery disease, incidence of myocardial ischemia, myocardial infarction, death, and cause of death. The type of surgery was classified as intermediate or high risk according to the guidelines of the ACC/AHA (TABLE 13.1)[14]. Furthermore we also extracted data on possible beta-blocker side effects including bradycardia, hypotension, AV-block, bronchospasm, and pulmonary edema. Because of known difficulties in quality scoring of randomized trials, we did not score the quality of the included trials.

**TABLE 13.1** Classification of surgical procedures according to the ACC/AHA guidelines[14].

| | |
|---|---|
| **High Risk Surgical Procedures** | Emergent major operations |
| | Aortic and major vascular surgery |
| | Peripheral vascular surgery |
| | Anticipated prolonged surgical procedures |
| **Intermediate Risk Procedures** | Carotid endarterectomy |
| | Head and neck surgery |
| | Intraperitoneal and intrathoracic surgery |
| | Orthopedic surgery |
| | Prostate surgery |

High risk surgical procedures, > 5% chance on cardiac death or non-fatal MI, and intermediate risk surgical procedures, 1-5% chance on cardiac death or non-fatal MI.

**TABLE 13.2** Definitions of myocardial ischemia in 12 trials that reported perioperative myocardial ischemia.

| Study | Definition of myocardial ischemia |
|---|---|
| Bayliff et al.[15] | Not specified |
| Coleman et al.[17] | ST segment changes |
| Cucchiara et al.[18] | Transient ST-shifts |
| Davies et al.[19] | Chest pain |
| Magnusson et al.[21] | $ST_{60}$-depression exceeds or is equal to 1.0 mm in males and 1.5 mm in females, or T-inversion appeared, or both |
| Magnusson et al.[22] | Downward sloping ST-segments |
| Raby et al.[24] | ST-segment depression that is horizontal and down-sloping, >1 mm from a predefined baseline, and lasting >1 min |
| Rosenberg et al.[25] | Change in ST level >0.1 mV from baseline measured at 60 ms from the J point |
| Stone et al.[26] | New ST-segment depression of at least 1 mV with a horizontal or downsloping configuration |
| Urban et al.[27] | ST-segment depression that is horizontal and down-sloping, >1 mm from a predefined baseline, and lasting >1 min |
| Wallace et al.[28] | Reversible ST segment changes ≥ 1 min and involving a shift from baseline of ≥ to 0.1 mV of ST depression ( slope <or= to 0), or a shift from baseline of ≥ 0.2 mV of ST-T elevation at J-point |
| Zaug et al.[29] | New horizontal or downsloping ST-segment depressions ≥ 0.1 mV, persisting ≥ 60 ms after the J point, or ST-segment elevations of ≥ 0.2 mV lasting > 2 min. With ST depression at baseline, a further depression of ≥ 0.15 mV was necessary |

## Definitions of efficacy and safety endpoints

Myocardial ischemia, infarction, and/or cardiac death were part of the composite efficacy endpoint of all trials, but the applied definitions were different (see TABLES 13.2 and 13.3). Still, since we know that heterogeneity in an endpoint definition will not lead to invalid results, we applied the trial-specific definition of myocardial infarction for practical reasons. There were also between-trial differences with regard to the definition of adverse effects, i.e. bradycardia, hypotension, AV-block, bronchospasm and pulmonary edema. The trial-specific definitions were retained.

**TABLE 13.3** Definitions of myocardial infarction in all 15 trials.

| Study | Definition of myocardial infarction |
|---|---|
| Bayliff et al.[15] | Not specified |
| Bohm et al.[16] | Not specified |
| Coleman et al.[17] | Not specified |
| Cucchiara et al.[18] | Not specified |
| Davies et al.[19] | CK-MB > 80 units, and new Q-waves on ECG |
| Jakobsen et al.[20] | Not specified |
| Magnusson et al.[21] | Not specified |
| Magnusson et al.[22] | Not specified |
| Poldermans et al.[23] | Serum creatine kinase level > than 110 U per liter, with an MB isoenzyme fraction of > 10 percent, and a finding of new Q waves lasting > 0.03 second on the electrocardiogram |
| Raby et al.[24] | Any creatine kinase (CK) increase associated with a CK MB increase >5% |
| Rosenberg et al.[25] | Not specified |
| Stone et al.[26] | Not specified |
| Urban et al.[27] | Serum CPK-MB fraction isoenzyme index >=3.0. ECG changes included new ST-T changes, T inversions, Q waves, and/or a bundle branch block |
| Wallace et al.[28] | (1) a CPK-MB isoenzyme concentration ≥ to threshold (0.83 mmol per liter per second [or 50 units/liter]), and (2) either new Q waves (Minnesota Code I or II), or persistent (4 days) changes in the ST-T wave (Minnesota Code IV or V), or autopsy evidence of acute infarction |
| Zaug et al.[29] | new Q wave, persistent ST–T wave changes as defined by Minnesota Codes, association with any elevation of creatine kinase with creatine kinase MB increase > 5% |

## Statistical analysis

From each of the randomized trials, a 2 x 2 frequency data was calculated for each of the available endpoints and side effect data. The 2 x 2 frequency data was input into the Comprehensive Meta AnalysisTM program (www.meta-analysis.com, version 1.0.25). Available data from each trial was input into this program for calculation of individual and summary odds ratio (95% CI) data. Summary odds ratios (95% CI) were calculated for cardiac death, all-cause death, combined cardiac death or myocardial infarction, nonfatal myocardial infarction, and ischemia. For side effects, a summary odds ratio (95% CI) was AV block, bradycardia, bronchospasm, hypotension, pulmonary edema, as well as for a summary side effect odds ratio (95% CI). A chi-square test for heterogeneity (Mantel-Haenszel) was calculated in order to examine the combinability of each of the endpoints and side effects. The adequacy of combining the data was noted when the p-value was non-significant ($p>0.05$). The Number Needed to Treat (NNT) is defined as the number of patients who need to be treated to prevent 1 adverse outcome. We reported the NNT as a whole number and it was calculated as 1/odds ratio and accompanied by its 95% confidence interval (CI). The calculation was applied based upon methods defined by http://www.jr2.ox.ac.uk/bandolier/band36/b36-2.html#Table, access date: June 25, 2005.

## RESULTS

Based on the trial selection criteria, 15 trials were identified and subsequently analysed[15-29]. The characteristics of the analyzed trials are shown in TABLE 13.4.

### Patients' characteristics

The trials altogether enrolled 1,077 patients. There were no important differences in baseline characteristics between patients randomized for beta-blocker therapy (n=551) and those randomized for placebo or control (n=526, TABLE 13.5). Two hundred fifty one patients underwent non-cardiac vascular surgery, 561 general surgery, 134 thoracic non-cardiac surgery, 107 orthopedic surgery, and 24 ENT procedures. In total 188 patients received atenolol, 123 bisoprolol, 88 metoprolol, 52 a combination of esmolol and metoprolol, 51 esmolol only, and 49 received propanolol treatment. High-risk surgery was performed in 211 patients (3 trials) and intermediate risk in 866 patients (13 trials). None of the trials reported on the effects of beta-blockers in low risk surgery. Beta-blocker therapy resulted in a lower preoperative heart rate (72.9 ± 6.8 bpm vs. 78.8 ± 4.9 bpm, p=0.001).

### Efficacy endpoints

The occurrence of myocardial ischemia was reported in 12 trials, including 410 treated and 407 control patients. Beta-blocker use was associated with a 65% relative reduction in the odds of perioperative myocardial ischemia (11.0% versus 25.6%; OR 0.35, 95%CI 0.23-0.54; p<0.001, FIGURE 13.1). The absolute risk reduction was over 14% (number needed to treat = 7). There was no statistical evidence of heterogeneity in treatment effect among the separate trials.

All trials reported the occurrence of non-fatal myocardial infarction. Overall, beta-blocker use was associated with a 56% decreased risk on myocardial infarction (p=0.04, FIGURE 13.1). The number needed to treat (NNT) for this endpoint was 32.

The use of beta-blockers was not significantly associated with a reduction in cardiac death (0.54% vs. 2.22%, p=0.14). This might be due to a type II error since only 3 patients in the treated group and 12 patients in the control group died due to cardiac causes. On the other hand, beta-blocker use resulted in a 67% relative reduction in the combined endpoint of cardiac death and non-fatal MI (1.1% vs. 6.1%, OR 0.33, 95% CI 0.17-0.67; p=0.002, NNT = 20, FIGURE 13.1).



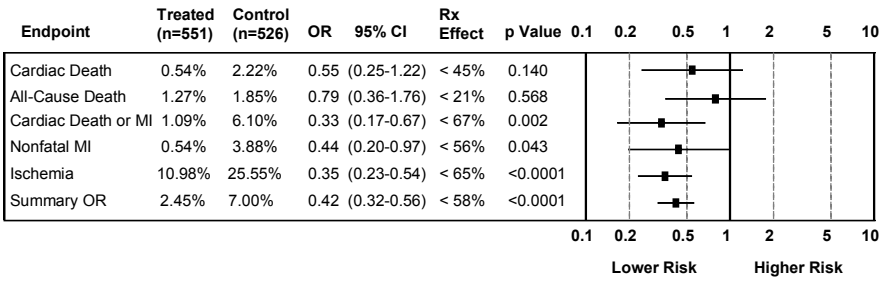


**FIGURE 13.1** Comparison of perioperative/near-term outcomes in patients treated with beta-blocker therapy vs. no drug/placebo.
Ischemic event data was available from 11/15 studies (n=410 treated and n=407 controls); OR, odds ratio; Rx, treatment; MI, myocardial infarction.

**TABLE 13.4** Randomized controlled trials of the effectiveness of perioperative β-blockade.

| Study | Year | Type of surgical procedure | Cardiac inclusion criteria | β-blocker therapy (no. of analyzed patients) | Control therapy (no. of analyzed patients) | Preoperative drug dosing | Postoperative drug dosing | Duration of treatment |
|---|---|---|---|---|---|---|---|---|
| Bayliff et al.[15] | 1999 | Thoracic | None described | Propanolol (49) | Placebo (50) | 10 mg PO | 40 mg/d PO | 5 days |
| Bohm et al.[16] | 2003 | General | NYHA class III or IV | Bisoprolol (64) | Placebo (64) | 2.5-10 mg/d PO | 2.5-10 mg/d PO | Chronic |
| Coleman et al.[17] | 1980 | General | None described | Metoprolol (27) | Placebo (15) | 2 or 4 mg IV | | Premedication |
| Cucchiara et al.[18] | 1986 | Vascular | None described | Esmolol (36) | Placebo (37) | 500 µg/kg/min for 4 min<br>300 µg/kg/min for 8 min | | Premedication |
| Davies et al.[19] | 1992 | Vascular | None described | Atenolol (20) | Placebo (20) | 50 mg PO | | Premedication |
| Jakobsen et al.[20] | 1997 | Thoracic | None described | Metoprolol (18) | Placebo (17) | 100 mg PO | | 4 to 10 days |
| Magnusson et al.[21] | 1986 | ENT | None described | Metoprolol (11) | No drug (13) | 200 µg/kg IV | | Premedication |
| Magnusson et al.[22] | 1986 | General | None described | Metoprolol (13) | No drug (14) | 200 mg/d<br>15 mg IV peroperative | | 14-34 days + Premedication |
| Poldermans et al.[23] | 1999 | Vascular | Ischemia during DSE | Bisoprolol (59) | No drug (53) | 5-10 mg/d PO | 5-10 mg/d PO or metoprolol IV | 37 days |
| Raby et al.[24] | 1999 | Vascular | Preoperative ischemia | Esmolol (15) | Placebo (11) | | | 2 days |
| Rosenberg et al.[25] | 1996 | General | None described | Metoprolol (19) | Placebo (19) | 100 mg PO | | Premedication |
| Stone et al.[26] | 1988 | General | Hypertension | Atenolol (44) | No drug (39) | 50 mg PO | | Premedication |
| Urban et al.[27] | 2000 | Orthopedic | Probable IHD | Esmolol/metoprolol (52) | No drug (55) | | 250 mg/h IV, 50 mg/d PO | 2 days |
| Wallace et al.[28] | 1998 | General | CAD | Atenolol (101) | Placebo (99) | 5-10 mg IV | 10-20 mg/d IV or 50-100 mg/d PO | 7 days |
| Zaugg et al.[29] | 1999 | General | CAD | Atenolol (23) | No drug (20) | 5-10 mg IV | 10-20 mg IV | 3 days |

NYHA = New York Heart Association; iv = intravenous; ENT = ear nose throat; DSE = dobutamine stress echocardiography; IHD = ischemic heart disease; CAD = coronary artery disease

**TABLE 13.5** Clinical characteristics of the 15 published reports.

| | Beta Blocker N = 551 | No Drug / Placebo N = 526 |
|---|---|---|
| Mean age (years) | 62.8 | 62.8 |
| Prior MI | 27.1% | 27.5% |
| Angina | 32.7% | 21.9% |
| COPD | 30.4% | 25.0% |
| Hypertension | 52.7% | 60.7% |
| CHF | 8.2% | 7.6% |
| Diabetes | 24.0% | 21.8% |
| Hypercholesterolemia | 15.3% | 16.0% |
| Chronic renal failure | 4.3% | 0.0% |
| CVA or TIA | 1.9% | 0.0% |
| Current smoker | 34.4% | 36.3% |

This table looks at the rate in the trials where each of the historical variables were reported. MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; CVA = cerebrovascular accident; TIA = transient ischemic attack

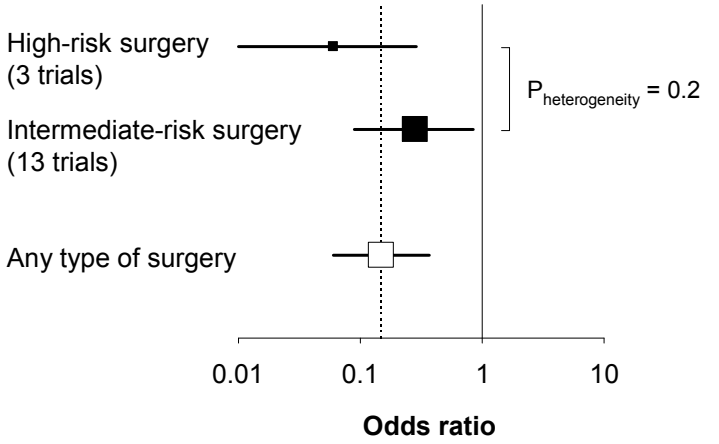


**FIGURE 13.2** Odds ratio according to type of surgery.

As is shown in FIGURE 13.2, the cardioprotective effect of beta-blockers was comparable in patients undergoing high and intermediate risk surgery according to the AHA classification. The odds ratio for the composite endpoint of myocardial infarction and cardiac death in respectively high risk and intermediate risk surgery was 0.06 (95% CI 0.01-0.29, NNT = 6) and 0.28 (95% CI 0.09-0.84, NNT = 42), and the p-value for heterogeneity 0.2.

### Safety endpoints

Nine trials reported bradycardia as a safety-endpoint. In these studies which included 350 treated patients and 346 control patients, beta-blocker use was associated with a 4.3 fold increased risk of bradycardia (p=0.006, TABLE 13.6). Patients on beta-blocker therapy did not have a significantly increased risk on hypotension (14.1% vs. 10.7%, p=0.73). Other side effects were reported less frequently; AV-block was systematically reported in 1 study (27 treated, 30 controls), pulmonary edema in 2 studies (93 treated, 89 control), and bronchospasm in 2 studies (85 treated, 87 control). None

**TABLE 13.6** Weighted average difference in the rate of side effects for β-blocker therapy vs. no drug/placebo.

| Side Effects | Treated | Control | Rate | 95% CI | P-value |
|---|---|---|---|---|---|
| AV block | 1 / 27 | 0 / 30 | 2.5% | -7.8% - 12.8% | 0.63 |
| Bradycardia | 51 / 530 | 14 / 346 | 4.3% | 1.3% - 7.4% | 0.006 |
| Bronchospasm | 13 / 85 | 16 / 87 | 1.2% | -5.5% - 8.0% | 0.72 |
| Hypotension | 64 / 315 | 59 / 309 | 0.8% | -3.9% - 5.6% | 0.73 |
| Pulmonary edema | 17 / 93 | 9 / 89 | 8.1% | -1.9% - 18.0% | 0.11 |
| Overall S.E. | 146 / 870 | 98 / 861 | 3.3% | 1.0% - 5.6% | 0.005 |

of these three safety endpoints were statistically associated with beta-blocker use. However overall, beta-blocker therapy was associated with a 1.5 fold risk of the combined safety endpoints (p=0.005, TABLE 13.6).

## DISCUSSION

This meta-analysis indicates that perioperative beta-blocker use is associated with a substantial reduction in perioperative myocardial ischemia, myocardial infarction, and the composite end point of cardiac death and non-fatal myocardial infarction in patients undergoing non-cardiac surgery. No difference was observed in the cardioprotective effect of beta-blockers in subgroups of patients according to type of surgery. As expected the use of beta-blockers was associated with a higher incidence of bradycardia. However, the risk of bronchospasm and pulmonary edema was not increased by beta-blockers.

Beta-blockers are well established in the treatment of ischemic heart disease and heart failure and have been shown to improve outcome in non-surgical cardiac patients[30]. Hence it is not surprising that perioperative beta-blocker use in patients at risk for CAD undergoing non-cardiac surgery reduced risk of cardiac complications. We did not observe statistical evidence for heterogeneity in the treatment effect of beta-blockers in subgroups according to type of surgery. The absolute treatment effect was highest (and the NNT lowest) in patients undergoing high-risk surgery. The mechanisms by which beta-blockers exert their perioperative cardioprotective effect are multifactorial. Beta-blockers decrease myocardial oxygen demand by reduction of heart rate and myocardial contractility[31,32]. Furthermore, beta-blockers reduce the adrenergic activity, which results in reduced levels of free fatty acid, thus causing a shift in the myocardial metabolism towards glucose uptake[33].

Our results are in line with a previously reported meta-analysis that showed a positive association between beta-blocker use and reduction of perioperative cardiovascular mortality and morbidity. In an analysis of 11 randomized trials (866 patients), Stevens et al.[34] found a significant decrease in perioperative myocardial ischemia (OR 0.32, 95% CI 0.17-0.58), postoperative myocardial ischemia (OR 0.46, 95% CI 0.26-0.81), non-fatal MI (OR 0.19, 95% CI 0.08-0.68), and cardiac mortality (OR 0.25, 95% CI 0.09-0.73). Auerbach and Goldman describe the results of 5 randomized trials[35]. The reported NNT of these trials were between 2.5 to 6.7 for myocardial ischemia, and between 3.2 and 8.3 for cardiac or all-cause mortality, indicating a substantial benefit for patients on beta-blocker therapy. In our study the benefits of beta-blocker therapy on perioperative myocardial ischemia were similar to those reported by Stevens et al. Recently Devereaux et al. reported no difference in a meta-analysis of 22 studies[36]. However, in that meta-analysis also studies that were presented at scientific meetings only (and not yet published in peer-reviewed journals) were included. Besides this, they also included trials not reporting on myocardial damage but on side effects only while our meta-analysis was primarily focused on the cardioprotective value of perioperative beta-blocker therapy.

Tight heart rate control in patients on beta-blockers indeed seems to reduce perioperative ischemia as has been shown by Raby et al[24]. In their study 150 patients were monitored by ambulatory ECG. In 26 of these patients ischemia occurred. These patients were then randomized to receive either tight heart rate control, i.e. 20% less than the ischemic threshold but >60 bpm, or normal beta-blocker therapy. Tight heart rate control in patients on beta-blockers was associated with a reduced incidence of myocardial ischemia. Unfortunately it is practically impossible to achieve such a control by oral medication alone. Intravenous administration of beta-blockers is possible but continuous infusion of beta-blockers in every patient on a normal care ward is simply not feasible. However close monitoring and dose adjustment of intravenous medication can and should be done during surgery and at the intensive care unit.

Another important question that remains to be answered is when to start beta-blocker therapy and when to discontinue after surgery. In the trials analyzed in this study, the time window of treatment differed preoperatively from hours to 37 days and postoperative from just a single dose to a week or more. So far no study has assessed the optimal run-in period for beta-blockers. However, based on the evidence of published trials it is probably safe to conclude that beta-blocker therapy should be initiated prior to surgery and dose titration has to be done up to the induction of anesthesia. Recent publications suggest that for high-risk patients, e.g. vascular surgery patients, beta-blocker therapy has to be continued lifelong[37]. Coronary artery disease remains an important risk factor for later cardiac complications. Therefore proper cardiac medication is just as important for these patients as for patients with established CAD who are not referred for surgery. Whether this is also true for patients at moderate or low risk remains undefined. However, prolonging beta-blocker therapy beyond the surgical procedure seems to be important for all patients since the risk of myocardial ischemia and infarction remains high in the first postoperative week.



*Side effects*

In our meta-analysis we found a higher incidence of bradycardia in patients on beta-blocker therapy. This finding was also reported in the study by Stevens et al., in which they found an OR of 3.76 (95% CI 2.45-5.77). The rate of pulmonary adverse events was similar between treated and untreated patients, a finding that is confirmed in recent publications on cardioselective beta-blockers. Based on these publications, obstructive pulmonary disease should not be considered a contraindication for the perioperative use of beta-blockers. Also AV-block and hypotension were not more frequently noted in patients using beta-blockers. Though this might be due to relatively low number of patients, it seems that the benefits of beta-blocker therapy outweigh the potential side effects. Another side effect ascribed to beta-blocker therapy in vascular surgery patients is worsening of intermittent claudication. None of the analyzed trials reported on the incidence of claudication. However other publications suggest that there is no negative effect on microcirculation or symptoms in claudicants on beta-blocker therapy[38,39].

*Conclusion*

This meta-analysis showed that the use of beta-adrenergic receptor antagonists is associated with a significant reduction in cardiac morbidity in patients undergoing non-cardiac surgery, irrespective whether patients were scheduled for high or intermediate risk surgery.

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# Chapter 14

## Safety and efficacy of beta-blocker therapy in patients undergoing esophagectomy for cancer

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*Submitted*

## ABSTRACT

**Background:** Perioperative beta-blocker therapy is associated with a reduction in cardiac events. However, concerns exist regarding beta-blocker use in patients undergoing esophagectomy because of a possible increased risk of ischemia and leakage of the esophagogastric anastomosis. Therefore, we selected patients from the randomized DECREASE IV undergoing esophagectomy and evaluated the efficacy and safety of beta-blocker therapy.

**Methods:** A total of 101 patients scheduled for esophagectomy were randomized to beta-blocker therapy (n=52) or no beta-blocker therapy (n=49). Postoperatively data on troponin release and ECG were collected on day 1, 3, 7, and before discharge. Results of radiology, gastroscopy, and clinical signs of ischemia or leakage of the esophagogastric anastomosis were noted.

**Results:** Beta-blocker use was associated with a reduction in the combination of myocardial damage, myocardial infarction and cardiac death (16% vs. 4%, p=0.04). The rate of radiological anastomotic leakage was similar in both groups (16% vs. 16%, p=0.96), as well as the rate of ischemia at gastroscopy (26% vs. 17%, p=0.32) and the number of reoperations (16% vs. 14%, p=0.69).

**Conclusion:** Perioperative beta-blocker use in patients undergoing esophagectomy is associated with a reduction in cardiac events and is not associated with an increased risk for ischemic complications.

## INTRODUCTION

Patients undergoing major non-cardiac surgery are at significant risk of cardiovascular morbidity and mortality. Although the perioperative event rate has declined over the past 30 years, 30-day cardiovascular mortality in major non-cardiac surgery remains as high as 3% to 6%[1]. Myocardial infarction (MI) is the most frequent fatal complication in this respect, accounting for up to 50% of postoperative fatalities[2,3].

Due to the role of sympathetic activation in adverse perioperative cardiac outcomes, beta-adrenergic receptor blocking drugs have been proposed as a means for providing cardioprotection. Potential cardioprotective mechanisms of beta-blockers include a reduced heart rate and contractility and subsequently lower myocardial oxygen demand; a shift in energy metabolism from free fatty acids to the more energy efficient glucose; anti-arrhythmic effects; anti-renin/angiotensin properties; and anti-inflammatory effects possibly promoting plaque stability[4,5]. Several studies have suggested that perioperative beta-blocker use is indeed associated with a reduction of perioperative cardiac complications in patients at high cardiac risk[6,7].

According to the recent ACC/AHA guidelines patients undergoing esophagectomy for cancer are at increased risk for perioperative events[8]. Therefore this group of patients might benefit from perioperative beta-blocker therapy. However, there are serious concerns on the safety of perioperative beta-blocker use in this patient population. The blood flow to the new esophagogastric anastomosis after esophagectomy is of critical importance and might be compromised by the use of beta-blockers. Consequently this might lead to an increased incidence of anastomotic leakage and reoperation, resulting in major morbidity.

The randomized Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography IV study (DECREASE IV) was set up to test whether patients at intermediate cardiac risk benefit from perioperative beta-blocker and/or statin therapy. We used data of patients undergoing esophagectomy in this study to evaluate the possible cardioprotective effect of beta-blocker use and assess the safety of beta-blockers after esophagectomy.

## METHODS

### Patient population

The study design of the DECREASE IV study has been published previously[9]. A total of 1,066 patients were randomized for the DECREASE IV trial and received either perioperative beta-blocker therapy, statin therapy, both or neither[10]. For the current study we selected those patients who underwent esophagectomy for cancer, either by means of extended transthoracic resection or by limited transhiatal resection, and compared patients who were allocated to perioperative beta-blocker therapy (with or without statins) or no beta-blocker therapy (with or without statins).

Briefly, patients who were (1) aged 40 years or older, (2) scheduled for elective non-cardiac surgery and (3) have an estimated risk for cardiovascular death of more than 1%, were eligible for enrollment in the DECREASE-IV trial. Importantly, according to the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery[8] esophagectomy should be considered an intermediate risk surgical procedure with a cardiac risk of >1%.

Exclusion criteria for the trial were: (1) current use of beta-blockers, (2) contraindication for beta-blocker use, (3) the use of statins prior to randomization, (4) a contraindication for statin use, (5) unstable coronary artery disease, (6) extensive stress induced myocardial ischemia suggestive for left main disease or equivalent, (7) emergency surgery, (8) previous participation in the same trial study, (9) inability or unwillingness to provide written informed consent.

### Beta-blocker treatment regimen

The starting dose of bisoprolol, a so-called cardioselective beta-blocker, was 2.5 mg orally per day, if resting heart rate was >50 bpm. During hospitalization, resting heart rate was evaluated on a daily basis and drug dose was modified with steps of 1.25 or 2.5 mg per day, up to a maximum dose of 10 mg, aiming at a heart rate of 50-70 bpm. The use of an open-label design was therefore necessary in order to titrate the bisoprolol dose to the therapeutic heart rate. Patients unable to take bisoprolol orally received intravenous metoprolol until the patient was able to switch back to oral medication. Bisoprolol administration was temporarily withheld if any of the following developed: resting heart rate <50 bpm; systolic blood pressure <100 mmHg; heart failure; bronchospasm; PR interval >0.30 s; second or third degree AV block.

### Efficacy endpoint

The efficacy endpoint for the current study was a composite of myocardial damage, assessed by cardiac troponin T (cTnT) release, cardiac death and non-fatal myocardial infarction (MI) until 30-days after surgery. Cardiac troponin T was sampled systematically on days 1, 3 and 7 postoperatively and whenever clinically indicated. Additionally ECGs were collected on the same days. Nonfatal MI required any two of the following: (1) characteristic ischemic symptoms lasting > 20 minutes; (2) ECG changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists for at least 24 hours; (3) a positive troponin T measurement with characteristic rise and fall[11]. All deaths were classified as either cardiovascular or non-cardiovascular. Cardiovascular death is defined as any death with a cardiovascular complication as the primary or secondary cause, and includes deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Non-cardiovascular death is defined as any death with a primary non-cardiovascular cause, including surgery-related bleeding complications, cancer, trauma and infection. Sudden death in a previously stable patient is considered as cardiovascular[12].

### Safety endpoint

The safety endpoints for the current analysis consisted of radiological anastomotic leakage, clinical anastomotic leakage or infection of the cervical wound requiring opening of the wound, signs of ischemia during gastroscopy, and reoperation. It should be noted that these endpoints were not pre-specified in the original DECREASE IV study design. Data on these safety endpoints were identified independently by two investigators by meticulous screening of medical charts, radiology reports and reports of gastroscopy. If consensus could not be reached, the opinion of a third, independent investigator was final.

### Statistical analysis

Continuous data are presented as median values and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical characteristics between patients with or without beta-blocker therapy evaluated by Wilcoxon's nonparametric tests, Chi-square tests or Fisher's exact tests, as appropriate. Differences in the incidence of the endpoints were evaluated by a Chi-square test or Fisher's exact tests. The limit of statistical significance was set

at p = 0.05 (two-sided). All analysis was performed using the statistical software SPSS for Windows 15.0.1 (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

### Baseline characteristics

A total of 101 patients underwent esophagectomy, 72 by transhiatal resection and 29 by transthoracic resection. Baseline clinical characteristics are shown in TABLE 14.1. Due to randomization there were no statistically significant differences in baseline characteristics and medication use. Preoperative ECG abnormalities were found in 39 (39%) patients; Q-waves in 10 (10%), right bundle branch block in 8 (8%), left bundle branch block in 5 (5%), left ventricular hypertrophy in 4 (4%), and preventricular contractions in 6 (6%). Heart rate was similar at baseline in both groups, i.e. 77 ± 12.4 beats/min in patients allocated to beta-blocker therapy and 80 ± 12.7 beats/min in patients allocated to the control group. Importantly at the day of hospital admission, median 34 days after the start of beta-blocker therapy, patients on beta-blocker therapy had a significantly lower mean heart rate (62 ± 7.4 beats/min vs. 79 ± 12.6 beats/min, p<0.001).

**TABLE 14.1** Baseline characteristics and medication use per treatment group.

| | Beta-blocker (N=52) | Control (N=49) | P-value |
|---|---|---|---|
| **Baseline characteristics** | | | |
| Male gender (%) | 46 (85) | 37 (76) | 0.23 |
| Age, years (IQR) | 64.5 (56,72) | 61.8 (57,71) | 0.64 |
| Diabetes Mellitus (%) | 3 (6) | 5 (10) | 0.48 |
| Angina Pectoris (%) | 1 (2) | 3 (6) | 0.35 |
| Myocardial infarction (%) | 2 (4) | 3 (6) | 0.67 |
| Chronic heart failure (%) | 1 (2) | 0 | 1 |
| Stroke (%) | 1 (2) | 0 | 1 |
| Renal failure (%) | 0 | 0 | 1 |
| **Medication use** | | | |
| Statins (%) | 24 (46) | 21 (42) | 0.67 |
| Diuretics (%) | 4 (8) | 2 (4) | 0.68 |
| Aspirin (%) | 4 (8) | 1 (2) | 0.36 |
| Calcium antagonists (%) | 2 (4) | 0 | 0.50 |
| ACE inhibitors (%) | 5 (10) | 4 (4) | 0.44 |
| Angiotensin II inhibitors (%) | 3 (6) | 2 (4) | 1 |
| Anticoagulants (%) | 1 (2) | 1 (2) | 1 |
| Oral antidiabetics (%) | 1 (2) | 1 (2) | 1 |
| Insuline (%) | 1 (2) | 4 (8) | 0.20 |
| Glucocorticoids (%) | 4 (8) | 4 (8) | 1 |

*IQR denotes interquartile range; ACE denotes angiotensin converting enzyme

### Perioperative cardiac outcome

A total of 10 (9.9%) patients reached the combined efficacy endpoint of myocardial damage, myocardial infarction and cardiac death. Patients on beta-blocker therapy had a significant reduced risk for perioperative events; 3.8% vs. 16.3% (OR 0.21, 95% CI 0.04-0.98, p=0.036, FIGURE 14.1). The majority of cardiac events were asymptomatic. If no routine sampling of cTnT would have been performed 8

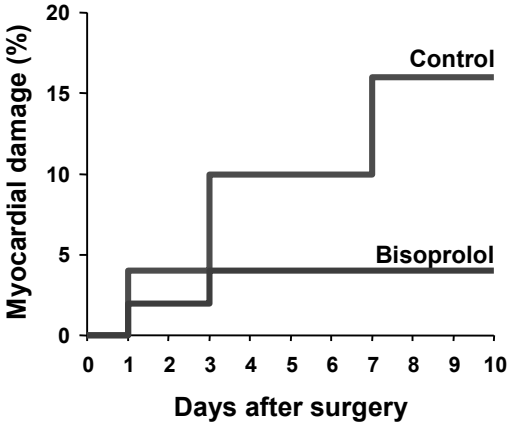


**FIGURE 14.1** Perioperative cardiac damage in beta-blocker users vs. control

out of 10 events would have been missed. Of the 10 patients who reached the combined efficacy endpoint 5 met the criteria for myocardial infarction. All of these patients were allocated to the control group.

### Safety outcome

The safety outcomes are shown in TABLE 14.2. Of the 101 patients 87 (86%) underwent X-ray with contrast. There was no difference in the incidence of radiological anastomotic leakage; 7/44 (15.9%) patients on beta-blockers vs. 7/43 (16.3%) patients not on beta-blockers (p=0.96). Clinical leakage or infection of the cervical wound requiring opening of the wound was scored in 19 patients, 9/52 (17.3%) vs. 10/49 (20.4%) for users and non-users respectively (p=0.69). Gastroscopy was performed in 91 (91%) patients. Ischemia was found in 8/48 (16.7%) using beta-blockers and in 11/43 (25.6%) of patients not using beta-blockers (p=0.32). In total 15 (16.8%) patients underwent reoperation, 7/52 (13.5%) beta-blocker users and 8/49 (16.3%) non-users (p=0.69). Overall 41 (40.6%) patients had either a radiological and/or clinical anastomotic leakage and/or ischemia during gastroscopy or a reoperation. There was no difference in the incidence of the combined safety endpoint between both groups; 38.5% vs. 42.9% for users and non-users respectively (p=0.65).



**TABLE 14.2** Safety outcome.

| | Beta-blocker | Control | P-value |
|---|---|---|---|
| Radiological anastomotic leakage | 7/44 | 7/43 | 0.96 |
| Clinical leakage or infection of the cervical wound | 17.3% | 20.4% | 0.69 |
| Ischemia at gastroscopy | 8/48 | 11/43 | 0.32 |
| Reoperation, any | 13.5% | 16.3% | 0.69 |
| Reoperation, because of ischemia | 5.8% | 6.1% | 1.0 |
| Combined | 38.5% | 42.9% | 0.65 |

Combined is the combination of radiological anastomotic leakage, clinical leakage or infection of the cervical wound, ischemia at gastroscopy, and reoperation.

## DISCUSSION

The current study shows that perioperative beta-blocker therapy in patients undergoing esophagectomy for cancer is associated with a reduction in cardiac events. Importantly the blood flow to the gastroesophageal anastomosis seems not to be affected by the use of selective beta-blockers as the rate of anastomotic leakage and ischemia is similar in users and non-users.

Patients undergoing major non-cardiac surgery are at increased risk for perioperative cardiac events even if the number of clinical risk factors is limited. As described in the ACC/AHA guidelines esophagectomy should be considered an intermediate risk surgical procedure in terms of cardiac risk[8]. The pathophysiology of perioperative cardiac events is complex and not fully understood. However, similar to the non-operative setting two mechanisms seems to be involved in most cases: (1) coronary plaque rupture leading to thrombus formation and subsequent vessel occlusion, and (2) increased myocardial oxygen demand (e.g. tachycardia and increased contractility) leading to myocardial oxygen supply/demand mismatch that when sustained might lead to myocardial infarction. In patients undergoing noncardiovascular surgical procedures in particular the latter mechanism seems to play an important role. Due to the role of myocardial oxygen/supply mismatch in adverse perioperative cardiac outcomes, beta-adrenergic receptor blocking drugs have been proposed as a means for providing cardioprotection. In particular beta-blockers reduce heart rate and contractility and subsequently lower myocardial oxygen demand, cause a shift in energy metabolism from free fatty acids to the more energy efficient glucose, have anti-arrhythmic effects and some other potentially cardioprotective characteristics.

Large series of patients undergoing esophagectomy have shown cardiac complication rates, such as myocardial infarction, of approximately 1%[13-15]. It must be noted however that in these studies there was no systematic screening for adverse cardiac events such as the frequent sampling of cardiac troponins which was performed in the current study. This might explain why the event rate in the current study was higher than what has been reported in literature so far. It should be noted that 80% of perioperative cardiac events in the current study would have been missed if routine sampling of cTnT had not been performed. In postoperative patients, symptoms of cardiac complications might very well be atypical or absent even when ECG and/or biomarkers are abnormal. It is important to realize that myocardial infarction might occur with atypical symptoms, or even without symptoms, being detected only by ECG, biomarker elevations, or cardiac imaging. Classical symptoms of myocardial ischemia include various combinations of chest, upper extremity, jaw, or epigastric discomfort with exertion or at rest. Often, the discomfort is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnea, diaphoresis, nausea, or syncope. Considering these classical symptoms it is hardly surprising that such a large number of episodes of myocardial ischemia and infarction are missed in the perioperative period because symptoms are masked by residual anesthetic effects, administration of analgesic agents, competing somatic stimuli such as incisional pain, and other factors.

Though beta-blockers have shown to be effective in reducing the risk of cardiac events, they have also been linked to serious adverse events in the perioperative period. The recently published POISE trial showed that starting high doses of metoprolol hours before surgery resulted in an increased risk for postoperative stroke[16]. Most of these strokes seem to have been attributable to perioperative episodes of hypotension, which might have been caused by beta-blocker use. On the other hand, in the DECREASE trials, starting bisoprolol at a relatively low dose of 2.5 mg approximately 30 days prior to surgery, there was no association between beta-blocker use and perioperative stroke[17]. Similar to

the brain the new gastroesophageal anastomosis after esophagectomy is vulnerable for hypotensive episodes. These episodes may lead to an insufficient blood flow to the anastomosis resulting in ischemia and subsequently leakage of the anastomosis. This fear might prevent the prescription of perioperative beta-blocker therapy in these patients. However, as shown in the current study, a regimen of perioperative beta-blocker use starting low dose cardioselective beta-blockers approximately 30 days prior to surgery did not result in an increased risk for anastomotic leakage or ischemia nor in an increased risk for reoperation.

In conclusion, though the number of studied patients is relatively small, patients undergoing esophagectomy seem to benefit from perioperative beta-blocker therapy, as it is associated with improved cardiac outcome while the gastroesophageal anastomosis is not compromised.

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# Chapter 15

## Pro: Beta-blockers are indicated for patients at risk for cardiac complications undergoing non-cardiac surgery

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Perioperative cardiac complications are a major cause of morbidity and mortality in patients undergoing non-cardiac surgery. Annually an estimated 100 million adults undergo non-cardiac surgery. The incidence of cardiac death after non-cardiac surgery is estimated at 0.5%[1]. Consequently, each year approximately 500 000 patients die perioperatively due to cardiac causes. According to the study by Lee et al. in a relatively unselected group of patients the overall risk for myocardial infarction (MI) after non-cardiac surgery is 1.1%[2], i.e. 1.1 million MI's annually worldwide.

Although the pathophysiology of a perioperative MI is not entirely clear, coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion seems to be an important causative mechanism behind such complications, similar to myocardial infarctions occurring in the non-operative setting[3]. The incidence of plaque rupture, with superimposed thrombosis, is possibly increased by the stress response to major surgery. This stress response includes a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation and consequent hypercoagulability[4]. In patients with severe stenotic CAD, perioperative MI may also be caused by a sustained myocardial supply / demand imbalance due to prolonged tachycardia and increased myocardial contractility. The association of perioperative MI with prolonged, severe, perioperative myocardial ischemia, and the frequency of non-transmural or circumferential subendocardial infarction in the perioperative setting support this mechanism[5]. At least two studies evaluating the pathophysiology of perioperative MI using non-invasive tests, coronary angiography, and autopsy results showed that coronary plaque rupture and thrombus formation occurred in around 50% of all fatal cases, while a sustained mismatch of oxygen supply and demand was responsible for the remaining 50%[3,6].

## Mechanism of the protective effect of beta-blockers

The mechanisms by which beta-blockers exert their cardioprotective effect are multifactorial. Beta-blockers reduce heart rate and contractility and subsequently myocardial oxygen demand; induce a shift from free fatty acids as the main cardiac energy substrate towards glucose resulting in improved energy efficiency and an improved outcome; possess an anti-arrhythmic effect and anti-renin/angiotensin properties; and have anti-inflammatory qualities[7-9]. The effects on heart rate, contractility, and energy substrate shift occur almost instantly. However, the effect on inflammatory response may only be observed after a prolonged period of beta-blocker use. For example, in a randomized study of 200 surgical patients at risk for CAD Mangano et al. found no difference in the incidence of perioperative cardiac events among beta-blocker users, but there was a reduced incidence of late fatal cardiac events[10]. The benefits of beta-blocker use were not immediately apparent but evolved over the first 6 to 8 months after initiation of beta-blocker therapy[11].

## Clinical evidence for the effectiveness of perioperative beta-blocker therapy

Although widely prescribed during non-cardiac surgery, the evidence for perioperative beta-blocker use is mainly based on only two small randomized prospective clinical trials and several observational studies. The first trial evaluated the effect of atenolol in high-risk patients undergoing non-cardiac surgery[10]. In this study 200 patients with risk factors for or known ischemic heart disease were randomized for atenolol (50 or 100 mg) or placebo prior to surgery. Atenolol therapy was not associated with an improved in-hospital outcome (cardiac death or myocardial infarction), however, continuous 3-lead Holter monitoring showed a 50% reduction of myocardial ischemia in the atenolol treated group during the first 48 hours after surgery. The second trial showed, in a selected high-risk population of 112 vascular surgery patients, a tenfold reduction in the incidence of perioperative cardiac death and myocardial infarction, compared to patients without beta blockers (3.4% vs. 34%)[12]. The high incidence of perioperative cardiac events was explained by the patient selection: from a

population of 1,351 patients only 112 were included with stress-induced myocardial ischemia during dobutamine echocardiography.

These promising results were not supported by two recent trials evaluating the effect of beta-blockers in respectively vascular surgery patients and diabetics[13,14]. In the POBBLE trial low-risk patients, those with a history of ischemic heart disease were excluded, scheduled for vascular surgery were randomized for metoprolol (n=55) or placebo (n=48). Metoprolol, 25 mg or 50 mg, depending on patient's weight was started the day before surgery. Holter monitoring and repeated troponin measurements were performed during hospital stay. No difference was observed in the incidence of perioperative cardiovascular events; 15 (34%) vs. 17 (32%), in patients on placebo vs. metoprolol. The only difference was observed in the length of hospital stay, which was significantly shorter in those taking metoprolol, 10 vs. 12 days. The more recently presented DIPOM study, evaluating the cardioprotective effect of a fixed dose of metoprolol on the evening before major non-cardiac surgery in 921 diabetics showed no difference in 30 day morbidity and mortality. However the study was powered for a 10% difference after one year of follow-up.

## How can the conflicting results of perioperative beta-blocker trials be explained?

*Dosing of perioperative beta-blocker therapy*

In a study by Raby et al. of 150 patients ischemia was observed prior to vascular surgery using ambulatory ECG monitoring in 26 patients[6]. The heart rate at which ischemia occurred was noted (ischemic threshold), these patients were randomized to either tight heart rate control, i.e. 20% less than the ischemic threshold but >60 bpm, or normal, non adjusted beta-blocker therapy. In 13 patients with heart rates below the ischemic threshold 1 (7.7%) had postoperative ischemia versus 12 out of 13 (92%) patients with less tight control. Based on this study it seems obvious that beta-blockers should not be considered a "fire-and-forget" therapy. Monitoring of the heart rate and consequent dose adjustment of beta-blockers in case of inadequate lowering of the heart rate is of critical importance.



The design of the POBBLE trial was such that patients received a fixed dose of metoprolol according to weight, i.e. 25 or 50 mg, and dosage was not adjusted in case of unsatisfactory heart rate control. Double-blind randomized controlled trials are very important in medical research. However, a double blind trial in case of perioperative beta-blockers is simply not possible since heart rate control seems to play such a pivotal role in the effectiveness of perioperative beta-blocker therapy. This same critique also applies for the DIPOM trial. Also in this trial patients received a fixed dose of metoprolol and dosage was not adjusted in case of inadequate lowering of the heart rate. It might be argued that even a small reduction in heart rate is beneficial to patients, though the benefits might be less pronounced. Consequently, such trials should be powered on a less extensive effect of beta-blockade.

*Timing of perioperative beta-blocker therapy*

The onset of the cardioprotective effect has important implications for perioperative management. The effects on heart rate, contractility, and energy substrate shift occur almost instantly. However, the effect on inflammatory response may only be observed after a prolonged period of beta-blocker use. In a randomized study of 200 surgical patients at risk for CAD Mangano et al. found no difference in the incidence of perioperative cardiac events among beta blocker users, but there was a reduced incidence of late fatal cardiac events[10]. The benefits of beta-blocker use were not immediately apparent but evolved over the first 6 to 8 months after initiation of beta-blocker therapy. It could be possible that immediately after initiation of therapy not all effects are achieved and the benefits of beta-blockers will become evident only after weeks to months of treatment. Both the DIPOM and POBBLE trial started beta-blocker therapy on the day before surgery as well. Based on the unknown time interval between

initiation and optimal effectiveness it might be argued that beta-blocker therapy should be initiated well before surgery. The DECREASE-trial showed the largest effect of perioperative beta-blocker therapy. The time between beta-blocker therapy initiation and surgery was 37 days in this trial.

*Other aspects influencing effectiveness of beta-blocker therapy*

Besides timing and dosage some other factors may influence the effectiveness of beta-blocker therapy. Recently Lanfear et al. described the influence of gene polymorphisms and response to beta-blockers[15]. In their article they conclude that survival in patients receiving beta-blocker therapy after an acute coronary syndrome is different according to different types of ADRB2 genotypes. Whether this also plays a role in perioperative beta-blocker therapy remains unclear but is very likely. The idea of genotyping patients before surgery to identify those who will benefit most of perioperative beta-blockade is tempting though currently not yet feasible.

Another point that might influence the effectiveness of beta-blocker therapy is its withdrawal just shortly prior to surgery or in the immediate postoperative days. As has been reported sudden withdrawal of beta-blockers lead to a "rebound" effect resulting in blood pressure and heart rate increase, and plasma noradrenalin concentrations changes[16]. This might lead to an excess in cardiac complications in the perioperative setting. Recently, Redelmeier et al. provided new evidence for these concerns[17]. In their study they showed that the long-acting atenolol was superior to the short-acting metoprolol in the perioperative setting, probably due to the acute withdrawal effect after missed doses in short-acting beta-blockers.

## Should all patients at increased cardiac risk be on perioperative beta-blocker therapy?

Based on existing evidence, a simple answer would obviously be "yes". However the next question would then be which patients are at increased risk for perioperative cardiac complications and how is this increased risk defined? In a recent large cohort study performed by Lindenauer et al. in 663 635 patients it was shown that patients at intermediate or high risk, i.e. ≥ 2 risk factors according to the Revised Cardiac Risk Index, benefited from beta-blocker therapy[18]. On the other hand, in patients at low risk perioperative beta-blocker therapy was associated with no benefit and even possible harm. This finding indicates that perioperative beta-blocker therapy is effective but patients should be selected based on their cardiac risk as assessed by preoperative screening.

The Revised Cardiac Risk Index by Lee et al. identified 6 predictors (high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, and renal failure) of major cardiac complications[2]. Based on the presence of 0, 1, 2, or 3 or more of these predictors, the rate of major cardiac complications was estimated to be 0.4%, 0.9%, 7%, and 11%, respectively. Though the Lee index is considered by many clinicians and researchers as the most relevant index for predicting perioperative cardiac risk in non-cardiac surgery, the patients studied by Lee et al can hardly be considered as an average non-cardiac surgical population. Thoracic, vascular and orthopedic patients were overrepresented in this study population. Recently Boersma et al. validated the Lee risk index in a large cohort (n=108,593) of all types of non-cardiac surgical procedures[1]. The Lee index was predictive of cardiovascular mortality with odds ratios of 1 (reference), 2.0, 5.1, and 11.0. When the Lee index was adapted and information of preoperative ECG and more detailed information on the surgical risk of the procedure were added, the predictive value improved substantially.

## Conclusion

Perioperative beta-blocker use is effective in patients at high cardiac risk when beta-blockers are administered in such a way that tight-heart rate control is achieved. It is recommended to start

beta-blocker therapy well before surgery to achieve the optimal protective effect. In patients at intermediate cardiac risk the benefits of perioperative beta-blocker use seems less clear. The results of randomized trials in patients at intermediate risk conducted so far (i.e. DIPOM and POBBLE) can not be considered conclusive since poor heart rate control and the short interval between initiation and surgery may have seriously influenced the outcome of these two studies. The results of two large ongoing trials, i.e. POISE and DECREASE IV, have to be awaited to make firm conclusions on the effectiveness of perioperative beta-blocker use in patients at intermediate risk.

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# Chapter 16

## Perioperative strokes and beta-blocker use

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Recently the results of the PeriOperative Ischemic Evaluation (POISE) study have caused concern regarding beta-blocker use in the perioperative setting[1]. Though beta-blocker therapy was associated with an improved cardiac outcome, overall mortality was increased in the metoprolol treated group. This was partially related to the increased incidence of postoperative stroke occurring early after surgery. These findings might have important implications on perioperative beta-blocker use, not only for initiation of therapy prior to surgery in beta-blocker naïve patients but also whether or not to continue therapy throughout surgery. This commentary reviews the incidence and pathophysiology of perioperative stroke and the relation of beta-blockers and perioperative stroke, focusing on non-cardiac surgery.

The risk of clinically apparent perioperative brain injury such as stroke varies widely among different types of surgery. Whereas patients undergoing general surgery appear to be at low risk (0.08-0.7%), those undergoing heart valve surgery and aortic arch repair have a high incidence of perioperative stroke (8-10%)[2]. In Europe annually 40 million general surgical procedures are performed. Therefore it is estimated that 32,000–280,000 patients suffer from postoperative stroke. However, the true incidence of cerebral complications is probably underestimated as subtle forms of brain injury are commonly classified as delirium that may only be detected by rigorous neuropsychological testing.

The knowledge of the pathophysiology of postoperative cerebral complications is predominantly based on cardiothoracic surgery patients. It is estimated that 62% of strokes in this population have an embolic origin, 10% are related to hypoperfusion, and 10% have multiple causes[2]. Importantly, only 1% of strokes are caused by intracerebral hemorrhage. Early strokes are mostly attributable to manipulations of the heart and aortic arch and events caused by the cardiopulmonary bypass pump. In the other half (delayed) stroke seems to be related to adverse postoperative cardiac events such as myocardial infarction and atrial fibrillation.

Compared to stroke after cardiac surgery, the pathophysiology of stroke after non-cardiac surgery is ill defined. Perioperative hemodynamic instability and cardiac events, such as myocardial infarction and arrhythmias likely play a major role. Recently, the POISE study identified a new risk factor for perioperative ischemic strokes: high-dose metoprolol succinate initiated for cardiac protection in patients undergoing non-cardiac surgery.

## Perioperative beta-blockade

Beta-blockers in the non-surgical setting are used widely and proven effective in patients with documented coronary artery disease (CAD) to restore the balance of myocardial oxygen demand and supply[3]. Although initially contraindicated in patients with heart failure and peripheral atherosclerotic disease, beta-blockers are now recommended therapy for these patients[4,5]. Similar to the non-surgical setting, beta-blockers are advocated for patients with documented CAD undergoing vascular surgery. However, there is still controversy regarding perioperative beta-blocker use in the general surgical population.

Several randomized studies have shown a beneficial cardiac effect of perioperative beta-blocker use. In a placebo-controlled trial involving 200 high-risk patients, Mangano et al. found that atenolol (50 or 100 mg), administered intravenously beginning 30 minutes prior to surgery and then orally throughout hospitalization, did not lower the risk of death from cardiac causes or myocardial infarction during hospitalization[7]. However, it did result in a 50 percent reduction in myocardial ischemia as assessed by continuous 48-hour Holter monitoring. The authors observed a non-significant increase in incidence of stroke (i.e. 4% vs. 1%, p=0.21). The DECREASE study (Dutch Echocardiographic Cardiac

Risk Evaluation Applying Stress Echocardiography) confirmed the benefits of beta-blockers in non-cardiac surgery. In a high-risk population of 112 patients with a positive dobutamine echocardiography for CAD undergoing vascular surgery, the rate of perioperative cardiac death and myocardial infarction among patients who were randomly assigned to bisoprolol therapy (5 or 10 mg) started at least 30 days before surgery was 90 percent lower than that among patients assigned to standard care (3.4 percent vs. 34 percent)[8].

More recent studies have shown mixed results of beta-blocker therapy (FIGURE 16.1). The MaVS (Metoprolol After Vascular Surgery) trial randomized 496 patients to metoprolol or placebo starting 2 hours before surgery until hospital discharge or a maximum of 5 days after surgery[9]. No significant differences in outcome were observed at 30 days and 6 months after surgery. In the POBBLE (Perioperative Beta-Blockade) trial, 103 patients undergoing vascular surgery were randomized to metoprolol or placebo, starting less than 24 hours before surgery until 7 days after, and showed no difference in 30-day cardiovascular outcome[10]. Within 30 days, cardiovascular events occurred in 32% and 34% patients in the metoprolol and placebo groups, respectively (adjusted RR 0.87, 95% CI 0.48 to 1.55). The DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, which started therapy at the earliest in the evening before major non-cardiac surgery, again showed no difference in 30-day cardiac outcome[11].

These mixed results necessitated a large randomized trial. In the landmark study of the POISE investigators, 8351 patients were randomly assigned to either metoprolol succinate controlled release or placebo. The primary endpoint of cardiac death, non-fatal myocardial infarction, or non-fatal cardiac arrest was reduced in the metoprolol CR group compared with placebo (5.8% vs. 6.9%, hazard ratio 0.84, 95% CI 0.70–0.99, p=0.04). However, this beneficial cardiac effect was at the cost of an increased incidence of all-cause mortality and stroke. The incidence of stroke was increased from 0.5% to 1.0% in patients randomized to metoprolol treatment. Stroke was associated with perioperative hypotension, bleeding, atrial fibrillation, and a history of stroke or transient ischemic attack.



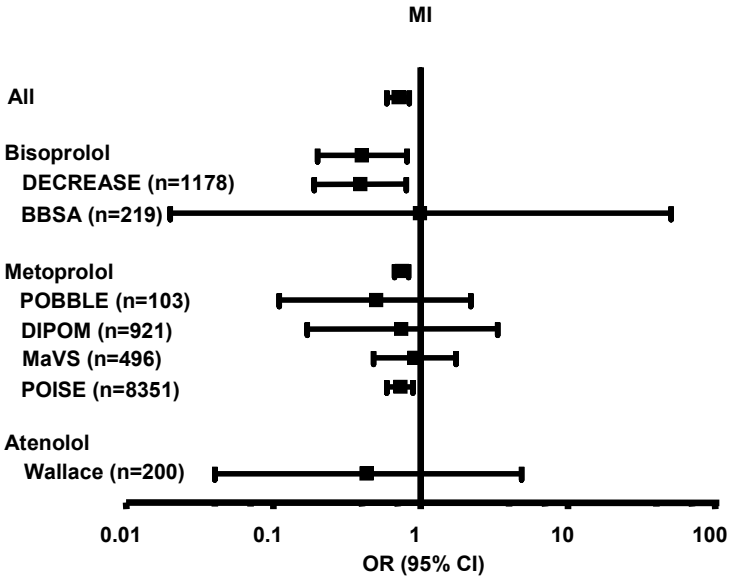


**FIGURE 16.1** Odds ratios of randomized beta-blocker trials for perioperative myocardial infarction.

## Perioperative beta-blocker therapy and stroke

The increased risk for perioperative stroke in the POISE trial has caused concerns on the safety profile of perioperative beta-blocker therapy. This has been augmented by the meta-analysis published in the same Lancet article. The meta-analysis demonstrated that overall perioperative beta-blocker therapy was associated with a 2.19-fold (95% CI 1.06-4.50) increased risk for nonfatal perioperative stroke; however, the DECREASE I and IV studies were not included. Importantly, the impact of different dosing regimens, timing of initiation and type of beta-blocker therapy were not fully appreciated in this analysis. If the results of DECREASE I and IV are added to the meta-analysis, beta-blockers are still associated with an increased risk for perioperative stroke. However, as is shown in FIGURE 16.2, the overall result in the randomized low-dose bisoprolol studies show no association with perioperative stroke at all (OR 1.06, 95% CI 0.32–3.56) in contrast to studies using metoprolol (OR 2.07, 95% CI 1.27–3.39). It should be noted that the cardioprotective effect was clear for both beta-blocker types; OR for bisoprolol 0.40 (95% CI 0.20–0.81) and OR for metoprolol 0.74 (95% CI 0.61–0.89, FIGURE 16.1). The key question is whether it is the type of beta-blockers that makes the difference or that other factors play a significant role in these results. Considering this, there are several potential pitfalls in the perioperative administration of beta-blockers that should be considered including: timing of initiation of therapy, dosage of beta-blockers, the impact of beta-blocker withdrawal, and treatment targets.

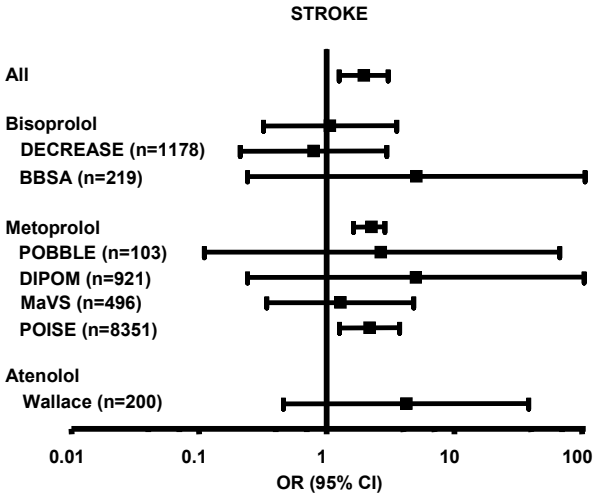


**FIGURE 16.2** Odds ratios of randomized beta-blocker trials for perioperative stroke.

## Timing

Timing of initiation of perioperative beta-blocker therapy seems to play a pivotal role in the risk of stroke, as shown in FIGURE 16.3. In studies starting beta-blocker therapy hours before surgery, the incidence of postoperative stroke was higher compared to those who were on beta-blockers for at least a week prior to surgery. It should be noted that the same study group performed the two trials that started beta-blockade weeks in advance of surgery, using bisoprolol. Although bisoprolol is not commonly used in the US for patients with proven CAD, it would be interesting to determine whether other centers achieve similar results with this low-dose bisoprolol regimen. In most non-surgical studies, in particular in heart failure, there is a similar up titration of beta-blockers. In other words, beta-blocker therapy is started at a relative low dose and is subsequently up titrated according to

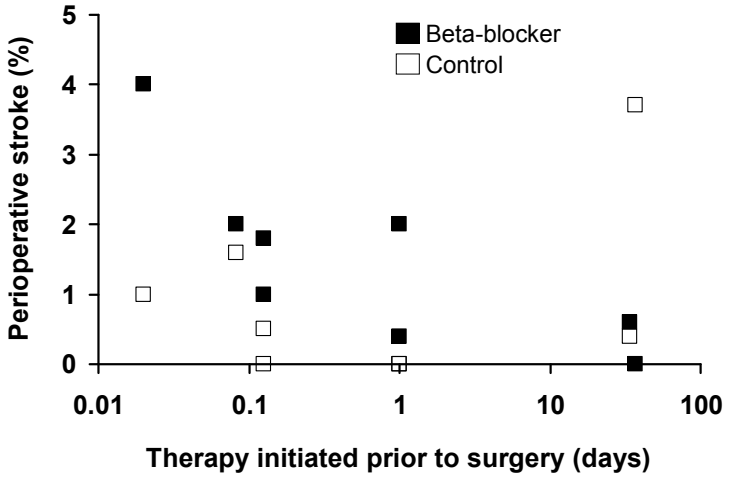


**FIGURE 16.3** Relation between timing of initiation of beta-blocker therapy and the risk for perioperative stroke.

blood pressure and heart rate. This approach has been shown to be effective and safe in heart failure patients[4]. In patients undergoing surgery in which beta-blocker therapy is initiated within hours before surgery, there might be an increased risk of hypotension and bradycardia if beta-blockers are administered too aggressively. The response to beta-blocker therapy cannot be adequately monitored during this short period of time leading to a danger of overdosing. Importantly, patients on chronic beta-blocker therapy should continue their therapy in the perioperative period as sudden beta-blocker withdrawal increases the risk of adverse cardiac events.[12]



## Dosing

Closely related to the issue of timing in perioperative beta-blocker therapy is the question regarding what dosing scheme should be used. In contrast to other beta-blocker studies, patients randomized in the POISE trial could receive up to 400 mg metoprolol succinate controlled release the day of surgery; 100 mg 2-4 hours prior to surgery, another 100 mg within 6 hours after surgery and 200 mg within 12-18 hours after the first postoperative dose. In the non-surgical setting, lower starting doses and slower up titration are commonly recommended. For instance, in patients with heart failure, 12.5–25 mg a day is started for 2 weeks and for hypertension the initial dose is 25–100 mg, usually increased at weekly intervals. This is important since a large proportion of high-risk elderly patients undergoing surgery may have some form of (asymptomatic) left ventricular dysfunction. The DECREASE treatment regimes start 2.5 mg bisoprolol, which is approximately the same strength as 50 mg of metoprolol. The starting dose of metoprolol succinate in the POISE trial was 2–8 times the commonly prescribed dose for perioperative beta-blocker therapy; other trials using metoprolol start usually at ranges from 50 to 100 mg per day[9-11]. It is noteworthy that in the DECREASE II trial, starting with 2.5 mg bisoprolol once daily, in approximately 75% of patients the target heart rate of 60-65 beats per minute was achieved without dose adjustment[13].

In conclusion, initiating prophylactic high-dose beta-blocker therapy in patients undergoing non-cardiac surgery is associated with fewer cardiac events but with an increase in strokes. However, if prophylactic beta-blocker therapy is initiated at a low dose and up titrated in the preoperative period, the risk of stroke seems to be similar to that of patients not on beta-blockers while the cardioprotective effect is maintained. Preferably these results should be confirmed in a large-scale trial, starting

beta-blocker weeks before surgery at a low dose, as well as determining the optimal approach in patients at high risk of perioperative cardiac morbidity and present the morning of surgery without having been placed on a beta-blocker.

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# Chapter 17

## Statins for the prevention of perioperative cardiovascular complications in vascular surgery

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*J Vasc Surg. 2006;44(2):419-24.*

## INTRODUCTION

Patients undergoing major non-cardiac vascular surgery are at significant risk of cardiovascular morbidity and mortality due to underlying symptomatic or asymptomatic coronary artery disease (CAD)[1]. Though developments in anesthesiological and surgical techniques, e.g. locoregional anesthesia and endovascular treatment modalities have improved postoperative cardiac outcome considerably, perioperative cardiac complications remain a significant problem. The incidence of perioperative myocardial infarction in major non-cardiac vascular surgery is around 3 to 4%[2] and the prevalence of (a)symptomatic perioperative myocardial ischemia as assessed by serum troponin I or serum troponin T is even 15 to 25%[3,4].

Although the pathophysiology of perioperative cardiac complications is not entirely clear, two causative mechanisms seem to be responsible for the majority of these complications: (1) vulnerable coronary plaque rupture[5,6], leading to thrombus formation and subsequent vessel occlusion, and (2) a sustained mismatch of coronary artery oxygen supply and demand due to increased oxygen demand during the perioperative period. Each of these mechanisms seem to account for approximately half of all fatal myocardial infarctions as was found in two studies using non-invasive tests, coronary angiography, and autopsy results[7,8]. A similar mechanism, i.e. vulnerable atherosclerotic plaque rupture, is proposed to explain perioperative strokes in patients undergoing carotid endarterectomy for carotid artery stenosis[9].

Recently, 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors (statins) have gained attention as a possible new strategy for the prevention of vulnerable atherosclerotic plaque rupture[10].

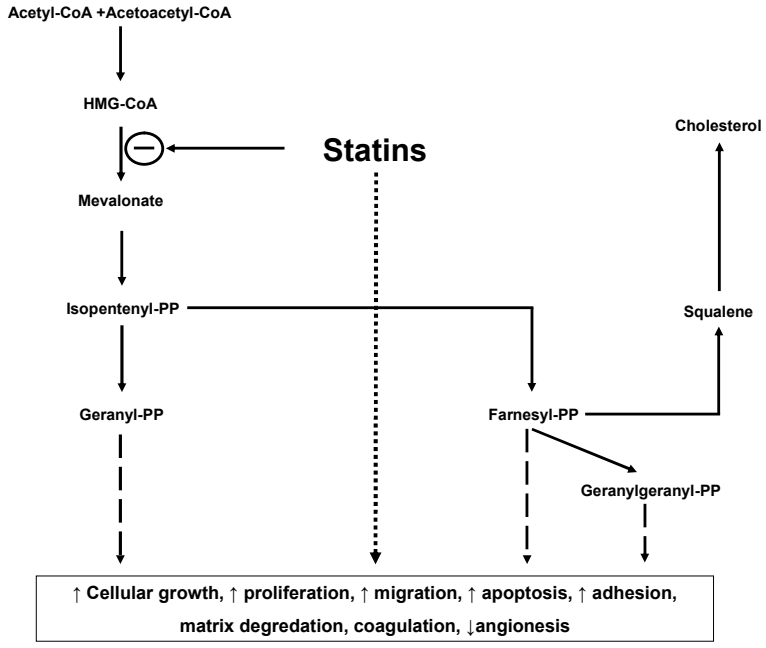


**FIGURE 17.1** Cholesterol-lowering and pleiotropic effects of statins.
(Partially derived from Schonbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? Circulation 2004;109:II18-26).

Numerous clinical trials have clearly demonstrated that statin use is associated with a substantial long-term reduction in the risk for cardiovascular morbidity and mortality in patients with or at risk of coronary heart disease. However, lipid lowering seems not to be the only beneficial effect of statins. Other, so-called pleiotropic, effects of statins have recently been described (FIGURE 17.1)[11]. One of these pleiotropic effects may be the stabilization of vulnerable plaques during surgical procedures. This may result in a reduced perioperative cardiovascular mortality and morbidity rate.

In this clinical update we will review recent clinical evidence on the efficacy and safety of statins and their role in the prevention perioperative cardiovascular complications.

## Vulnerable plaque and statins

Arterial plaques at high risk of rupture are known as vulnerable plaques. The prevalence of vulnerable plaques is high, also in seemingly stable patients. However, it is impossible to predict whether structurally vulnerable plaques may become unstable weeks, months, or years after their detection. For the cardiac situation, surgery imposes extra myocardial workload, resulting in mechanical stress, stress-induced inflammation and possibly spasms. This can cause vulnerable plaques to become unstable, leading to the cascade of plaque rupture, thrombus formation, myocardial ischemia and eventually myocardial infarction. Factors leading to unstable arterial plaques are multiple and complex. However, in general, the risk of plaque rupture is related to two factors: the intrinsic individual plaque characteristics and an extrinsic force triggering plaque disruption. Intrinsic factors include, for example, plaque morphology. As reported by Naghavi et al, in their extensive review on vulnerable plaques, inflammation is one of the major extrinsic factors involved in the rupture of vulnerable plaques[5,6].

The pleiotropic effects of statins include several possible plaque stabilizing effects such as the increased expression of endothelial nitric oxide synthase, the reduced production of endothelin-1 and the generation of reactive oxygen species, an improvement of the thrombogenic profile, and, importantly, a reduction in inflammation via the reduced expression of inflammatory cytokines, chemokines, adhesion molecules and a lowering of CRP levels. Therefore the perioperative prescription of statins might improve plaque stability.



## Statins in major vascular, non-cardiac surgery

There have been several recent studies that addressed the beneficial effect of statin use in patients undergoing non-cardiac surgery including vascular surgery (TABLE 17.1). In a case-control study among 2,816 patients who underwent major vascular surgery statin use was associated with a significant four-fold reduction in all-cause mortality (adjusted odds ratio 0.22 and 95% confidence interval, 0.10 to 0.47) compared to patients with no statin use[12]. The beneficial effect of statin use was consistent in subgroups of patients according to the type of vascular surgery, cardiac risk factors, and cardioprotective medication use including aspirin and beta-blockers.

Kertai et al. found similar effects of statins in vascular surgery patients for the composite endpoint of 30-day nonfatal myocardial infarction or all-cause death (adjusted odds ratio 0.24, 95% CI: 0.10-0.70). Importantly they also found the effect of statins to be independent of beta-blocker use[13].

The first blinded, placebo-controlled, randomized trial, in which the influence of statin use on perioperative cardiovascular complications was investigated, has been reported by Durazzo[14]. In their study, this research group randomly assigned 100 patients to treatment with either 20 mg atorvastatin or placebo. Patients received treatment for 45 days and at least 2 weeks before surgery. One month after surgery patients with elevated cholesterol levels were advised to continue or start statin therapy. The outcome of this trial was the endpoint of cardiovascular events, defined as cardiac

**TABLE 17.1** Studies of the effectiveness of perioperative statin use in major vascular, non-cardiac surgery.

| Author | Year | Type of study | N | Type of surgery | Rx prior to surgery |
|---|---|---|---|---|---|
| Poldermans et al.[12] | 2003 | Case-control | 480 | Vascular | Chronic use |
| Kertai et al.[13] | 2004 | Cohort | 570 | Vascular | Chronic use |
| Durazzo et al.[14] | 2004 | RCT | 100 | Vascular | 30 days |
| Lindenauer et al.[15] | 2004 | Cohort | 780,591 | General | Chronic use |
| O'Neil-Callahan et al.[16] | 2005 | Cohort | 1,163 | Vascular | Chronic use |

| Cont'd | End Point | Event rate in controls | Odds Ratio | NNT |
|---|---|---|---|---|
| Poldermans et al.[12] | 30-day all cause mortality | Not reported | 0.22 | Not reported |
| Kertai et al.[13] | 30-day mortality or nonfatal MI | 11.0% | 0.24 | 14 |
| Durazzo et al.[14] | Death, nonfatal MI, ischemic stroke, unstable angina within 6 months after surgery | 26% | 0.31 | 6 |
| Lindenauer et al.[15] | In-hospital all cause mortality | 3.2% | 0.71 | 109 |
| O'Neil-Callahan et al.[16] | Composite of death, MI, ischemia, congestive heart failure, ventricular tachycardia during hospitalization | 16.5% | 0.52 | 15 |

RCT = Randomized Controlled Trial; CEA = Carotid Endarterectomy; MI = Myocardial Infarction; NNT = Number Needed to Treat

death, non-fatal MI, stroke or unstable angina pectoris. Patients were followed up to 6 months after the surgical procedure. Of 100 patients 90, 44 statin users and 46 non-users, underwent elective vascular surgery. The 6-month incidence of cardiovascular events was 3.1-fold reduced in statin users compared with non-users (p = 0.022). Lindenauer et al. also confirmed the beneficial effects of statins based on the results of their large-scale retrospective studies. Lindenauer performed a retrospective cohort study based on the hospital discharge and pharmacy records of over 780,000 patients in 329 hospitals throughout the United States. All patients underwent elective major surgical procedures and survived at least the first two postoperative days. In total, 70,159 of these patients were identified as statin users. After correction for numerous baseline differences, statin users had a 1.4-fold reduced risk of in-hospital mortality. Subsequently, Lindenauer concluded that perioperative statin use might result in a reduced risk of death after major surgical procedures[15]. Finally, O'Neil-Callahan et al. collected data of 1,163 patients who underwent non-cardiac vascular surgery and found that patients who were statin users had a substantially lower perioperative cardiac complication rate than patients without statin use (odds ratio 0.52, 95% confidence interval, 0.35 to 0.77)[16]. The protective effect of statin use was similar across different risk group categories, and persisted after accounting for the likelihood of statin use in patients with hypercholesterolemia.

## Statins in carotid artery surgery

Another type of surgery, associated with less cardiac complications but a relatively high risk of cerebral complications, is carotid endarterectomy. Recently McGirt et al.[17] showed a decreased incidence in perioperative all-cause mortality in statin users (n= 657) compared to non-users (n = 909) who underwent carotid endarterectomy (adjusted OR 0.21, 95% CI 0.05–0.96, TABLE 17.2), a type of surgery considered to be an intermediate risk procedure according to the current ACC/AHA guidelines[18]. The incidence of myocardial infarction was not significantly different between statin users and non-users in this report (1.2% vs. 2.1%, p = 0.19), probably due to the relatively low number of events.

**TABLE 17.2** Studies of the effectiveness of perioperative statin use in carotid artery endarterectomy.

| Author | Year | Type of study | N | Type of surgery | Rx prior to surgery |
|---|---|---|---|---|---|
| Kennedy et al.*[9] | 2005 | Cohort | 2,031 | Carotid | Chronic use |
| McGirt et al.[17] | 2005 | Cohort | 1,666 | Carotid | Chronic use |

| Cont'd | End Point | Event rate in controls | Odds Ratio | NNT |
|---|---|---|---|---|
| Kennedy et al.*[9] | Perioperative stroke and all cause death* | 4.5% | 0.55 | 63 |
| | In hospital all-cause death* | 1.2% | 0.25 | 125 |
| McGirt et al.[17] | Perioperative stroke | 4.5% | 0.29 | 30 |
| | 30-day all-cause death | 2.1% | 0.21 | 56 |

* Only symptomatic patients are shown in this table. No significant benefit was found in asymptomatic patients. NNT = Number Needed to Treat

Unfortunately in their report the authors did not consider the combined endpoint of nonfatal MI and cardiac death. In the same report McGirt et al. showed a reduced incidence of perioperative strokes in patients undergoing carotid endarterectomy (1.2% vs. 4.5%, $p < 0.01$).

Previously Kennedy showed a similar 2-fold reduction in perioperative strokes in a group of 2,031 symptomatic patients (815 statin users) who underwent carotid endarterectomy (OR 0.55, 95% CI 0.32–0.95) and a 4-fold reduction in perioperative all-cause mortality (OR 0.25, 95% CI 0.07–0.90)[9]. However in the same report, no benefit was found for asymptomatic patients who underwent carotid endarterectomy, neither on the incidence of perioperative stroke, nor on the incidence of perioperative mortality. These findings might be explained by the proven presence of vulnerable (unstable) plaques in symptomatic patients. Though it is only circumstantial evidence, if statins indeed stabilize vulnerable atherosclerotic plaques, it seems logical that patients with vulnerable atherosclerotic plaques benefit more from statin use than patients without this type of lesions.



## Safety of perioperative statin use

A major concern of perioperative statin therapy has been the risk of statin-induced elevated serum transaminases, myopathy and rhabdomyolysis. Although elevated transaminases are observed frequently, no data are available on changes perioperatively, but there is little or no evidence that statins cause progressive liver disease[19]. In the non-operative setting Thompson et al. found a fatal rhabdomyolysis rate of <1 per million prescriptions, except for cerivastatin[20]. In their analysis of all randomized controlled trials published up to 2004 they found an incidence of persistent CK elevations (i.e. > 4x Upper Limit of Normal) of 0.07%, compared to 0.01% in the control groups.

An important potential risk factor in the perioperative setting is the use of concomitant medications. The risk of myopathy might increase with concomitant drugs that are myotoxic or increase serum statin levels. Though statins seem to be highly selective 3-HMG-CoA reductase inhibitors that do barely interfere with other drugs at their site of action, there are other factors that influence the pharmacokinetics of statins. Of special interest in this respect is the cytochrome P450 (CYP) isoenzyme system. Most drugs are metabolized in the liver by the CYP 3A4 isoenzyme[21]. This might cause interaction with statins, resulting in elevated plasma levels and consequently an increased risk of adverse events. Lovastatin, simvastatin, and atorvastatin are also metabolized by this pathway.

**TABLE 17.3** Clinically used drugs, metabolized by human cytochrome P450 isoenzymes.

| CYP2C9<br>**Fluvastatin** | CYP2C19<br>**Rosuvastatin** | CYP3A4<br>**Atorvastatin, lovastatin, simvastatin** |
|---|---|---|
| Hexobarbital | Diazepam | Clarithromycin |
| Phenytoin | Ibuprofen | Cyclosporine |
| Tolbutamide | Mephenytoin | Diltiazem |
| Warfarin | Methylphenobarbital | Erythromycin |
| Alprenolol | Omeprazole | Itraconazole |
| Diclofenac | Phenytoin | Ketoconazole |
| | Proguanil | Lacidipine |
| | | Mibefradil |
| | | Midazolam |
| | | Nefazodone |
| | | Nifedipine |
| | | Protease Inhibitors |
| | | Quinidine |
| | | Sildenafil |
| | | Amiodarone |
| | | Terbinafine |
| | | Verapamil |
| | | Warfarin |

Fluvastatin is primarily metabolized by CYP2C9, and less by CYP3A4 and CYP2C8. Rosuvastatin is not extensively metabolized but has some interactions with the CYP2C19 enzyme. Derived from Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. Circulation 2004;109:III50-7.

Fluvastatin and rosuvastatin on the other hand have only limited interactions with the CYP 3A4 pathway. Fluvastatin is mainly metabolized by the CYP 2C9 isoenzyme whereas rosuvastatin is not extensively metabolized and has only minor interaction with the 2C9 iosenzyme (TABLE 17.3). In the non-operative setting most statin induced rhabdomyolysis cases were associated with the use of mibefradil, fibrates, cyclosporine, macrolide antibiotics, warfarin, digoxin, or azole antifungals.

Besides concomitant medication use, other factors which might increase the risk of statin-induced myopathy are numerous in the perioperative setting, e.g. the impairment of renal function after major surgery, and the use of analgesic agents and postoperative pain which might mask signs of myopathy. Failure to detect statin-induced myopathy may then lead to continuous statin use and the subsequent development of rhabdomyolysis and acute renal failure. Probably on the basis of the assumptions of these risk factors, the guidelines of the ACC/AHA/NHLBI suggest that there is an increased risk of rhabdomyolysis during the perioperative period[22]. However, no studies have been published that support this fear, except for some case reports[23,24]. In a retrospective study of 885 consecutive patients undergoing major vascular surgery (211 on statins), no case of rhabdomyolysis or a significant higher creatinine kinase level in statin users was observed (FIGURE 17.2)[25]. Considering that the risk of cardiovascular complications is far greater than the risk of statin-induced myopathy and rhabdomyolysis, the potential benefits of perioperative statin use seem to outweigh the potential hazards. However, the safety of statins should be confirmed in blinded, randomized trials.

## Other considerations

The optimal timing and dosing of statins for the prevention of perioperative events has not yet been established. The pleiotropic effects of statins are thought to occur within a few days, though no clear evidence on the optimal run in period has been published so far. If there are no contraindications, starting statin therapy at the first preoperative outpatient clinic visit seems to be the most safe and practical way to ensure an optimal run-in period.

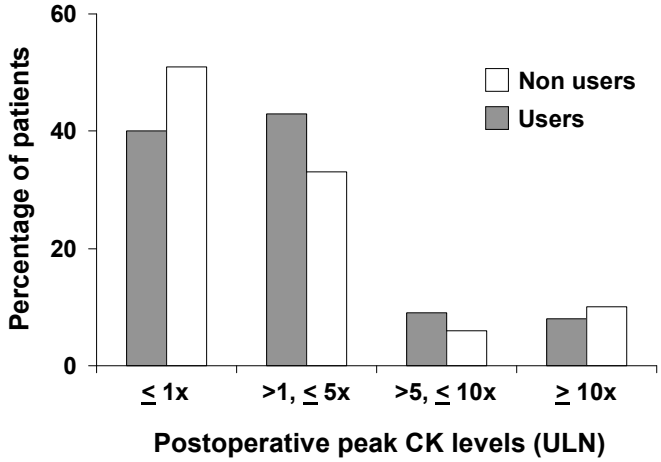


**FIGURE 17.2** Safety of perioperative use.
Percentage of statin users and nonusers with normal postoperative creatine kinase (CK) levels, moderately elevated CK levels, and severely elevated CK levels. ULN, Upper limit of normal.

In the acute coronary syndrome setting it has been suggested that acute statin withdrawal might result in a flare up of cardiac events[26]. So far, no data are available that show whether acute statin therapy withdrawal in the perioperative setting results in an increased risk for cardiac events. Patients with major abdominal surgical procedures, such as open abdominal aortic aneurysm repair, might be unable to take oral medication shortly after surgery. Since there are no intravenous formulas for statins the effect of acute statin withdrawal is a major concern. Therefore, statins with a prolonged half-life time or with a slow release formula are to be preferred in the perioperative setting until more data on the acute withdrawal effect are available.



## Recommendations

Perioperative statin use in vascular surgical patients is associated with an improved perioperative outcome, without signs of an increased incidence of side effects. The recommendations are summarized in TABLE 17.4.

*Safety*

Prior to the initiation of statin therapy liver function, i.e. ALAT and ASAT, and CK-levels should be measured (see TABLE 17.5)[22]. However, since side effects are difficult to assess clinically in the perioperative period repeated measurements immediately prior to surgery and in the perioperative period of CK-levels, e.g. on day 1, 3, and 7, and liver function is advisable until more data, preferably from blinded randomized trials are available.

*Selection of type of statin*

Several statins are currently available including: simvastatin, atorvastatin, pravastatin, fluvastatin, lovastatin, and rosuvastatin. In terms of adverse events no major difference could be identified so far. In the clinical studies performed on the effectiveness of perioperative statin use all types of statins except rosuvastatin have been described. Based on the currently available information no specific single type of statins seems to be preferable over other statins. However, it must be taken into account that sudden interruption of statin therapy in patients with acute coronary syndromes seems to worsen outcome. This may also apply to patients suffering adverse cardiac events after

| **Table 17.4** | Recommendations for perioperative statin use according to the ACC/AHA format. |
|---|---|
| Class I | |
| 1. Statins should be continued in patients already on statin therapy *(level B)* | |
| 2. Statins should be prescribed to patients according to the ACC/AHA guidelines *(level C)* | |
| 3. Prior to initiation of therapy liver function and CK levels should be assessed *(level A)* | |
| Class IIa | |
| 1. Perioperative statins use is reasonable in patients undergoing aortic, lower extremity vascular surgery or surgery for symptomatic carotid artery stenosis *(level B)* | |
| 2. It is reasonable to start statin therapy before surgery as early as possible *(level C)* | |
| 3. It is reasonable to measure liver function and CK levels in the perioperative period *(level C)* | |
| Class IIb | |
| 1. It might be reasonable to use statins with a slow-release formula or long half-life in the perioperative period *(level C)* | |
| 2. It might be reasonable to prescribe statins prior to surgery in patients undergoing surgery for asymptomatic carotid artery stenosis *(level B)* | |

| **Table 17.5** | Monitoring parameters in nonsurgical patients on statin therapy according to the ACC/AHA/NHLBI clinical advisory on the use and safety of statins[22]. |
|---|---|
| Headache, dyspepsia | Evaluate symptoms initially, 6 to 8 weeks after starting therapy, then at each follow-up visit. |
| Muscle soreness, tenderness or pain | Evaluate muscle symptoms and CK before starting therapy.<br>Evaluate muscle symptoms 6 to 12 weeks after starting therapy and at each follow-up visit.<br>Obtain a CK measurement when persons have muscle soreness, tenderness, or pain. |
| ALT, AST | Evaluate ALT/AST initially, approximately 12 weeks after starting therapy then annually or more frequently if indicated. |

major surgery. Therefore one should consider using statins with a prolonged half-life time or with a slow-release formula in patients who cannot take medication orally such as patients undergoing major vascular surgery.

*Dosing and timing*

The optimal dose and run in period of perioperative statin use is not yet defined. The pleiotropic effects of statins probably take place within several hours after initiation of statin therapy. A practical guideline would be to prescribe statins to patients on the preoperative outpatient screening visit or, according to recent ACC/AHA guidelines, start statins in patients with PAD at the first outpatient visit[27]. So far, there is no evidence that a high dose of statins results in more or other pleiotropic effects, and in a larger perioperative cardioprotective effect. Therefore it is advisable that dosing is done according to current national guidelines or according to the ACC/AHA guidelines which recommend a dosing to reach a target LDL cholesterol of less than 100 mg/dL or less than 70 mg/dL in patients at high risk of ischemic events.

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# Chapter 18

## Safety of perioperative statin use in high-risk patients undergoing major vascular surgery

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No clinical data are available on the influence of perioperative statin use on postoperative myopathy in patients undergoing major non-cardiac surgery except for some case reports[1-3]. Therefore, the current study aimed to clarify the potential risk of myopathy in statin users who underwent major non-cardiac surgery.

## METHODS

The study population was composed of patients who underwent major elective vascular surgery between January 1998 and January 2004 at Erasmus MC Rotterdam, the Netherlands. The study was approved by the medical ethics committee of our hospital.

All patients were screened for cardiac risk factors, including age, hypertension, angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure (serum creatinine > 2 mg/dl), and diabetes mellitus. Prior to surgery cholesterol levels were measured in all. Those patients with elevated total serum cholesterol levels, i.e. > 5.5 mmol/l[4], were prescribed statins, acute statin users. The type and dose of statin therapy was left to the discretion of the treating physician. The average time interval between the prescription of statins and surgery was 40 days (range 31-52). Patients already on statin therapy, chronic statin users, continued their statin use. In addition, potential confounding factors for statin myopathy[5] were evaluated including length of surgery, concomitant medical therapy, liver dysfunction, statin dose and hypothyroidism. Baseline characteristics of the analyzed patients are presented in TABLE 18.1. Statins were discontinued only if oral intake was not feasible and restarted as soon as possible, either orally or by naso-gastric tube.

Muscle complaints, i.e. weakness and pain, were assessed immediately prior to surgery (baseline), and at day 1, 3, and 7 after surgery and before discharge. At these same time points blood and plasma samples for the derivation of creatine phosphokinase (CK) levels, CK-MB, aspartate transaminase, alanine aminotransaminase and Troponin T, and electrocardiography were collected.

**TABLE 18.1** Baseline characteristics.

| | Statin User | | |
|---|---|---|---|
| | **Yes** | **No** | **p-value** |
| **Characteristic** | (N=211) | (N=674) | |
| Men – no. (%) | 152 (72%) | 524 (78%) | n.s. |
| Age (years) | | | |
| Mean | 64 | 68 | <0.001 |
| Range | 31-85 | 29-91 | |
| Myocardial infarction – no. (%) | 74 (35) | 161 (24) | 0.002 |
| Angina pectoris – no. (%) | 61 (29) | 107 (16) | <0.001 |
| Hypertension – no. (%) | 82 (39) | 194 (29) | 0.006 |
| Diabetes mellitus – no. (%) | 25 (12) | 74 (11) | n.s. |
| Congestive heart failure – no. (%) | 9 (4) | 34 (5) | n.s. |
| COPD – no. (%) | 23 (11) | 101 (15) | n.s. |
| CVA or TIA – no. (%) | 24 (11) | 81 (12) | n.s. |
| Renal failure – no. (%) | 9 (4) | 40 (6) | n.s. |
| Median of CK at baseline (U/L) | 75 | 46 | 0.002 |

CK = creatine phosphokinase, TIA = transient ischemic attack, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease

Patients with a non-fatal perioperative MI were excluded from analysis. Myocardial infarction was defined as the presence of 2 of the following 3 criteria: (1) Characteristic ischemic symptoms lasting >20 minutes, (2) Electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists >24 hours, and (3) A positive troponin T, i.e. >0.10 ng/ml, or peak CK-MB >8% of an elevated total CK with characteristic rise and fall[6].

Myopathy was defined as CK elevations, with or without muscle complaints. Rhabdomyolysis was considered present if CK levels exceeded the upper limit of normal > 10 times, with an elevated creatinine level consistent with pigment-induced nephropathy[7]. Use of analgesics and postoperative pain may mask signs of these muscle-related complaints. Therefore, we considered elevated CK levels as a sign of myopathy as well. CK levels were defined as normal if the upper limit of normal, i.e. 170 U/L for females and 200 U/L for males, was not exceeded. An increment of CK < 5 times upper limit of normal was defined as mildly elevated, between 5 and 10 times upper limit of normal as moderately elevated and > 10 times of upper limit of normal was considered as severely increased.

Continuous variables were described as mean value (range), and categorical variables as percent frequencies. Univariate differences between patient subgroups were evaluated by using the t-test or chi-square test, as appropriate. Multivariate linear regression analysis was performed to study the relation between statin use, cardiac risk factors and length of surgery, and CK levels. All analysis was performed using SPSS statistical software (SPSS Inc., Chicago, Illinois, version 10.1).



## RESULTS

A total of 981 patients were screened. In 44 (5%) patients serum cholesterol level was elevated and statins were prescribed, while 182 (19%) were already on statins. Patients on perioperative statin therapy were younger, had more often a history of hypertension, a history of a myocardial infarction, and angina pectoris. Other cardiac risk factors did not significantly differ between both groups (TABLE 18.1). A non-fatal perioperative myocardial infarction occurred in 98 (9.8%) patients, 81 (10.8%) in the non-user group and in 15 (6.7%) patients on statin therapy ($p< 0.01$). Perioperative death occurred in 35 patients, 5 (2.1%) statin users and 30 (3.9%) non-users. None of these deaths was ascribed to rhabdomyolysis. The combined end-point of perioperative death and myocardial infarction occurred in statin and non-statin users in respectively 22 (8.8%) vs. 111(14.7%), $p<0.01$. Thus, 885 patients, 674 non-users and 211 statin users, were left for analysis.

Simvastatin was prescribed to 87 (41%) patients, fluvastatin to 48 (23%), pravastatin to 44 (21%), and atorvastatin to 32 (15%). The dose of statins is shown in TABLE 18.2. Total serum cholesterol levels decreased substantially after initiation of statin therapy (6.9 mmol/L vs. 5.0 mmol/L, $p<0.001$). Patients on statin therapy had a significantly higher CK level at hospital admission (75 U/L vs. 46 U/L, $p=0.002$), though CK levels did not exceed the upper limit of normal and there were no muscle complaints. The prevalence of risk factors associated with statin induced myopathy is shown in TABLE 18.3.

Discontinuation of statin therapy was necessary in 124 (59%) patients, as oral intake was temporarily not feasible after surgery. Therapy was restarted after a median of 1 day (range 1-4 days). There was no relation between temporarily interruption of statins and perioperative myocardial infarction ($p=0.143$).

**TABLE 18.2** Type and dosage of prescribed statins.

| Statin | Dose (mg) | Maximum daily dose (mg) | N |
|---|---|---|---|
| Simvastatin | 10 | 80 | 37 |
| | 20 | | 41 |
| | 40 | | 9 |
| Fluvastatin | 80 | 80 | 48 |
| Pravastatin | 10 | 40 | 4 |
| | 20 | | 29 |
| | 40 | | 11 |
| Atorvastatin | 10 | 80 | 10 |
| | 20 | | 11 |
| | 40 | | 7 |
| | 80 | | 4 |
| Total | | | 211 |

Maximum daily dose as recommended in Pharmacotherapeutisch kompas, Amstelveen, the Netherlands.

**TABLE 18.3** Prevalence of risk factors for statin induced myopathy.

| Characteristic | Statin Users (N=211) |
|---|---|
| Renal dysfunction – no. (%) | 9 (4) |
| Hepatic dysfunction – no. (%) | 0 |
| Hypothyroidism – no. (%) | 7 (3) |
| *Concomitant medication* | |
| Fibric acid derivates – no. (%) | 6 (3) |
| Niacin – no. (%) | 0 |
| Cyclosporine – no. (%) | 5 (2) |
| Azole antifungals – no. (%) | 0 |
| HIV protease inhibitors – no. (%) | 0 |
| Nefadozone – no. (%) | 0 |
| Verapamil and diltiazem – no. (%) | 23 (11) |
| Amiodarone – no. (%) | 0 |
| Oral anticoagulants – no. (%) | 41 (19) |

Abdominal aortic repair was performed in 527 of the enrolled patients, 129 (61%) used statins and 398 (59%) were non-users. In 82 (39%) patients on statins and 276 (41%) non-users lower extremity revascularization was performed. Mean length of surgery was 295 ± 104 minutes in non-users and 304 ± 101 minutes in patients on statin therapy (p=0.225).

None of the patients reported muscle weakness or muscle pain in the perioperative period. Median maximum CK level was 301 U/L (range 16-13377) in statin users and 192 U/L (range 8–30390) in non-users (p=0.003). However, corrected for length of surgery, cardiac risk factors, and risk factors for myopathy, the difference between users and non-users was not significant (p=0.142). The only factor independently associated with CK elevation was length of surgery (p<0.001). The CK levels in acute vs. chronic statin users were similar (p=0.564). Statin users more often had mild elevated CK levels (p=0.003). The incidence of moderate and severe increment of CK levels on the other hand did not differ significantly between both groups (TABLE 18.4).

**TABLE 18.4** Postoperative CK-levels in statin users and non-users, divided into normal (≤1x ULN), mildly elevated (>1x, ≤5x ULN), moderately elevated (>5x, ≤10x ULN) and severely elevated CK-levels (>10x ULN).

| | Statin User | |
|---|---|---|
| | **Yes** | **No** |
| **Post-operative CK levels** | % (95% CI) | % (95% CI) |
| ≤1x ULN | 40 (33-47) | 51 (47-55) |
| >1x, ≤5x ULN | 43 (36-50) | 33 (29-37) |
| >5x, ≤10x ULN | 9 (5-13) | 6 (4-8) |
| >10x ULN | 8 (4-12) | 10 (8-12) |

ULN = Upper Limit of Normal, CI = Confidence Interval.

## DISCUSSION

In this study we found that perioperative statin use in a large group of patients was not associated with an increased risk of myopathy, i.e. CK elevation with or without muscle complaints, after major vascular surgery. Prior to surgery CK levels were higher in statin users, however there were no muscle complaints. In the perioperative period there were no differences in CK levels between statin users and non-users and no patient experienced muscle complaints. After correcting for cardiac risk factors and clinical risk factors for myopathy, length of surgery remained the only independent predictor for myopathy. No case of rhabdomyolysis was observed. Also we observed no difference in CK levels between patients on chronic statin therapy and patients who started statin therapy only shortly before surgery. Neither was there an association between statin dose and myopathy.



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# Chapter 19

## Effects of statins on renal function after aortic cross clamping during major vascular surgery

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## ABSTRACT

**Background:** Ischemic-reperfusion injury is an important cause for renal dysfunction after major vascular surgery and increases postoperative morbidity and mortality. The aim of the present study was to assess the effect of statins on renal function in patients at high-risk for renal dysfunction, i.e. those undergoing suprarenal aortic cross clamping-declamping.

**Methods:** All 77 patients (28 statin users, 57 men, age 69 ± 8 years) with a normal preoperative renal function requiring suprarenal aortic cross clamping-declamping during vascular surgery between 1995-2005 were studied. Creatinine levels were obtained prior to surgery, and on day 1, 2, 3, 7, and 30 after surgery. An ANOVA model for repeated measurements was applied to compare creatinine levels between statin users and non-users, with adjustment for clamping time and blood loss.

**Results:** There were no differences in baseline clinical characteristics, preoperative creatinine levels (0.93 mg/dL vs. 0.96 mg/dL; p=0.59), and glomular filtration rate (79 ml/min vs. 73 ml/min; p=0.1). Postoperative creatinine levels during 30 days after surgery were significantly lower in statin users than in non-users (ANOVA p-value <0.01, 1.17 mg/dL versus 1.98 mg/dL). Postoperative hemodialysis was required (temporarily) in 7 patients (9.1%), all non-users.

**Conclusion:** These findings suggest an association between statin use and preserved renal function after suprarenal aortic clamping.

## INTRODUCTION

In surgery requiring suprarenal aortic clamping-declamping renal hypoxia-reperfusion injury is an inevitable consequence of the procedure. Consequently, up to 20-30% of patients experience postoperative renal dysfunction[1,2]. This is attributed to impaired renal perfusion, with subsequent reperfusion leading to acute inflammatory changes and loss of function. Experimental studies have shown that statins might reduce this ischemic-reperfusion injury by altering the inflammatory response and an upregulation of endothelial nitric oxid synthase[3-7]. To investigate whether statins preserve renal function after major vascular surgery we selected a group of patients undergoing aortic aneurysm repair with suprarenal cross clamping-declamping and compared renal function between statin users and non-users.

## METHODS

The study population was composed of all consecutive patients who underwent elective abdominal aneurysm repair requiring suprarenal clamping-declamping between January 1995 and January 2005 at the Erasmus MC, Rotterdam, the Netherlands. Patients with impaired preoperative renal function were excluded from analysis. Baseline serum creatinine levels were considered elevated if they exceeded the upper limit of normal in our institution, i.e. creatinine >1.3 mg/dl for males and >1.1 mg/dl for females. The Cockroft-Gault formula was used to estimate the individual glomular filtration rate[8].

All patients were screened for cardiac risk factors, including age, hypertension, angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure, and diabetes mellitus. All prescription and over-the-counter medications were noted at the time of the first outpatient clinic visit and on the day of admission and were classified as follows: statins, β-blockers, aspirins, angiotensin converting enzyme inhibitors, calcium channel blockers; dihydropyridines or non-dihydropyridines, diuretics, nitrates, coumarins and digoxin. Statin users were on chronic therapy. Medication was continued until on the morning of surgery. Patients unable to take medication orally perioperatively were switched to intravenous formula. If no intravenous formula was available, i.e. statins and Angiotensin Converting Enzyme (ACE)-inhibitors, oral medication was restarted as soon as possible after surgery.

Repair was done through a thoracolaparotomy or midline laparotomy. The aortic clamp was placed above both renal arteries or above the celiac arteries, using a "clamp-and-sew" technique without protection of the kidneys apart from flushing the renal arteries with heparin. The site of clamping was dictated by aneurysm extent, i.e. juxta- or suprarenal. Possible intra-operative confounders for renal outcome were noted; duration of surgery, clamping time, perioperative blood loss, episodes of hypotension defined as a systolic blood pressure of < 70 mmHg lasting more than 5 minutes, transfusion requirements, body temperature, and use of antibiotics. Serum creatinine levels and glomular filtration rate were obtained prior to surgery (baseline), and on day 1, 2, 3, 7, and 30 after surgery. The necessity of dialysis was left to the discretion of the treating physician. Dialysis was scored as temporary or chronic, based on the status at discharge.

Dichotomous data are described as counts and percentages, continuous data as mean values with corresponding standard deviation. Differences in baseline characteristics between statin users and non-users were evaluated by unpaired Student's T-tests, chi-square tests or Fisher's exact tests, as appropriate. An ANOVA model for repeated measurements was applied to compare creatinine levels

between statin users and non-users, with adjustment for clamping time and blood loss. All statistical tests were 2-sided, and a p-value <0.05 was considered significant. All analyses were performed using SPSS statistical software (SPSS Inc., Chicago, Illinois, version 12.1).

## RESULTS

The study population consisted of 77 patients (74% men). Mean age was 69 ± 8 years. In total, 28 (36%) were statin users. Of these patients, 16 were on simvastatin therapy, 6 on atorvastatin, 3 on fluvastatin, and 3 on pravastatin. Prior to surgery, serum cholesterol levels were similar in users and non-users (5.3 ± 1.0 vs. 5.7 ± 0.8 mmol/L, p=0.1). The baseline clinical characteristics and medication use are presented in TABLE 19.1, no significance differences were observed between the two groups. Preoperative creatinine levels and glomular filtration rate (estimated by the Cockroft-Gault formula[8]) were similar in users vs. non users, respectively 0.93 ± 0.18 mg/dL vs. 0.96 ± 0.15 mg/dL (p=0.5) and 79 ± 21 ml/min vs. 73 ± 19 ml/min (p=0.1). All patients were treated with prophylactic systemic antibiotics prior to surgery. Operative characteristics are shown in TABLE 19.2.

Nine patients (11.7%) died within 30 days after surgery, 8 (16.3%) non-users and 1 (3.6%) user (p=0.09). Postoperative creatinine levels during 30 days after surgery were significantly lower in statin users than in non-users (ANOVA p-value <0.01, 1.17 mg/dL versus 1.98 mg/dL, FIGURE 19.1). In multivariable analysis, after correction for suprarenal clamping time, hypotension, type of aneurysm and blood loss, statin use was associated with lower median creatinine level at day 1 (1.17 vs. 1.74 mg/dL, p=0.005), 2 (1.10 vs. 1.97 mg/dL, p=0.005), 3 (1.07 vs. 1.98 mg/dL, p=0.016), 7 (0.85 vs. 1.47



**TABLE 19.1** Baseline clinical characteristics.

| | Statin users | | |
|---|---|---|---|
| | **Yes** | **No** | **P-value** |
| | (N=28) | (N=49) | |
| Male – no. (%) | 19 (68) | 38 (77) | 0.41 |
| Age – years (SD) | 68 (9.7) | 70 (7.9) | 0.37 |
| Total cholesterol – mgl/dl (SD) | 205 (39) | 220 (30) | 0.13 |
| Medical history | | | |
| Angina pectoris – no. (%) | 6 (21) | 11 (22) | 1.0 |
| Myocardial infarction – no. (%) | 8 (29) | 18 (37) | 0.62 |
| Congestive heart failure – no. (%) | 1 (4) | 5 (10) | 0.41 |
| Coronary bypass or angioplasty – no. (%) | 5 (18) | 10 (20) | 1.0 |
| Stroke or TIA – no. (%) | 3 (11) | 9 (18) | 0.52 |
| Diabetes mellitus – no. (%) | 1 (4) | 3 (6) | 1.0 |
| Hypertension – no. (%) | 10 (36) | 25 (51) | 0.24 |
| COPD – no. (%) | 7 (39) | 19 (39) | 1.0 |
| Medications | | | |
| ACE inhibitors – no. (%) | 6 (21) | 14 (29) | 0.59 |
| Aspirin – no. (%) | 8 (25) | 12 (29) | 0.79 |
| Calcium antagonists – no. (%) | 8 (29) | 21 (43) | 0.23 |
| Diuretics – no. (%) | 9 (32) | 10 (20) | 0.28 |
| Nitrates – no. (%) | 4 (14) | 12 (25) | 0.39 |
| Beta-blockers – no. (%) | 19 (68) | 26 (53) | 0.28 |

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

**TABLE 19.2** Operation characteristics.

| | Statin users | | |
|---|---|---|---|
| | Yes | No | P-value |
| | (N=28) | (N=49) | |
| Site of aneurysm | | | |
| Juxtarenal – no. (%) | 19 (68%) | 31 (63%) | 0.80 |
| Suprarenal – no. (%) | 9 (32%) | 18 (37%) | 0.80 |
| Intraoperative | | | |
| Mean time of suprarenal clamping – minutes (SD) | 47 (19) | 54 (21) | 0.13 |
| Mean duration of surgery – minutes (SD) | 250 (60) | 280 (72) | 0.14 |
| Total blood loss – ml (SD) | 3585 (2507) | 4100 (2779) | 0.39 |
| Units of homologues blood – (SD) | 3 (2.5) | 4 (4.7) | 0.20 |
| Hypotension – no. (%) | 3 (11%) | 5 (10%) | 0.86 |
| Mean body temperature – °C (SD) | 35.6 (0.7) | 35.6 (0.7) | 0.51 |

min, minutes; SD, standard deviation; ml, milliliter; °C, degrees Celcius.

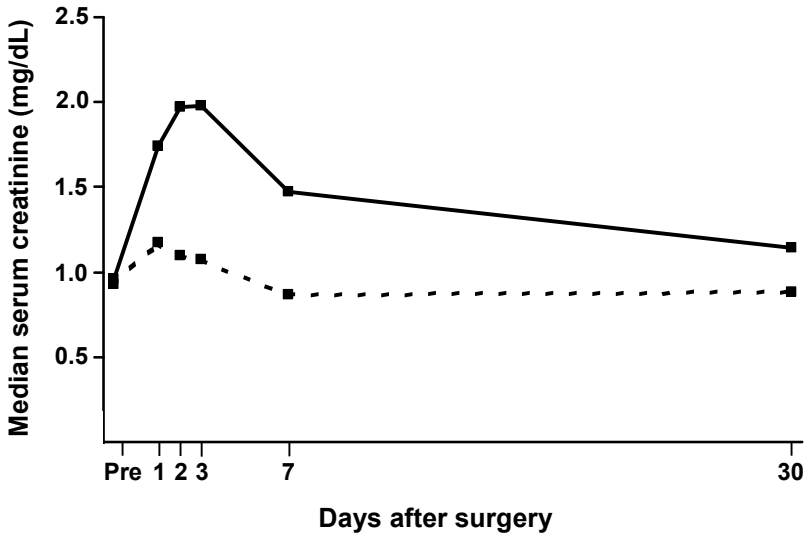


**FIGURE 19.1** Median creatinine levels preoperatively and 1, 2, 3, 7, and 30 days after surgery in statin users (dashed line) and nonusers (solid line), p <0.01 (analysis of variance for repeated measurements).

mg/dL, p=0.041), and 30 (0.88 vs. 1.14 mg/dL, p=0.038). Postoperative hemodialysis was required in 7 patients (9.1%), all non-users. Three out of these patients were on chronic hemodialysis at discharge.

## DISCUSSION

This study showed an association between statin use and preserved renal function after suprarenal aortic clamping-declamping in patients undergoing major vascular surgery. Serum creatinine levels were significantly lower up to 30 days after surgery in statin users compared to non-users. Moreover, 10% of the non-users required (temporary) hemodialysis whereas none of the statin users required such therapy.

Statins are frequently prescribed in the perioperative setting, as both retrospective and prospective studies have shown an improved outcome in statin users, mainly by a reduction of cardiac events[9-11]. As shown recently by Lindenauer et al, statin use was associated with a 1.4-fold reduction of post-operative mortality in 780,591 patients[12]. These effects were independent of serum cholesterol levels and attributed to the so-called pleiotropic or non-lipid lowering effects of statins. The same pleiotropic effects might be responsible for the prevention of renal ischemia-reperfusion injury.

Recently, statins have shown to poses a renal protective effect in animals after ischemic-reperfusion injury. This model is comparable to the suprarenal clamping-declamping injury during vascular surgery. For the renal protective effect two important pleiotropic effects of statins are considered: the influence on endothelial function and inflammation. Both disruption of endothelial function and inflammation have been described to play a pivotal role in ischemic-reperfusion injury[13,14]. As discussed by Liao in a recent review article statins influence endothelial function and inflammation[15]. This has been confirmed in several animal models of renal ischemic-reperfusion injury.

The present study is the first clinical report on the effects of statins on perioperative renal ischemic-reperfusion injury. Though our study suggests an association between statin use and preserved renal function after ischemic-reperfusion injury several issues remain unsolved. All patients in our study population were chronic statin users. It therefore remains to be assessed when statin therapy has to be initiated prior to surgery. In addition the optimal dosing of statins has to be assessed in terms of effectiveness and safety. In the perioperative setting with multiple drug interactions statin metabolism might be influenced resulting in an increased risk of adverse events[16]. Since no intravenous formula of statins are clinically available concern has risen about a possible detrimental effect of statin interruption[17]. Because of the impairment of intestinal function early after surgery patients are often unable to take medication orally. This is especially common in patients undergoing abdominal aortic repair. Until more data are available it is recommended to have this interruption period as short as possible and consider administration by a naso-gastric tube.



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# Chapter 20

## Statin use is associated with early recovery of kidney injury after vascular surgery and improved long-term outcome

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## ABSTRACT

**Background:** Acute kidney injury (AKI) after major vascular surgery is an important risk factor for adverse long-term outcomes. The pleiotropic effects of statins may reduce kidney injury caused by perioperative episodes of hypotension and/or suprarenal clamping and improve long-term outcomes.

**Methods:** Of 2170 consecutive patients undergoing lower extremity bypass or abdominal aortic surgery from 1995 to 2006, cardiac risk factors and medication were noted. A total of 515/1944 (27%) patients were statin users. Creatinine clearance (CrCl) was assessed preoperatively and at 1, 2 and 3 days after surgery. Outcome measures were postoperative AKI and long-term mortality. Postoperative kidney injury was defined as a >10% decrease in CrCl on Day 1 or 2, compared to the baseline. Recovery of kidney function was defined as a CrCl >90% of the baseline value at Day 3 after surgery. Multivariable Cox regression analysis, including baseline cardiovascular risk factors, baseline CrCl and propensity score for statin use, was applied to evaluate the influence of statins on early postoperative kidney injury and long-term survival.

**Results:** AKI occurred in 664 (34%) patients [median –25% CrCl, range (–10% to –71%)]. Of these 664 patients, 313 (47%) had a complete recovery of kidney function at Day 3 after surgery. Age, hypertension, suprarenal cross-clamping and baseline CrCl predicted the development of kidney injury during the postoperative period. The incidence of kidney injury was similar among statin users and non-users (29% versus 25%, OR 1.15, 95% CI 0.9–1.5). However, if kidney function deteriorated, statin use was associated with increased odds of complete kidney function recovery (OR 2.0, 95% CI 1.0–3.8). During a mean follow-up of 6.24 years, half of the patients died (55%). Importantly, statin use was also associated with an improved long-term survival, irrespective of kidney function change (HR 0.60, 95% CI 0.48–0.75).

**Conclusion:** Statin use is associated with improved recovery from AKI after major surgery and has a beneficial effect on long-term survival.

## INTRODUCTION

Acute kidney injury (AKI) is characterized by sudden (i.e. hours to days) impairment of kidney function[1]. AKI is now established to be an increasingly common complication in hospitalized patients, and the mortality is commonly 50–80% in critically ill patients[2,3]. Perioperative AKI is among the most common etiologies of kidney injury in hospitalized patients that markedly increases perioperative morbidity and mortality[1–4]. Despite benefits of acute dialysis therapy and numerous advances in critical care, perioperative AKI remains a catastrophic complication[1,5]. Therefore, the identification of interventions that have the potential of preventing the occurrence or shortening the course of postoperative AKI is essential.

3-Hydroxy-3-methylglutaryl coenzyme a reductase inhibitors (statins) have pleiotropic effects independent of lipid lowering[6–8]. Statins are known to be effective for primary and secondary prevention of cardiovascular events in hyperlipidaemic subjects[9,10] and patients with chronic kidney disease (CKD) not requiring dialysis[11–13]. Recently, statins have been reported to increase the survival of CKD patients with sepsis or infectious complications and to have a beneficial effect on the course of AKI in ageing rats[14–16]. However, the association of statins with the course of postoperative AKI in humans remains unknown. Furthermore, data regarding the association between statin therapy and long-term mortality of patients undergoing major vascular surgery are scarce.

In the present study, we hypothesized that statin usage would be associated with a shorter course of kidney dysfunction after controlling for other important risk factors. We examined the association of preoperative statin usage on the onset of AKI, the recovery of AKI in the postoperative period and the influence on long-term survival of patients undergoing major vascular surgery.

## SUBJECTS AND METHODS

### Study design and patient selection

Between January 1995 and June 2006, 2170 patients underwent major open non-cardiac vascular surgery at Erasmus Medical Center, Rotterdam, the Netherlands. All patients underwent lower limb arterial reconstruction (LLR) procedures or elective abdominal aortic aneurysm (AAA) surgery and were entered into a computerized database. The Medical Ethics Committee of the Erasmus Medical Center was informed about the study protocol, and no official approval was requested per institutional practice.

Patients on chronic haemodialysis, with a baseline creatinine clearance (CrCl) <30 mL/min, and those who required renal revascularization and died within 3 days after surgery were excluded. The analysis was made according to whether or not patients were taking statins on the day of hospital admission, and does not incorporate changes in medical treatment during the follow-up period.

### Baseline characteristics

On all patients the information on cardiovascular risk factors was recorded and included age, gender, hypertension (defined as systolic blood pressure 140 mmHg, diastolic blood pressure 90 mmHg or use of anti-hypertensive medication), diabetes mellitus (the presence of a fasting blood glucose 140 mg/dL or requirement for insulin or oral hypoglycemic agents), smoking status, hypercholesterolemia (total cholesterol of >200 mg/dL), chronic obstructive pulmonary disease (COPD) according to symptoms and pulmonary function tests (i.e. forced expiratory volume in one second (FEV1) <70% of

maximal age and gender predictive value), body mass index (BMI), serum creatinine, the presence of ischemic heart disease (prior myocardial infarction (MI), prior coronary revascularization and angina pectoris), heart failure (defined according to the New York Heart Association classification (NYHA)), cerebrovascular disease (history of cerebrovascular accident or transient ischemic attack), the occurrence of suprarenal cross-clamping during surgery and preoperative medication use (statins, β-blockers, diuretics, angiotensin-converting-enzyme inhibitors (ACE inhibitors), calcium antagonists, nitrates, aspirin and anti-coagulants). Of note, baseline body weight was used to calculate BMI. All prescription and over-the-counter medications were noted on the day of admission and ascertained if medication was documented at least 1–3 months prior to hospital admission for surgery.

### Kidney function assessment

Fasting serum creatinine was measured preoperatively at baseline in all patients, either at the outpatient preoperative screening visit or on the day of hospital admission, and on days 1, 2 and 3 after surgery. Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method. Kidney function was estimated with the Cockcroft and Gault equation from age, gender, serum creatinine and body weight[17]. Additional analyses were performed using the above definitions of AKI measured by the Modification of Diet in Renal Disease (MDRD) prediction equation[18].

### Clinical follow-up and end-points

Postoperative clinical information was retrieved from an electronic database of patients followed in our hospital. From the municipal civil registries, we obtained the survival status. The follow-up was complete in 98.2%.



The primary end-point of this study was postoperative AKI with and without complete recovery. AKI was defined as >10% decrease in CrCl on day 1 or 2, compared to the baseline value. Complete recovery of kidney function was defined as a CrCl >90% of the baseline value at day 3 after surgery.

The secondary end-point of this study was all-cause long-term mortality, which was defined as death occurring in the first 11 years after surgery.

### Statistical analysis

Continuous data are described as mean values and standard deviation (±SD) or median values and range, and dichotomous data are described as percentage frequencies. The chi-square test was used for categorical variables and the analysis of variance (ANOVA) was used for continuous variables. Multivariable logistic regression analysis was used to evaluate whether statin use prevented kidney injury within 2 days after surgery. If kidney injury was present, multivariable logistic regression analysis was used to evaluate if statin use was associated with an increased chance of complete recovery of kidney function at day 3 after surgery. Multivariable analysis included the following covariates: a propensity score for statin use, age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, BMI, type of surgery, history of MI, coronary revascularization, heart failure, angina, cerebrovascular disease, baseline kidney function, suprarenal aortic cross-clamping, year of surgery and statin, β-blockers, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin and anti-coagulation usage at baseline. Year of surgery was included as a categorical variable (January 1995 through December 1999 and January 2000 through June 2006). We included the time period of surgery to adjust for possible confounding (i.e. change in perioperative management) due to the long follow-up period of the analysis.

Incidence of patients requiring postoperative dialysis was compared between statin users and non-statin users, using the chi-square test. Postoperative dialysis requirement was defined as the need of renal replacement therapy in the perioperative period, during the initial 30 days of hospitalization or after hospital discharge but within 30 days after surgery. The relation between statin use and requirement of postoperative dialysis was further investigated using multivariable analysis including all baseline risk factors, propensity score for statin use, year of surgery and medication usage at baseline.

In addition, multivariable Cox regression analysis was performed to describe the influence of statin use on long-term all-cause mortality. Variables included in this model were propensity score for statin use, age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, BMI, type of surgery, history of MI, coronary revascularization, heart failure, angina, cerebrovascular disease, the presence of kidney injury, suprarenal aortic cross-clamping, year of surgery, baseline kidney function, postoperative dialysis and statin, β-blockers, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin and anti-coagulation usage at baseline.

Unadjusted and adjusted odds and hazard ratios (ORs and HRs) were reported with corresponding 95% confidence intervals (CIs). A p-value of <0.05 was considered to be significant. All computations were performed with SPSS software version 12.0.1 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Patient characteristics

A total of 2170 patients underwent non-cardiac vascular surgery. After the exclusion of patients on chronic haemodialysis (n = 31), with a baseline CrCl <30 mL/min (n = 140), those who required renal revascularization (n = 7), and those who died within 3 days after surgery (n = 48), the final study population included in the analysis was 1944 patients. All patients underwent open major vascular surgery, and none of the patients were treated with endovascular devices.

The mean age of the study population was 66.6 ± 11 years and 78% were male (TABLE 20.1). In total, 1031 patients (53%) underwent AAA surgery and 913 patients (47%) underwent LLR surgery. The mean serum creatinine at baseline was 1.17 ± 0.8 mg/dL, and the mean CrCl was 74.9 ± 33 mL/min.

A total of 515 patients (26.5%) were statin users. An approximately twofold increase in statin prescription was observed over time. In the period from January 1995 through December 1999, a total of 190/1035 patients (18.4%) were statin users, and in the period from January 2000 through June 2006, this number increased to 325/909 statin users (35.8%) ($p < 0.001$).

### Primary end-point

Of the 1944 patients, AKI within 2 days after surgery occurred in 664 patients (34%). The median change of kidney function, using the Cockcroft and Gault equation, for these patients was –24.7% (–10%, –71%) on day 1 or day 2, compared to CrCl at baseline. The remaining 1330 patients (66%) had no AKI with a median change of +10.5% (–10%, +43%) from baseline. Patients with kidney injury were older, underwent more frequently AAA surgery and suprarenal aortic cross-clamping, had higher incidences of COPD and hypertension and received more β-blockers and calcium antagonists. Importantly, no differences in baseline serum creatinine and CrCl were observed between patients with and without kidney injury.

**TABLE 20.1** Baseline characteristics of all patients, according to the presence of renal dysfunction within two days after major vascular surgery.

| | All patients 1944 (100%) | No renal dysfunction 1280 (66%) | Renal dysfunction 664 (34%) | P-value |
|---|---|---|---|---|
| **Demographics (%)** | | | | |
| Mean age (± SD) | 66.6 (± 11) | 66.1 (± 11) | 67.6 (± 11) | 0.04 |
| Male | 77 | 76 | 78 | 0.5 |
| Abdominal aortic surgery | 53 | 45 | 68 | <0.001 |
| Lower limb arterial reconstruction | 47 | 55 | 32 | <0.001 |
| Suprarenal clamping | 10 | 4 | 19 | <0.001 |
| **Cardiovascular risk factor (%)** | | | | |
| Hypertension | 48 | 45 | 55 | <0.001 |
| Diabetes Mellitus | 16 | 16 | 16 | 0.7 |
| Current smoker | 28 | 28 | 28 | 0.8 |
| Hypercholesterolemia | 20 | 19 | 20 | 0.7 |
| COPD | 22 | 20 | 24 | 0.04 |
| Body mass index (± SD) | 24.8 (± 5) | 24.5 (± 4) | 25.5 (± 6) | 0.005 |
| Myocardial Infarction | 29 | 28 | 30 | 0.5 |
| Coronary revascularization | 26 | 27 | 26 | 0.5 |
| Heart failure | 7 | 6 | 7 | 0.6 |
| Angina | 17 | 17 | 18 | 0.5 |
| Cerebrovascular disease | 8 | 7 | 8 | 0.6 |
| **Baseline kidney function (%)** | | | | |
| Serum creatinine (mg/dl ± SD) | 1.17 (± 0.8) | 1.17 (± 0.85) | 1.17 (±0.80) | 0.8 |
| Creatinine clearance (ml/min ± SD) | 74.9 (± 33) | 74.0 (± 30) | 76.5 (± 38) | 0.2 |
| **Medication use (%)** | | | | |
| Statins | 27 | 25 | 29 | 0.1 |
| β-blockers | 36 | 35 | 40 | 0.03 |
| Diuretics | 21 | 21 | 20 | 0.6 |
| ACE-inhibitors | 34 | 34 | 35 | 0.9 |
| Calcium antagonists | 36 | 34 | 41 | 0.004 |
| Nitrates | 21 | 21 | 20 | 0.8 |
| Aspirin | 32 | 32 | 31 | 0.9 |
| Anti-coagulation | 24 | 26 | 19 | 0.001 |

ACE-inhibitors = angiotensin-converting-enzyme inhibitors; COPD = chronic obstructive pulmonary disease; *renal dysfunction = >10% decrease in creatinine clearance on day 1 or 2, compared to baseline value

**TABLE 20.2** Independent predictors for developing renal dysfunction after major vascular surgery.

| | Multivariate odds ratio, 95% confidence interval |
|---|---|
| Age (per 1 year increase) | 1.03 (1.02 – 1.04) |
| Hypertension | 1.40 (1.10 – 1.78) |
| Suprarenal cross-clamping | 4.47 (3.09 – 6.50) |
| AAA surgery vs. LLR surgery | 1.96 (1.54 – 2.48) |
| Baseline creatinine clearance (per 1 ml/min increase) | 1.01 (1.006 – 1.014) |

Of note, the incidence of statin use was similar between patients with and without AKI, 322/1280 patients (29%) versus 193/664 patients (25%), p = 0.11. In multivariable analysis, statin use was not associated with decreasing incidence of kidney injury 2 days after surgery (adjusted OR 1.15, 95% CI 0.86–1.54). Independent predictors for postoperative AKI were age, hypertension, suprarenal aortic cross-clamping, AAA surgery versus LLR surgery and baseline CrCl per 1 mL/min increase of CrCl (TABLE 20.2).

In total, 46 patients (2.4%) required postoperative dialysis within 30 days after surgery (37 and 9 patients required temporary and chronic therapy, respectively). The proportion of statin users and non-statins users was similar between patients who did and did not require dialysis therapy (26.7% non-statin users versus 19.6% statin users, p = 0.28). In multivariable analysis, statin use was not associated with the prevention of postoperative dialysis (adjusted OR 0.80, 95% CI 0.31–2.08). Patients with suprarenal aortic cross-clamping had a sevenfold increased risk for the requirement of dialysis (adjusted OR 7.08, 95% CI 2.92–17.18). Furthermore, patients with lower levels of baseline CrCl were also at a higher risk (adjusted OR 0.987, 95% CI 0.974–0.999 per 1 mL/min increase).

Perioperative blood loss and suprarenal aortic cross-clamping time were found to be significantly associated with the presence of postoperative kidney injury. In addition, statin users had the same total perioperative blood loss and suprarenal aortic cross-clamping time, compared with non-statin users (2565 mL versus 2245 mL (p = 0.13) and 57.7 min versus 58.5 min (p = 0.93), respectively).

Of the 664 patients with AKI, 313 patients (47%) had a complete recovery of kidney function at day 3 after surgery. The median change of kidney function for these patients was –7.4% (–10%, +24%) at day 3, compared with CrCl at baseline. The remaining 351 patients (53%) did not achieve complete recovery and their median decrease in kidney function was –27.8% (–10%, –91%), compared with CrCl at baseline.

In multivariable analysis, statin use and diabetes mellitus were independently associated with complete recovery of kidney function. Statin use was associated with increased odds of complete recovery of kidney function (adjusted OR 1.96, 95% CI 1.02–3.75), while diabetes mellitus was associated with decreased odds of renal recovery (adjusted OR 0.52, 95% CI 0.26–0.99). In addition, we observed no differences between the two different surgical groups, regarding the effect of statin therapy on kidney injury recovery. Patients undergoing AAA surgery had a 1.85-fold increased chance of complete kidney function recovery (95% CI 1.09–3.52). Patients undergoing LLR surgery had a 2.24-fold increased chance of recovery (95% CI 1.05–4.07).

### Secondary end-point

In total, 1062 patients (55%) died during 6.2 ± 3.6 years of follow-up. Statin use was associated with long-term all-cause mortality, irrespective of the presence of kidney injury after surgery (FIGURE 20.1). The adjusted HR for statin use was 0.60 (95% CI 0.48–0.75). Importantly, statin use was associated with an improved outcome for patients who develop kidney injury (adjusted HR 0.53, 95% CI 0.37–0.77), as well as for patients without AKI (adjusted HR 0.65, 95% CI 0.49–0.86).

Other independent predictors for long-term all-cause mortality are listed in TABLE 20.3. Importantly, the presence of AKI after surgery was associated with an adverse outcome (adjusted HR 1.24, 95% CI 1.06–1.45). Baseline CrCl (per 1 mL/min increase) was also independently associated with all-cause mortality, with an adjusted HR of 0.993, 95% CI 0.990–0.996. In a sub-analysis among the 48 patients who died within 3 days after surgery, statin therapy was associated with a decreased chance of

| **Table 20.3** | Independent predictors for all-cause mortality during 6.24 ± 4.2 years follow-up. |
|---|---|
| | Multivariate hazard ratio, 95% confidence interval |
| Age (per 1 year increase) | 1.04 (1.03 – 1.05) |
| Diabetes Mellitus | 1.23 (1.02 – 1.49) |
| COPD | 1.42 (1.19 – 1.70) |
| Smoking | 1.32 (1.13 – 1.54) |
| Old myocardial infarction | 1.24 (1.04 – 1.48) |
| Baseline creatinine clearance (per 1 ml/min increase) | 0.992 (0.989 – 0.996) |
| Renal dysfunction | 1.34 (1.13 – 1.48) |
| Statin use | 0.56 (0.44 – 0.70) |

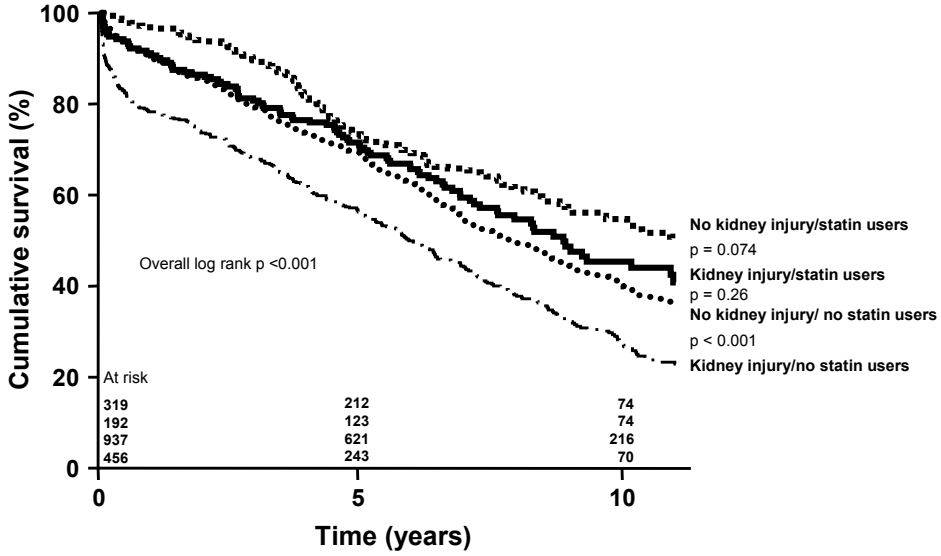


**Figure 20.1** All-cause long-term mortality in vascular surgery patients, according to the presence of kidney injury and statin use.
Kidney injury: >10% decrease in creatinine clearance on day 1 or 2, compared to the baseline value.
Mean follow-up is 6.24 ± 4.2 years.

immediate postoperative death (unadjusted OR 0.40, 95% CI 0.17–0.94, p-value = 0.035). We were unable to perform multivariate analysis, because of decreased statistical power to detect differences in outcomes in this subgroup.

## DISCUSSION

The main finding of our study is that in patients who developed AKI in the postoperative period, statin usage was associated with a twofold increase in kidney function recovery when compared to participants not receiving statins. Statin usage was not associated with lower total perioperative blood loss, shorter suprarenal aortic cross-clamping time or a decrease in dialysis requirement in the postoperative period. Moreover, statin use was associated with increased long-term survival independent of change in kidney function in the postoperative period. In this study, age, hypertension,

suprarenal cross-clamping and baseline kidney function were significant predictors of AKI. To our knowledge, there are few observational studies examining the relationship of statins on the recovery of AKI caused by major vascular surgery and long-term outcome. In addition, the results of our study remained the same when kidney function was calculated with the Cockcroft and Gault or the MDRD prediction equations.

AKI occurred in 34% of the cohort within 2 days after undergoing major vascular surgery. The comparison of the incidence of kidney injury with earlier studies is complicated by the lack of a standardized definition for AKI. Two recent prospective studies observed an incidence of 20% and 48%, respectively, when AKI was defined as a 20–25% increase in plasma creatinine from the baseline within 3 days after surgery[19,20]. These reports suggest that the etiology of AKI post-vascular surgery is multifactorial, including pre-existing atherosclerosis, hypertension, suprarenal aortic cross-clamping time, nephrotoxic agents as well as inflammatory and neuroendocrine stress response to surgery[1,19,20]. In the current analysis, statin use was associated with a twofold increased odds of complete recovery of kidney function at day 3 after surgery. However, recovery from AKI at 7 or 30 days after surgery could not be assessed. This does limit the inferences that could be drawn regarding statin therapy and recovery from AKI.

Clinical studies have shown a significant association of statin usage with decreased mortality from bacterial infections or sepsis in a CKD and non-CKD patient population[21,22]; however, similar studies evaluating the effects of statin on the course of AKI in the post-surgical period are lacking. In the animal model of sepsis induced AKI (i.e. cecal ligation and puncture)[23], pretreatment with simvastatin improved kidney function, as measured by serum creatinine and blood urea nitrogen. In this study, simvastatin was observed to improve tubular vacuolar degeneration and reverse the increase vascular permeability, renal microperfusion and hypoxia seen in this model. Similarly, Sabbatini and colleagues[24] examined whether treatment with atorvastatin could improve the course of AKI after ischemia-reperfusion injury in ageing rats compared with untreated age-matched rats. These investigators were able to show that pre-administration of atorvastatin mitigated renal vasoconstriction and restored glomerular filtration values to the baseline by increasing nitric oxide availability and, therefore, improving renal hemodynamics. In addition to preserving endothelial nitric oxide synthase function, statins have also been shown to regulate other mediators of vascular permeability, including vascular endothelial growth factors and matrix metalloproteinases[25,26]. Our findings extend previous observations to patients with AKI after major vascular surgery.

Another important observation in the current analysis is that statin therapy is associated with an improved long-term outcome in patients undergoing major vascular surgery, irrespective of the presence of kidney injury after surgery. Patients undergoing major vascular surgery are at an increased risk of morbidity and mortality in the postoperative period. In the current analysis, about half of the patients (55%) died during long-term follow-up. During 6 years of follow-up, patients receiving statins had a 40% reduced rate of all-cause mortality, compared to patients not receiving statins. Similarly, Kertai and colleagues examined the long-term benefit of statins in 510 patients undergoing AAA surgery[27]. These investigators observed that statin therapy was associated with reduced all-cause and cardiovascular mortality during 4.7 years of follow-up (60% and 70% reduction, respectively). Hence, the juxtaposition of the above results suggests that statin therapy has a long-term protective effect in patients undergoing major vascular surgery. Besides reducing cholesterol synthesis, lipid-lowering agents have been shown to lower peripheral vascular resistance, have antithrombotic effects, improve endothelial function and even reduce inflammation[28,29]. These effects may stabilize atherosclerotic plaques present in patients undergoing major vascular surgery, resulting in prevention of plaque rupture and myocardial ischemia in the postoperative period[30].

Our study has certain limitations. First, observational studies are limited due to confounding by indication for treatment because of lack of randomization. Despite using a propensity score to adjust for the bias inherent in the decision about statin therapy, we cannot exclude the possibility of residual confounding. Second, the arbitrary definition of AKI used in this study is conservative when compared to other available definitions. Although we investigated small changes of kidney function (e.g. >10% decrease of CrCl) in the postoperative period, a recent publication illustrated that these subtle changes are related with a worse short- and long-term outcome after major vascular surgery, independent of baseline cardiovascular risk factors, kidney function and postoperative complications[31]. Third, the association of time of statin exposure with short- and long-term outcomes was also not investigated, since the data on duration of therapy were not available. Fourth, kidney function estimating equations (e.g. Cockcroft Gault) are derived in patients who are in a steady state. Since we reported perioperative estimates of CrCl changes (within 3 days after surgery) such a steady state is difficult to establish, which might underestimate true changes in kidney function. Unfortunately, there are no practical ways to readily measure kidney function in the acute setting. Finally, our findings are based on an almost entirely Caucasian (96%) patient population without advanced kidney disease who only underwent two specific types of vascular surgery (LLR and AAA) and caution should be used in the generalization of these findings.

In this large observational study, the perioperative usage of statins was associated with clinically significant recovery of AKI after undergoing high-risk elective vascular surgery. More importantly, statin therapy was associated with a beneficial effect during long-term follow-up, irrespective of the presence of AKI. Although the data reported in this cohort suggest a beneficial association of statins with recovery of kidney injury and long-term outcomes, clinical trials are needed to evaluate the safety and efficacy of statins in patients with AKI post-vascular surgery.



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# Chapter 21

## Effect of statin withdrawal on frequency of cardiac events after vascular surgery

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## ABSTRACT

**Background:** Discontinuation of statin therapy in patients with an acute coronary syndrome has been associated with an increase of adverse coronary events. Patients undergoing major surgery frequently are not able to take oral medication shortly after surgery. Since there is no intravenous formula for statins, interruption of statins in the postoperative period is a serious concern. The objective of this study was to assess the effect of perioperative statin withdrawal on postoperative cardiac outcome. Also, the association between outcome and type of statin was studied.

**Methods:** In 298 consecutive chronic statin users undergoing major vascular surgery a detailed cardiac history was obtained and medication use was noted. Postoperatively troponin levels were measured on day 1,3,7,30 and whenever clinically indicated by electrocardiographic changes. Endpoints were postoperative troponin release, myocardial infarction, and a combination of non-fatal myocardial infarction and cardiovascular death. Multivariable analyses and propensity score analyses were performed to assess the influence of type of statin and discontinuation of statins for these endpoints.

**Results:** Statin discontinuation was associated with an increased risk for postoperative troponin release (HR 4.6, 95%CI 2.2–9.6), and the combination of myocardial infarction and cardiovascular death (HR 7.5, 95% CI 2.8–20.1). Fluvastatin extended release was associated with less perioperative cardiac events compared to atorvastatin, simvastatin, and pravastatin.

**Conclusion:** The present study showed that statin withdrawal in the perioperative period is associated with an increased risk for perioperative adverse cardiac events. Furthermore there seems to be a better outcome in patients who received statins with an extended release formula.

## INTRODUCTION

Patients undergoing major vascular surgery frequently are not able to take oral medication shortly after surgery, for example because of postoperative paralytic ileus. Since there is no intravenous formula for statins, interruption of statin therapy in the immediate postoperative period is a serious concern, especially since it is known that these vascular surgical patients are at highest risk for adverse cardiac events in the first 3 days after operation[1]. We hypothesized that statin withdrawal among chronic statin users undergoing major vascular surgery might be associated with an increased risk of adverse cardiac events. Therefore, we evaluated the effect of sudden perioperative statin withdrawal compared to continuous use on postoperative adverse events. In addition, the association between outcome and the type of statin was studied.

## METHODS

The study population consisted of 298 patients on chronic statin therapy undergoing elective major vascular surgery at Erasmus MC in Rotterdam, the Netherlands, during the period July 2000 to August 2006. Chronic statin therapy was defined as the use of statins at the first preoperative vascular outpatient clinic visit. These patients were identified in a prospectively maintained database of all patients undergoing vascular surgery at this institution. The study was approved by the Medical Ethics Committee of Erasmus MC.

Prior to surgery, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure >140/90 mmHg, or medical therapy to control hypertension), diabetes mellitus (fasting glucose level >7.0 mmol/L, or medication to control diabetes), and renal failure (serum creatinine level ≥ 2.0 mg/dL). The presence of coronary artery disease was indicated by a previous myocardial infarction, previous coronary intervention, present stable angina pectoris, and positive cardiac stress test. Other cardiovascular risk factors scored in all patients included a history of a cerebrovascular accident or transient ischemic attack, age over 70 years, chronic heart failure, and chronic obstructive pulmonary disease (defined as a FEV1 < 70% of age and gender predictive value or medication use). The type and dosage of chronic statin therapy was noted in all.

All patients received perioperative beta-blocker therapy. At our institution beta-blockers are withheld if patients presented with a systolic blood pressure <100 mmHg or with a heart rate <50 beats per minute. The dosage of beta-blockers on the day of surgery and after surgery is kept similar to the preoperative beta-blocker dose. It is ascertained that beta-blockers are administered on the morning of surgery and on each day after surgery until discharge. There was no strict protocol on the use of statins in the perioperative period, i.e. the decision to continue or withhold statin therapy was left to the discretion of the treating physician. Medication use in the perioperative period was extracted from medical charts and/or the electronic hospital registration system in which all medication use is recorded. Interruption of statin therapy was defined as any missed dose of statins. Surgical procedures were classified as abdominal aortic surgery (154 patients, 52%), and lower extremity revascularization (144 patients, 48%).

At our institution troponin T levels are routinely measured in patients undergoing major vascular surgery on postoperative day 1, 3, 7, 30 and whenever clinically indicated by electrocardiographic changes, consistent with myocardial ischemia or infarction. Routinely electrocardiograms were

recorded preoperatively and on day 1, 3, 7, and 30 after surgery. Troponin T level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany).

Endpoints were postoperative troponin release (myocardial damage), non-fatal myocardial infarction, cardiovascular death within 30 days after surgery, and a combination of non-fatal myocardial infarction and cardiovascular death within 30 days after surgery.

Myocardial infarction was defined as the presence of 2 out of the following 3 criteria: (1) Characteristic ischemic symptoms lasting > 20 minutes, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists > 24 hours, and (3) a positive troponin T, i.e. >0.10 ng/ml, or peak creatine kinase-MB >8% of an elevated total creatinine phosphokinase with characteristic rise and fall[2]. Cardiovascular death was defined as any death with a cardiovascular cause, including those deaths following a cardiac procedure, cardiac arrest, myocardial infarction, pulmonary embolus, stroke, or sudden deaths not ascribed to other causes[3].

The cardiac risk score for each patient in our dataset was calculated according to the score of the DECREASE I and II studies[4,5] and one point was assigned to each of the following characteristics: history of myocardial infarction, history of angina pectoris, history of congestive heart failure, history of cerebrovascular disease, diabetes mellitus, renal failure, and age over 70 years. Patients with no risk factors are considered to be at low cardiac risk, with one or two risk factors to be at intermediate cardiac risk, and with ≥ 3 risk factors to be at high cardiac risk.



Dichotomous data are described as numbers and percentages, and continuous data are presented as means with standard deviations (SD). Differences in baseline characteristics between statin users were evaluated by analysis of variances (ANOVA) and Chi-square tests, where appropriate. We developed a propensity score for the likelihood of receiving continuous statin therapy, and used applied multivariable logistic regression analysis to calculate the propensity score. The variables included in the model were: type of surgery, gender, year of surgery, hypertension, chronic obstructive pulmonary disease, cardiac risk factors, calcium-channel blockers, angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, oral nitrates, antiplatelet agents. The performance of the propensity score model was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish statin continuation from statin interruption; it was quantified by the c-statistic. Calibration refers to whether the predicted probability of continuous statin use is in agreement with the observed probability and was measured with the Hosmer-Lemeshow goodness-of-fit-test. The method of Kaplan-Meier was used to describe the incidence of myocardial infarction and cardiac death over time. A log-rank test was applied to study differences in survival between continuous users and stoppers. These relations were further evaluated by multivariable Cox' proportional hazard regression analysis, with adjustment for confounders and propensity score. All potential confounders were entered in the multivariable model to ensure giving an as unbiased as possible estimate for the relation between statin discontinuation and perioperative cardiac outcome. Crude and adjusted Hazard ratios are reported with corresponding 95% confidence intervals (CI). For all tests, a p-value <0.05 (two-sided) was considered significant. All statistical analyses were performed using SPSS statistical software.

## RESULTS

The baseline characteristics of the 298 patients (mean age 64.9 +/- 10.5, 75% male) are presented in TABLE 21.1. Patients were on fluvastatin extended release (n=100), simvastatin (n=86), atorvastatin (n=35), or pravastatin (n=77). There was no difference in total cholesterol levels, high density lipoprotein, and low density lipoprotein between the different statin types measured at the first outpatient clinic visit as is shown in TABLE 21.2.

In a total of 70 (23%) patients statin therapy was interrupted in the perioperative period. The median duration of statin interruption was 3 days (interquartile range 2.7–8 days). Within the propensity score analysis, baseline variables that significantly predicted interruption of statin therapy were aortic surgery (HR = 23.8, 95%CI = 8.6–66.0), and number of cardiac risk factors (HR = 2.6, 95% CI 0.9–7.2, for intermediate risk and 4.6, 95% CI 1.2-16.8, for high-risk). The c-statistic of the propensity score was 0.79. Calibration with use of the Hosmer and Lemeshow test gave a non-significant outcome.

Myocardial damage, myocardial infarction, and cardiovascular death occurred in 26.8%, 11.4%, and 3.0% respectively for the entire study cohort. In univariable analysis patients who continued statin therapy had a significantly better cardiac outcome compared to patients who interrupted statin therapy: myocardial ischemia 16.7% vs. 60.0%, myocardial infarction 5.7% vs. 30.0%, cardiovascular death 1.8% vs. 7.1% and the combination of cardiovascular death and non-fatal myocardial infarction

**TABLE 21.1** Patient characteristics.

| | Total (N=298) | Continuation (N=228) | Withdrawal (N=70) | P-value |
|---|---|---|---|---|
| Male – no. (%) | 233 (75) | 168 (74) | 55 (79) | 0.44 |
| Mean age, years (SD) | 64.9 (10.5) | 64.2 (10.5) | 67.0 (10.3) | 0.02 |
| Myocardial infarction – no. (%) | 98 (33) | 70 (31) | 28 (40) | 0.15 |
| Angina pectoris – no. (%) | 92 (31) | 57 (25) | 35 (50) | 0.001 |
| Heart failure – no. (%) | 12 (4) | 7 (3) | 5 (7) | 0.16 |
| CVA or TIA – no. (%) | 53 (18) | 36 (16) | 17 (24) | 0.15 |
| CABG or PTCA – no. (%) | 77 (26) | 50 (22) | 27 (39) | 0.008 |
| Renal failure – no. (%) | 11 (4) | 7 (3) | 4 (6) | 0.30 |
| Diabetes mellitus – no. (%) | 82 (28) | 64 (28) | 18 (26) | 0.76 |
| Hypertension – no. (%) | 133 (45) | 97 (43) | 36 (51) | 0.27 |
| COPD – no. (%) | 108 (36) | 75 (33) | 33 (47) | 0.05 |
| Clinical cardiac risk | | | | 0.002 |
| Low cardiac risk* – no. (%) | 67 (23) | 58 (25) | 9 (13) | |
| Intermediate cardiac risk* – no. (%) | 169 (57) | 131 (58) | 38 (54) | |
| High cardiac risk* – no. (%) | 62 (21) | 39 (17) | 23 (33) | |
| Type of Surgery | | | | 0.001 |
| Aortic – no. (%) | 154 (52) | 91 (40) | 63 (90) | |
| Lower extremity revascularization – no. (%) | 144 (48) | 137 (60) | 7 (10) | |
| Type of statin | | | | 0.48 |
| Fluvastatin extended release – no. (%) | 100 (34) | 78 (34) | 22 (31) | |
| Simvastatin – no. (%) | 86 (29) | 65 (29) | 21 (30) | |
| Pravastatin – no. (%) | 35 (12) | 30 (13) | 5 (7) | |
| Atorvastatin – no. (%) | 77 (26) | 55 (24) | 22 (31) | |

* According to the Erasmus index; SD = standard deviation

(5.7% vs. 31.4%). Other univariable predictors of adverse cardiac outcome are shown in TABLES 21.3A-C. Also in multivariable analysis statin interruption remained an independent predictor of adverse cardiac outcome (TABLES 21.3A-C). When the propensity score was included in the model with all the covariates to adjust for the chance of interruption of statins, the effect of continuous statin therapy and withdrawal was comparable to the analysis adjusted for only covariates (TABLES 21.3A-C).

**TABLE 21.2** Characteristics of patients on different types of statins.

| Variable | Fluvastatin (N=100) | Simvastatin (N=86) | Pravastatin (N=35) | Atorvastatin (N=77) |
|---|---|---|---|---|
| Cholesterol, mg/dL – mean (SD) | 184 (42) | 181 (41) | 182 (44) | 182 (63) |
| Low density lipoprotein, mg/dL – mean (SD) | 114 (40) | 106 (39) | 103 (41) | 110 (58) |
| High density lipoprotein, mg/dL – mean (SD) | 49 (46) | 47 (16) | 47 (14) | 47 (19) |
| Triglycerides, mg/dL – mean (SD) | 184 (100) | 183 (111) | 170 (97) | 187 (129) |
| Statin dosing (mg) | | | | |
| 10 – no. (%) | 0 | 10 (12) | 5 (14) | 19 (25) |
| 20 – no. (%) | 0 | 50 (58) | 11 (31) | 25 (33) |
| 40 – no. (%) | 0 | 24 (28) | 19 (54) | 28 (36) |
| 80 – no. (%) | 100 (100) | 2 (2) | 0 | 5 (7) |
| Aortic surgery – no. (%) | 48 (48) | 51 (59) | 11 (31) | 44 (57) |
| Cardiac risk | | | | |
| Low cardiac risk – no. (%) | 27 (27) | 14 (16) | 8 (23) | 18 (23) |
| Intermediate cardiac risk – no. (%) | 56 (56) | 48 (56) | 19 (54) | 46 (60) |
| High cardiac risk – no. (%) | 17 (17) | 24 (28) | 8 (23) | 13 (17) |

SD= standard deviation



**TABLE 21.3A** Predictors for myocardial damage.

| Variable | Univariable analysis HR | Univariable analysis 95% confidence interval | Multivariable analysis HR | Multivariable analysis 95% confidence interval | Multivariable analysis* HR | Multivariable analysis* 95% confidence interval |
|---|---|---|---|---|---|---|
| Statin interruption | 7.5 | 4.2 – 13.6 | 5.1 | 2.5 – 10.4 | 4.6 | 2.2 – 9.6 |
| Cardiac Risk | | | | | | |
| Low risk | 1 | | 1 | | 1 | |
| Intermediate risk | 2.8 | 1.2 – 6.7 | 3.2 | 1.2 – 8.4 | 3.0 | 1.1 – 8.9 |
| High risk | 8.6 | 3.4 – 21.7 | 9.3 | 3.1 – 27.7 | 8.5 | 2.4 – 30.2 |
| Type of statin | | | | | | |
| Fluvastatin | 1 | | 1 | | 1 | |
| Simvastatin | 2.8 | 1.4 – 5.8 | 2.5 | 1.1 – 6.1 | 2.7 | 1.1 – 6.5 |
| Pravastatin | 3.2 | 1.3 – 7.9 | 6.1 | 2.0 – 18.2 | 6.6 | 2.2 – 19.6 |
| Atorvastatin | 3.3 | 1.6 – 6.9 | 4.3 | 1.8 – 10.7 | 4.2 | 1.7 – 10.4 |
| Surgical Site | | | | | | |
| Peripheral | 1 | | 1 | | 1 | |
| Aortic | 3.6 | 2.1 – 6.4 | 2.6 | 1.2 – 5.4 | 2.2 | 0.7 – 7.3 |
| COPD | 1.5 | 0.9 – 2.6 | 1.2 | 0.6 – 2.2 | 1.2 | 0.6 – 2.2 |
| Hypertension | 1.9 | 1.1 – 3.1 | 1.8 | 0.9 – 3.5 | 1.8 | 0.9 – 3.4 |
| C-index | | | | 0.82 | | 0.83 |

*Propensity score included in analysis; HR = Hazard ratio

**Table 21.3b** Predictors for myocardial infarction.

| Variable | Univariable analysis | | Multivariable analysis | | Multivariable analysis* | |
|---|---|---|---|---|---|---|
| | HR | 95% confidence interval | HR | 95% confidence interval | HR | 95% confidence interval |
| Statin interruption | 7.1 | 3.3 – 15.1 | 7.1 | 2.7 – 18.7 | 7.5 | 2.8 – 20.1 |
| Cardiac Risk | | | | | | |
| Low risk | 1 | | 1 | | 1 | |
| Intermediate risk | 8.8 | 1.2 – 67.4 | 7.7 | 1.0 – 62.0 | 9.5 | 1.1 – 82.6 |
| High risk | 17.5 | 2.2 – 138.4 | 12.3 | 1.4 – 105.3 | 17.8 | 1.8 – 181.2 |
| Type of statin | | | | | | |
| Fluvastatin | 1 | | 1 | | 1 | |
| Simvastatin | 4.7 | 1.5 – 14.8 | 4.1 | 1.2 – 14.2 | 3.7 | 1.0 – 13.3 |
| Pravastatin | 4.0 | 1.0 – 15.9 | 5.2 | 1.1 – 24.1 | 5.1 | 1.1 – 23.9 |
| Atorvastatin | 4.0 | 1.2 – 13.1 | 3.8 | 1.1 – 13.6 | 4.0 | 1.1 – 14.1 |
| Surgical Site | | | | | | |
| Peripheral | 1 | | 1 | | 1 | |
| Aortic | 2.1 | 1.0 – 4.5 | 0.9 | 0.3 – 2.7 | 1.5 | 0.3 – 7.2 |
| COPD | 0.9 | 0.4 – 2.0 | 0.7 | 0.3 – 1.6 | 0.7 | 0.3 – 1.7 |
| Hypertension | 1.6 | 0.8 – 3.4 | 1.3 | 0.6 – 2.9 | 1.3 | 0.6 – 3.1 |
| C-index | | | | 0.82 | | 0.83 |

*Propensity score included in analysis; HR = Hazard ratio; COPD = chronic obstructive pulmonary disease

**Table 21.3c** Predictors for the combined endpoint of nonfatal myocardial infarction and cardiac death.

| Variable | Univariable analysis | | Multivariable analysis | | Multivariable analysis* | |
|---|---|---|---|---|---|---|
| | HR | 95% confidence interval | HR | 95% confidence interval | HR | 95% confidence interval |
| Statin interruption | 7.6 | 3.6 – 16.1 | 7.3 | 2.8 – 18.9 | 7.5 | 2.8 – 20.1 |
| Cardiac Risk | | | | | | |
| Low risk | 1 | | 1 | | 1 | |
| Intermediate risk | 8.9 | 1.2 – 67.4 | 8.0 | 1.0 – 64.6 | 8.8 | 1.0 – 76.5 |
| High risk | 19.3 | 2.4 – 151.4 | 14.6 | 1.7-123.9 | 17.3 | 1.7 – 174.8 |
| Type of statin | | | | | | |
| Fluvastatin | 1 | | 1 | | 1 | |
| Simvastatin | 4.7 | 1.5 – 14.8 | 4.4 | 1.3– 15.1 | 4.1 | 1.1 – 14.8 |
| Pravastatin | 4.0 | 1.0 – 15.9 | 5.9 | 1.3– 27.6 | 5.7 | 1.2 – 26.8 |
| Atorvastatin | 4.4 | 1.4 – 14.3 | 4.5 | 1.3 – 16.1 | 4.6 | 1.3 – 16.3 |
| Surgical Site | | | | | | |
| Peripheral | 1 | | 1 | | 1 | |
| Aortic | 2.2 | 1.1 – 4.7 | 1.0 | 0.4 – 2.8 | 1.3 | 0.3 – 6.1 |
| COPD | 1.0 | 0.5 – 2.1 | 0.8 | 0.3 – 1.7 | 0.8 | 0.3 – 1.8 |
| Hypertension | 1.5 | 0.7 – 3.1 | 1.2 | 0.5 – 2.6 | 1.2 | 0.5 – 2.8 |
| C-index | | | | 0.83 | | 0.84 |

* Propensity score included in analysis; HR = Hazard ratio; COPD = chronic obstructive pulmonary disease

In univariable analysis patients who were on fluvastatin extended release therapy had a lower risk of adverse cardiac events compared to patients on simvastatin, pravastatin, or atorvastatin. Troponin T release was present in 14.0%, 31.4%, 34.3%, and 35.1% respectively for fluvastatin, simvastatin, pravastatin, and atorvastatin, while myocardial infarction occurred in 4.0%, 16.3%, 14.3%, and 14.3% respectively. The incidence of cardiovascular death did not differ significantly between statin types, 2.0%, 3.5%, 5.7%, and 2.6% respectively. As is shown in TABLES 21.3A-C also in multivariable analysis, adjusting for covariates and propensity score, patients who were on fluvastatin extended release had a significantly lower rate of adverse cardiac events.

## DISCUSSION

This study showed that acute statin withdrawal in the perioperative period is associated with an increased risk of perioperative cardiac events compared to statin continuation among chronic users. The extended release formula of fluvastatin appears to have beneficial effects over other statins in patients who discontinued statin therapy.

The possible detrimental effects of sudden statin withdrawal have been reported previously in chronic statin users with an acute coronary syndrome[6-9]. In a cohort study the GRACE-investigators found that 428 chronic statin users in whom statin therapy was discontinued at admission for an acute coronary syndrome had the same risk for the composite of death, stroke, and myocardial infarction as non-users[6]. In contrast, 3,628 patients who continued statin therapy throughout the admission had a significant 34% relative risk reduction compared to non-users. Another large observational study found the same effect of statin withdrawal in patients admitted for non-ST-segment elevation myocardial infarction: no difference in in-hospital death rate between 4,870 patients who discontinued statin therapy and 54,635 non-users whereas 9,001 patients who continued statin therapy had a highly significant 45% relative risk reduction compared to non-users[7].



The lipid-lowering effects of statins might explain most of the beneficial effects of chronic statin use in patients at increased risk for coronary artery disease. However, this might not explain the effects of sudden statin withdrawal in the current study. All patients were chronic statin users up to the day of surgery and significant changes in serum lipid levels may take days to weeks. Another explanation might be the effect of sudden statin withdrawal on its pleiotropic properties. These pleiotropic effects include inhibition of inflammation, modulation of endothelial function, and antithrombotic effects. Pleiotropic effects of statins are present within hours to days after statin therapy initiation. Importantly, several studies have shown that these pleiotropic effects might be lost within hours after statin withdrawal while lipid levels remained continuously low. Vulnerable coronary plaque rupture[10,11], leading to thrombus formation and subsequent vessel occlusion is one of the main causative mechanisms of perioperative cardiac complications. The pleiotropic effects of statins are thought to influence the susceptibility of vulnerable plaques for rupture. While the surgical patient is at highest cardiac risk within the first three days after surgery, possibly also because of the detrimental effects of surgery on mechanisms leading to vulnerable plaque rupture, statin therapy is discontinued.

The current study showed that statin therapy is interrupted in about 25% of patients undergoing major non-cardiac surgery. The main cause for interruption was the inability to take oral medication shortly after surgery. Since statins are not available as intravenous formulas this leads to unintended statin withdrawal. Our current study suggests that fluvastatin might be associated with a better outcome after major non-cardiac surgery compared to other statins. There are several possible

explanations for these observations. Fluvastatin is the only statin with an extended release formula. Since most patients with statin withdrawal restarted statin therapy within 3 to 4 days after surgery it might be hypothesized that the fluvastatin extended release formula is capable of extending the duration of pleiotropic effects of statins. Furthermore the pharmacokinetics of statins might be influenced by concomitant drug use in the perioperative period. Of special interest in this respect is the cytochrome P450 (CYP) isoenzyme system. Most drugs are metabolized in the liver by the CYP 3A4 isoenzyme. As a consequence this might cause interaction with simvastatin and atorvastatin that are also metabolized by this pathway[12]. Fluvastatin on the other hand has only limited interactions with the CYP 3A4 pathway since it is mainly metabolized by the CYP 2C9 isoenzyme. As was shown in a review by Bellosta et al. other differences between statins include half-life, systemic exposure, maximum plasma concentration, bioavailability, protein binding, lipophilicity, presence of active metabolites, and excretion routes[13]. Fluvastatin is the only statin that is a racemic compound, half of the molecule being presumably inactive at reducing plasma cholesterol. It is not excluded that some of the beneficial pleiotropic effects may be shared by the "non-active" half therefore potentially increasing that capacity.

The non-randomized nature of the current study has certain limitations. It could be argued that patients with more complex, lengthy and difficult operations in a rather poorer general condition were less likely to recover soon and have their oral medication. These are however the type of patients that is more likely to end up with cardiovascular complications. The propensity score indeed showed that patients with aortic aneurysms and high cardiac risk were more likely to be in the statin withdrawal group. However, in multivariate analysis the propensity score was included to minimize the potential bias resulting from this.

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# Chapter 22

## The effect of fluvastatin extended release on perioperative cardiac complications in patients undergoing vascular surgery

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## ABSTRACT

**Background:** Coronary plaque instability due to the stress of surgery is an important cause of adverse cardiac events after vascular surgery. We hypothesized that lipid lowering therapy with anti-inflammatory effects would stabilize coronary plaques, prevent rupture and improve postoperative outcome.

**Methods:** In this double-blind, placebo-controlled trial, statin naïve patients were randomly assigned to receive, in addition to beta-blocker, either 80 mg fluvastatin extended release once daily or placebo, starting 37 days prior to surgery. Interleukin-6 and C-reactive protein were measured at randomization and prior to surgery. The primary endpoint was the occurrence of myocardial ischemia, defined as transient ECG abnormalities and troponin T release within 30 days after surgery. The secondary endpoint was the composite of cardiac death and myocardial infarction.

**Results:** Two hundred fifty patients were assigned to fluvastatin and 247 to placebo. Interleukin-6 and C-reactive protein levels remained unchanged in the placebo group (-4% and +3% respectively) and decreased in the fluvastatin group (-33% and -21% respectively, P<0.001). The incidence of myocardial ischemia in the fluvastatin and placebo groups was, respectively, 10.8% vs. 19.0%, hazard ratio 0.55; 95% confidence interval [CI] 0.34 to 0.88. The incidence of cardiac death or myocardial infarction was 4.8% vs. 10.1%, hazard ratio 0.47; 95% CI 0.24 to 0.94. Importantly, fluvastatin use was not associated with an increased risk for myopathy, liver dysfunction or all-cause death.

**Conclusions:** In patients undergoing vascular surgery, fluvastatin therapy is associated with an improved postoperative cardiac outcome and a reduction of inflammation activity.

## INTRODUCTION

Vascular patients are at high risk for postoperative cardiac events, such as myocardial infarction (MI) and cardiac death. Cardiac events occur in up to 24 percent in high-risk cohorts[1] and are related to the high incidence of underlying coronary artery disease. Hertzer et al, routinely performing coronary angiography in 1000 patients scheduled for vascular surgery, found that only 8% had a normal coronary artery tree[2].

Although the pathophysiology of perioperative MI is not entirely understood, it is well accepted that coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, plays an important role. The surgical stress response elicits a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability[3]. Inflammatory processes in general and monocyte-derived macrophages in particular, play a critical role in coronary plaque progression and plaque destabilization.

Large trials in the non-surgical population have shown a beneficial role for long-term 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors (statins) on cardiac outcome[4]. These effects are related to a reduction of low-density lipoprotein (LDL) cholesterol levels and inflammation[5]. Reduction in inflammation might, independent of patients' cholesterol levels, prevent coronary plaque destabilization induced by the stress of surgery. So far, no adequately powered placebo-controlled trial has been conducted to assess the effect of statins on postoperative outcome[6].

We therefore conducted a single-center, double-blind placebo-controlled trial: the Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo III (DECREASE III) trial. We hypothesized that perioperative statin therapy with fluvastatin extended release would reduce the perioperative incidence of adverse cardiac events in patients undergoing elective vascular surgery.

## METHODS

### Study participants

All patients over 40 years of age scheduled for non-cardiac vascular surgery at Erasmus MC, Rotterdam, the Netherlands, between June 2004 and April 2008 were candidates for inclusion in the trial. Patients had to be scheduled for abdominal aortic aneurysm repair, abdominal aortic stenosis surgery, lower limb arterial reconstruction or carotid artery stenosis repair. Furthermore, patients were to have at least 51 points on the pre-specified risk index (appendix A).

Exclusion criteria for the trial were: (1) current statin therapy, (2) contraindication for statin therapy, (3) surgery which interferes with continuous 12-lead ECG recording, such as thoracic and upper abdominal surgery, (4) emergency surgery, (5) unstable coronary artery disease, (6) extensive stress induced myocardial ischemia suggestive for left main disease or equivalent, (7) previous participation in this study, (8) reoperation within 30 days of an initial surgical procedure.

All patients were on perioperative beta-blockers according to the DECREASE protocols[7]. Patients on chronic beta-blocker therapy continued their medication, otherwise bisoprolol 2.5 mg once a day was initiated at the screening visit. The beta-blocker dose was adjusted at admission to surgery to achieve a resting heart rate of 60 to 65 beats per minute. The same dose was continued postoperatively except in patients who were unable to take medication orally. In these patients, heart rate was

monitored continuously at the intensive care unit or hourly at the ward, and intravenous metoprolol was administered to maintain a target heart rate of 60-65 beats per minute. The heart rate and blood pressure were measured immediately before each scheduled dose of beta-blockers. Beta-blockers were withheld if the heart rate was <50 beats/min or the systolic blood pressure was <100 mm Hg.

### Study intervention

Patients were randomized to receive either placebo or fluvastatin extended release (Novartis, Basel, Switzerland) at a dose of 80 mg once daily. Placebo was identically supplied and formulated. Treatment was started at the outpatient clinic on the day of randomization, at a median of 37 days prior to the surgical procedure and was continued for at least 30 days after surgery. Patients remained on the same treatment allocation throughout the study. A computer-generated randomization list was drawn up by the study statistician and given to the pharmacy department. Independent pharmacists dispensed either active or placebo drugs according to this computer generated randomization list. The researchers responsible for seeing the patients allocated the next available number on entry into the trial. Study personnel and participants were blinded to the treatment assignment for the duration of the study. The treatment assignment code was broken when recruitment, data entry and laboratory analyses were complete.

### Study objectives

The objective of this trial was to study the relationship between fluvastatin therapy and the incidence of cardiac complications in patients undergoing non-cardiac vascular surgery.



### Study outcomes

The primary study outcome was the occurrence of myocardial ischemia, defined as the composite of transient electrocardiographic signs of ischemia and troponin T release. Electrocardiographic monitoring was performed using continuous ECG registration in the 48 hours following surgery and ECG recordings on days 3, 7 and 30. Troponin T measurements were performed on days 1, 3, 7, and 30. If patients were discharged prior to day 7, troponin T was measured at the day of discharge.

Electrocardiographic data were initially processed by a technician and analyzed by 2 experienced cardiologists who were blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the ambulatory ECG recordings were analyzed for ST segment deviations. A continuous ST segment trend was generated, and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST segment changes, lasting at least 1 minute and shifting from baseline to more than 0.1 mV (1 mm). ST segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST segment change was measured 40 ms after that point.

The secondary endpoint was the composite of cardiovascular death and nonfatal MI. All deaths were classified as either cardiovascular or non-cardiovascular. Cardiovascular death was defined as any death with a cardiovascular complication as the primary or secondary cause, and includes deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Non-cardiovascular death was defined as any death with a primary non-cardiovascular cause, including surgery-related bleeding complications, cancer, trauma and infection. Sudden death in a previously stable patient was considered as cardiovascular[8].

A nonfatal MI was defined if any two of the following criteria occurred: (1) characteristic ischemic symptoms lasting > 20 minutes; (2) ECG changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for

at least 24 hours, or new ST segment depression which persisted for at least 24 hours; (3) a positive troponin T measurement with characteristic rise and fall[9].

The other secondary study outcome was the relationship between fluvastatin and inflammatory markers, i.e. high-sensitivity C-reactive protein and Interleukin-6, and their relation to postoperative cardiac events. These markers were measured prior to initiation of treatment and on the day of admission for the surgical procedure.

The safety outcome measures included: (1) creatinine kinase (CK) elevations; (2) alanine aminotransferase (ALAT) elevations; (3) myopathy; (4) rhabdomyolysis. Blood samples were drawn prior to randomization, on the day of hospital admission and on days 1, 3, 7, and 30 after surgery. Study drug was withheld if ALAT levels exceeded by more than 3-fold the upper limit of normal, or if CK levels exceeded by more than 10-fold the upper limit of normal, or if patients experienced myopathy or rhabdomyolysis.

### Sample size

Based on previous study results the anticipated incidence of the primary endpoint, perioperative myocardial ischemia, was 18.0% in the placebo group. Treatment with fluvastatin was expected to be associated with a 50% relative risk reduction. A sample size of 500 – 250 in each treatment group – would yield over 80% power to detect the anticipated 50% risk reduction associated with fluvastatin therapy, with an $\alpha = 0.05$ (two-sided).

### Statistical analysis

The time to the first occurrence of the primary efficacy endpoint was determined according to the Kaplan-Meier method, and differences between allocated groups were evaluated by log-rank statistics. The Cox proportional hazards model was applied to obtain treatment effects on the primary and secondary efficacy endpoints, which are presented as hazard ratio's (HR) and 95% confidence intervals (CI). The assumption of proportional hazards (PH) was assessed by visual judgment of the log-minus-log survival plots. These plots demonstrated reasonably parallel lines, indicating that the PH assumption was not violated. Analyses of other endpoints were based on Mann-Whitney U tests, independent-samples T tests and chi-square tests. Exploratory analyses for the primary outcome were evaluated with the use of tests for interaction for baseline features. All analyses were performed according to the intention-to-treat principle. All statistical tests were 2-sided, and a p-value $<0.05$ was considered significant.

## RESULTS

### Baseline characteristics

Patient characteristics are presented in TABLE 22.1. Of the 497 patients included 253 (51%) had a baseline total cholesterol level of less than 5.5 mmol per liter and 194 (39%) had a baseline LDL-cholesterol level of less than 3.0 mmol per liter (TABLE 22.2).

The primary analysis was intention-to-treat and included all patients who were randomly assigned to either fluvastatin or placebo. Between randomization and the surgical procedure no patient experienced an adverse cardiac outcome. Four patients did not receive the intended treatment strategy; 3 patients allocated to fluvastatin did not take the study drug and 1 patient allocated to placebo mistakenly received preoperative statin treatment because of elevated cholesterol levels. In total 34

**TABLE 22.1** Clinical characteristics, medication use, and type of surgery*.

| | Placebo N=247 | Fluvastatin N=250 |
|---|---|---|
| Age – yr | 65.8 ± 11.5 | 66.0 ± 10.5 |
| Male – no. (%) | 178 (72) | 194 (78) |
| **Risk factors** | | |
| Myocardial infarction – no. (%) | 66 (27) | 73 (29) |
| Angina pectoris – no. (%) | 59 (24) | 52 (21) |
| Congestive heart failure – no. (%) | 19 (8) | 13 (5) |
| Diabetes mellitus – no. (%) | 42 (17) | 55 (22) |
| CVA or TIA – no. (%) | 66 (27) | 75 (30) |
| Renal insufficiency – no. (%) | 31 (13) | 23 (9) |
| Hypertension – no. (%) | 143 (58) | 142 (57) |
| COPD – no. (%) | 71 (29) | 74 (30) |
| **Medication use** | | |
| Beta-blocker – no. (%) | 247 (100) | 250 (100) |
| Antiplatelet therapy – no. (%) | 146 (59) | 160 (64) |
| Anticoagulant therapy – no. (%) | 73 (30) | 62 (25) |
| ACE-inhibitor – no. (%) | 73 (30) | 76 (30) |
| Calciumantagonist – no. (%) | 59 (24) | 56 (22) |
| A-II antagonist – no. (%) | 37 (15) | 40 (16) |
| Nitrates – no. (%) | 23 (9) | 20 (8) |
| Prednison – no. (%) | 63 (26) | 54 (22) |
| Diuretics – no. (%) | 78 (32) | 64 (25) |
| **Surgery** | | |
| Carotid artery surgery – no. (%) | 32 (13) | 37 (15) |
| Abdominal aortic surgery – no. (%) | 115 (47) | 121 (48) |
| Open surgery – no. (%) | 54 (22) | 58 (23) |
| Endovascular surgery – no. (%) | 61 (25) | 63 (25) |
| Lower limb arterial surgery – no. (%) | 100 (41) | 92 (37) |

*CVA denotes cerebrovascular accident, TIA transient ischemic attack, COPD chronic obstructive pulmonary disease, ACE angiotensin-converting enzyme and A-II angiotensin II.



(6.8%) patients discontinued study treatment due to side effects; 16 (6.4%) in the fluvastatin group and 18 (7.3%) in the placebo group. After surgery, study treatment was temporarily discontinued in 115 (23%) patients because of an inability to take the study drug orally (appendix B, CONSORT flowchart).

## Primary Outcome

Myocardial ischemia was detected in 74 (14.9%) patients within 30 days of the initial vascular surgical procedure. A total of 27/250 (10.8%) patients allocated to fluvastatin reached the primary endpoint compared to 47/247 (19.0%) patients allocated to placebo treatment (HR 0.55; 95% CI 0.34-0.88, FIGURE 22.1A). Hence, the number needed to treat (NNT) to prevent one patient experiencing myocardial ischemia was 12 patients.

## Secondary Outcome

A total of 18 (3.6%) patients died within 30 days after surgery of which 12 (67%) deaths were attributable to cardiovascular causes. Eight patients allocated to placebo died due to cardiovascular causes versus 4 patients allocated to fluvastatin. Additionally, 25 (5.0%) patients experienced a nonfatal MI;

**TABLE 22.2** Levels of lipids and inflammatory markers at baseline and at day of admission after a median treatment of 37 days.

| | Placebo | Fluvastatin | P-value |
|---|---|---|---|
| **Level at baseline** | | | |
| Cholesterol (mmol/l) | | | |
| Total | 5.30 ± 1.20 | 5.40 ± 1.14 | 0.34 |
| LDL | 3.26 ± 0.93 | 3.36 ± 1.06 | 0.27 |
| HDL | 1.53 ± 0.70 | 1.61 ± 0.81 | 0.27 |
| Triglycerides (mmol/l) | 1.46 | 1.63 | 0.67 |
| Median – interquartile range | (1.07 to 2.32) | (1.28 to 2.30) | |
| High-sensitivity C-reactive protein (mg/l) | 5.80 | 5.93 | 0.32 |
| Median – interquartile range | (3.00 to 10.40) | (2.42 to 10.89) | |
| Interleukin-6 (pg/ml) | 8.76 | 8.55 | 0.80 |
| Median – interquartile range | (2.54 to 15.66) | (1.26 to 16.59) | |
| **Level before surgery** | | | |
| Cholesterol (mmol/l) | | | |
| Total | 5.09 ± 1.16 | 4.32 ± 0.79 | <0.001 |
| LDL | 3.16 ± 0.91 | 2.55 ± 0.84 | <0.001 |
| HDL | 1.55 ± 0.51 | 1.59 ± 0.53 | 0.40 |
| Triglycerides (mmol/l) | 1.62 | 1.64 | 0.90 |
| Median – interquartile range | (1.18 to 2.40) | (1.26 to 2.36) | |
| High-sensitivity C-reactive protein (mg/l) | 6.00 | 4.66 | 0.02 |
| Median – interquartile range | (2.90 to 11.90) | (1.99 to 8.83) | |
| Interleukin-6 (pg/ml) | 8.45 | 5.75 | 0.005 |
| Median – interquartile range | (2.28 to 15.35) | (1.00 to 11.41) | |
| **Percent change from baseline** | | | |
| Cholesterol | | | |
| Total | - 3.9 ± 4.6 | - 19.0 ± 9.6 | <0.001 |
| LDL | - 3.1 ± 6.4 | - 23.2 ± 11.4 | <0.001 |
| HDL | + 4.3 ± 14.8 | + 2.5 ± 16.1 | 0.20 |
| Triglycerides | 0 | + 1.0 | 0.58 |
| Median – interquartile range | (-10.2 to 19.4) | (-23.8 to 32.1) | |
| High sensitivity C-reactive protein | +3.3 | - 20.5 | <0.001 |
| Median – interquartile range | (-20.5 to 30.3) | (-26.8 to -12.0 ) | |
| Interleukin-6 | -4.2 | - 32.7 | <0.001 |
| Median – interquartile range | (-16.7 to 10.2) | (-42.3 to -21.6) | |

17 patients allocated to placebo and 8 patients allocated to fluvastatin. The combined endpoint of cardiovascular death and nonfatal MI was reached in 37 (7.4%) patients. A total of 12/250 (4.8%) patients allocated to fluvastatin therapy reached the combined endpoint, compared to 25/247 (10.1%) allocated to placebo. Hence, fluvastatin therapy was associated with a 53% relative reduction in the incidence of cardiovascular death or nonfatal MI (HR 0.47; 95% CI: 0.24-0.94, FIGURE 22.1B). The NNT for the composite endpoint of cardiovascular death or nonfatal MI was 19.

The median baseline high-sensitivity C-reactive protein level was 5.93 mg per liter; levels were similar in patients allocated to fluvastatin (5.93 mg per liter) or placebo (5.80 mg per liter). At hospital admission, median 37 days after randomization, fluvastatin treated patients had a median decrease in high-sensitivity C-reactive protein levels of 21% compared with an increase of 3% in the placebo group ($p<0.001$, TABLE 22.2). The median Interleukin-6 levels at baseline were similar in patients allocated

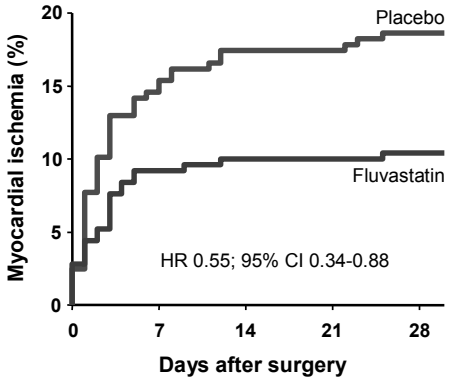


**FIGURE 22.1A** Kaplan–Meier curves of the cumulative probability of perioperative myocardial ischemia (primary outcome).

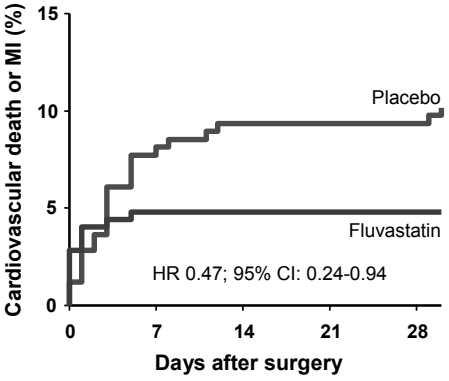


**FIGURE 22.1B** Kaplan–Meier curves of the cumulative probability of perioperative cardiovascular death or nonfatal MI (secondary outcome).

to fluvastatin (8.55 pg per milliliter) or placebo (8.76 pg per milliliter), and were significantly lower at the time of surgery in patients on fluvastatin (-33% vs -4%, p=<0.001).

## Adverse events

The proportion of patients experiencing a CK increase >10 times upper limit of normal was 4.0% in the fluvastatin group and 3.2% in the placebo group, respectively (TABLE 22.3). The median peak CK level was 141 U per liter in patients assigned to fluvastatin and 113 U per liter in patients assigned to placebo (p=0.24). The proportion of patients with significant increase in ALAT levels (i.e. > 3 times upper limit of normal) was 3.2% in the fluvastatin group and 5.3% in the placebo group. The median peak ALAT level was 24 U per liter in patients allocated to fluvastatin and 23 U per liter in patients allocated to placebo (p=0.43). Myopathy or rhabdomyolysis within 30 days after surgery was not reported.



**TABLE 22.3** Safety measures of statin use*.

| | Placebo N=247 | Fluvastatin N=250 | P-value |
|---|---|---|---|
| Discontinuation of treatment | | | |
| Temporarily – no. (%) | 54 (22) | 61 (24) | 0.53 |
| Permanently – no (%) | 18 (7.3) | 16 (6.4) | 0.73 |
| CK > 10x ULN – no. (%) | 8 (3.2) | 10 (4.0) | 0.81 |
| CK (U/L), median – interquartile range | 113 (66-369) | 141 (77-380) | 0.24 |
| ALAT > 3x ULN – no. (%) | 13 (5.3) | 8 (3.2) | 0.27 |
| ALAT (U/L), median – interquartile range | 23 (15-37) | 24 (17-50) | 0.43 |
| Myopathy – no. (%) | - | - | |
| Rhabdomyolysis – no. (%) | - | - | |
| All-cause death – no. (%) | 12 (4.9) | 6 (2.4) | 0.14 |
| Non-cardiovascular death – no. (%) | 4 (1.6) | 2 (0.8) | 0.40 |

*CK denotes creatinine kinase , ULN upper limit of normal, U/L units/liter, and ALAT alanine aminotransferase.

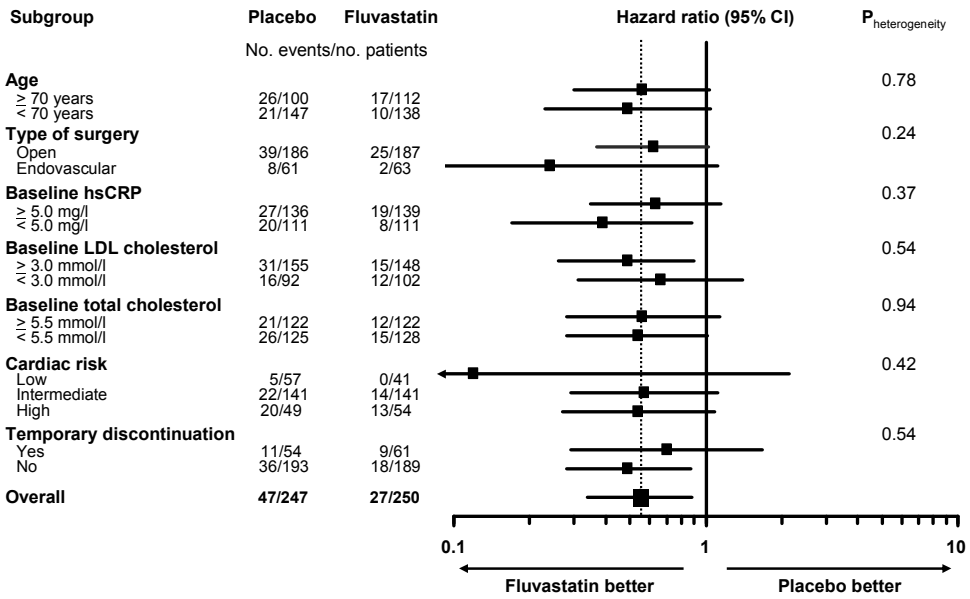


**FIGURE 22.2** Hazard ratios for the primary outcome of myocardial ischemia according to post hoc specified baseline characteristics.

### Exploratory findings

The relative difference with regard to the primary outcome of perioperative myocardial ischemia between the groups assigned to fluvastatin or placebo was consistent across multiple exploratory subgroup analyses (FIGURE 22.2). In light of recent concerns about the safety of perioperative beta-blockers we also evaluated the incidence of stroke. Three patients suffered a nonfatal postoperative stroke; 2 (0.8%) in patients allocated to placebo and 1 (0.4%) to fluvastatin.

## DISCUSSION

In our study, we compared fluvastatin extended release 80 mg once daily, initiated 37 days prior to vascular surgery, with placebo in statin-naive patients with mean total cholesterol of 5.35 mmol per liter. We showed that fluvastatin reduced the risk of perioperative myocardial ischemia. Though the trial was not powered for this endpoint, we also found a reduction in the composite of cardiovascular death and nonfatal MI while the safety profile appeared to be favorable. Furthermore, fluvastatin treatment was associated with a significant decrease in inflammatory activity, reflected by a reduction in high-sensitivity C-reactive protein and Interleukin-6 levels.

The exact pathophysiology of perioperative cardiac events remains complex. Autopsy studies suggest that approximately half of fatal MIs are attributable to a sustained myocardial oxygen-demand supply mismatch while coronary plaque rupture is accountable for the other half[10,11]. It is thought that statins might be particularly well suitable for influencing the latter pathophysiological mechanism by stabilizing unstable coronary plaques. Factors leading to unstable coronary plaques are complex. In general, the risk of plaque rupture is related to two factors: intrinsic plaque morphology characteristics and an extrinsic force triggering plaque disruption[12,13]. Although it has been proven that statins

are capable of positively altering plaque morphology, it is implausible that this would occur within a few weeks, however, statins might play a pivotal role in counteracting the extrinsic factors causing plaque disruption. The pleiotropic effects of statins include several plaque-stabilizing effects such as the increased expression of endothelial nitric oxide synthase, the reduced production of endothelin-1, and the generation of reactive oxygen species, an improvement of the thrombogenic profile, and importantly, a reduction in inflammation via the reduced expression of inflammatory cytokines, chemokines, adhesion molecules, and a lowering of C-reactive protein levels[14,15]. As demonstrated by the findings from the DECREASE III trial fluvastatin reduces inflammatory activity within weeks even in patients without hypercholesterolemia. Whether, indeed, the decrease in inflammation is responsible for the beneficial effects of perioperative statin use remains unclear.

These findings on the perioperative benefits of statins are in line with previous retrospective studies and one small randomized trial. In the double-blind randomized trial 100 patients were allocated to 20 mg atorvastatin or placebo once a day for 45 days, irrespective of their serum cholesterol levels[16]. Vascular surgery was performed on average 31 days after randomization, and patients were followed up over 6 months. During these 6 months of follow-up, atorvastatin significantly reduced the incidence of cardiac events (8% vs 26%, p=0.03). Though not powered to assess 30-day postoperative outcome there was a clear trend indicating the beneficial effect of statins: 3 (6%) of patients on atorvastatin had a nonfatal MI or cardiac death versus 9 (18%) in the placebo group (OR 0.23, 95% CI 0.09-1.30). This relative risk reduction was similar to the 4.5-fold relative risk reduction in perioperative mortality that was found in a case control study conducted by our group comparing chronic statin users with non-users (adjusted OR 0.22, 95% CI 0.10 to 0.47)[17]. Since then several other retrospective studies have reported a potential beneficial effect for perioperative statin use with respect to various cardiovascular outcomes with ORs ranging from 0.24 to 0.71.[18-20] The findings of the DECREASE III trial, with a relative risk reduction of 45% for myocardial ischemia and 53% for the composite of cardiac death or nonfatal MI, are consistent with these previous reports. Importantly, we found no heterogeneity of effects in patients with several different baseline characteristics, such as clinical cardiac risk, cholesterol levels, type of surgery and inflammatory status.



A concern with perioperative statin treatment is the inability to avoid treatment interruption when oral administration is not feasible in the early postoperative phase. This might be potentially hazardous as sudden withdrawal of statins in the non-surgical setting has been associated with diminished beneficial effect. In a cohort study the GRACE-investigators observed that 428 patients with an acute coronary syndrome who stopped statins had the same risk for the composite of late death, stroke, and myocardial infarction as non-users[21]. In contrast, 3,628 patients who continued statin therapy throughout the admission had a significant 34% relative risk reduction compared to non-users. In the present study, in approximately a quarter of patients fluvastatin had to be interrupted for a median of 2 days after surgery. However, when corrected for baseline characteristics and type of surgery, we did not observe a significant increase in adverse outcome in patients who interrupted fluvastatin compared with those who continued on fluvastatin treatment (OR 1.1, 95% CI 0.48-2.52). To our knowledge the relationship between the time course or extent of a possible rebound in inflammation or of thrombogenic effects following statin interruption after surgery and specific pharmacokinetic or pharmacodynamic characteristics of statins has not been investigated. However, the present findings support the hypothesis that fluvastatin extended release therapy is capable of bridging a period of one to two days after surgery, when oral intake is not yet feasible.

Recent guidelines, based on retrospective studies, from the American College of Cardiology/American Heart Association (ACC/AHA)[22] and the TransAtlantic Inter-Society Consensus document on the

treatment of patients with peripheral arterial disease[23] indicate that statin use is appropriate for patients undergoing vascular surgery with or without other clinical risk factors. The results of the current study confirm these recommendations. It should also be noted that current guidelines state that long-term treatment with a statin is indicated for all patients with peripheral arterial disease. However, the timing of initiation of statin therapy remained a matter of debate. Should the patient start with statin therapy at the preoperative screening visit while there is (1) a possible increased risk for perioperative statin-induced side effects such as myopathy, as suggested by the ACC/AHA/NHLBI clinical advisory on the use and safety of statins, (2) a possibly increased cardiac risk if statin therapy has to be interrupted in the perioperative period, as is to be expected in approximately 25% of patients, and (3) the evidence supporting the perioperative use of statins is based on retrospective studies. With the results of DECREASE III it now seems clear that the benefit of perioperative statin use outweigh the risks. To initiate or continue statin treatment during preoperative screening of candidates for vascular surgery should therefore be considered in order to prevent cardiovascular events during the immediate perioperative period as well as for long-term cardiac risk reduction in these patients.

In conclusion, fluvastatin therapy is associated with an improved postoperative cardiac outcome and a reduction of inflammation activity in patients undergoing vascular surgery, irrespective of baseline cholesterol levels. It should be emphasized that the findings of the current study do not imply that statins are to be prescribed for all patients undergoing non-cardiac surgery. Vascular surgery patients represent a group of patients with a high atherosclerotic burden and a high cardiac risk. Results from further trials will be necessary in order to make firm conclusions on the effectiveness of perioperative statin use in non-vascular patients.

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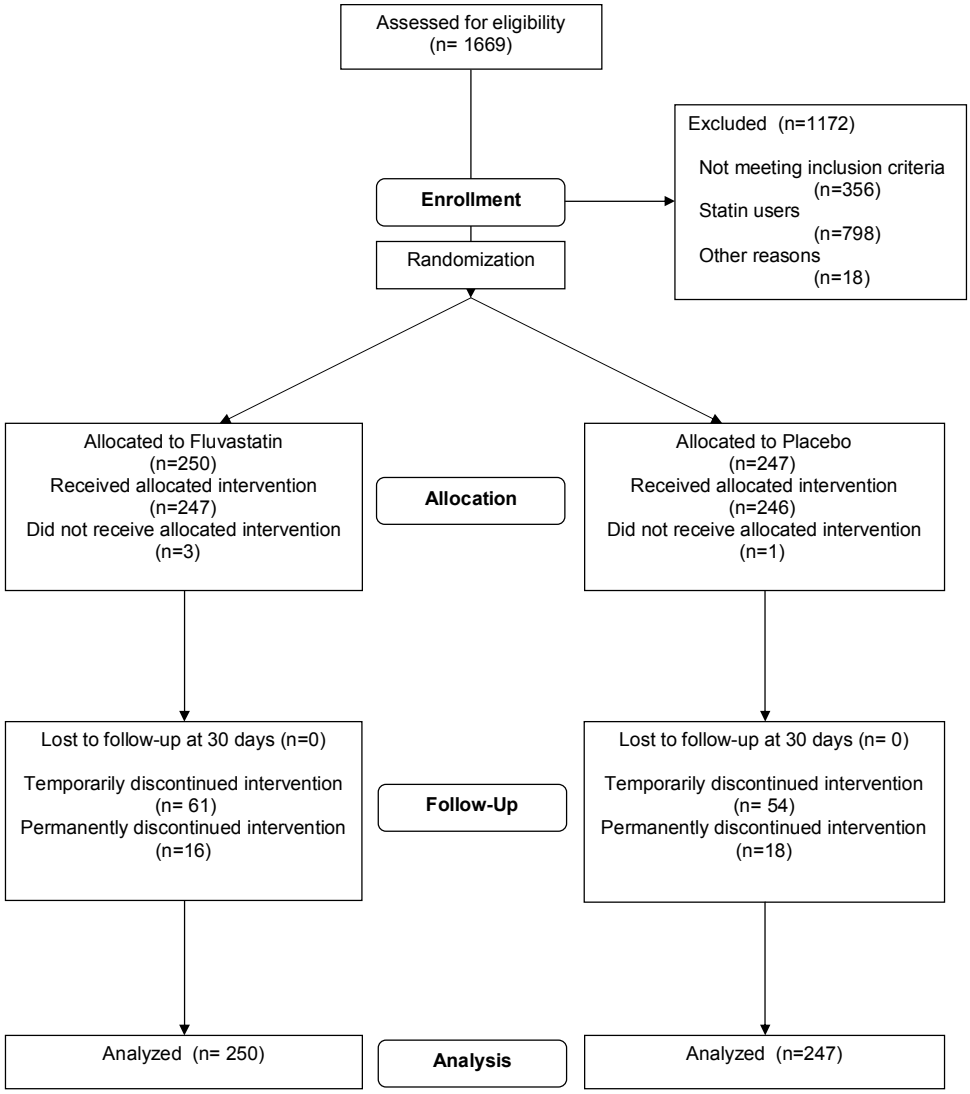
**Appendix A. Erasmus MC risk index**

| | | |
|---|---|---|
| **AGE** | | __ __ POINTS |
| ≤ 40 years | 0 | |
| 41 – 50 | 5 | |
| 51 – 60 | 10 | |
| 61 – 70 | 15 | |
| 71 – 80 | 20 | |
| > 80 | 25 | |
| **GENDER** | | __ __ POINTS |
| Female | 0 | |
| Male | 1 | |
| **TYPE OF SURGERY** | | 3 0 POINTS |
| Vascular | 30 | |
| **PROCEDURE** | | __ __ POINTS |
| Endovascular | 0 | |
| Open | 5 | |
| **CLINICAL RISK FACTORS** | | __ __ POINTS |
| CAD | 2 | |
| Renal Failure | 2 | |
| DM | 5 | |
| Hypertension | 5 | |
| Heart failure | 10 | |
| **TOTAL** | | __ __ POINTS |

**Appendix B. Flowchart of the DECREASE III study**



# Chapter 23

## Management of patients with cardiac stents undergoing non-cardiac surgery

Olaf Schouten
Jeroen J. Bax
Don Poldermans

*Curr Opin Anaesthesiol. 2007;20(3):274-8.*

## ABSTRACT

**Purpose of review:** Coronary stenting is performed in over 4 million patients annually. Approximately 5% of these patients undergo a non-cardiac surgical procedure within 1 year after stenting. Surgery might induce hypercoagulability. This causes increased concern on the effects of previous coronary stenting on postoperative cardiac outcome, in particular in-stent thrombosis. On the other hand, patients with multiple cardiac risk factors are at high risk for postoperative adverse cardiac events and might even benefit from preoperative prophylactic coronary revascularization.

**Recent findings:** Early non-cardiac surgery after coronary stent placement is associated with an increased risk of major adverse cardiac events. The majority of these events are attributable to in-stent thrombosis. Antiplatelet therapy interruption in the perioperative period seems to be associated with an increase in adverse cardiac events, in particular in patients who undergo non-cardiac surgery early after coronary stenting. Furthermore, prophylactic coronary revascularization for high cardiac risk patients is not associated with an improved outcome.

**Summary:** Early non-cardiac surgery after coronary stenting increases the risk of postoperative cardiac events. Interruption of antiplatelet therapy seems to play an important role in this increased event rate. Prophylactic coronary revascularization in cardiac stable, but high-risk patients does not seem to improve outcome.

## INTRODUCTION

Percutaneous coronary angioplasty with stenting is commonly used for treatment of symptomatic coronary artery disease, with annually over 4 million stents being implanted worldwide. The introduction of stents has reduced the incidence of restenosis, one of the major drawbacks of coronary angioplasty, and proved to be an alternative treatment for bypass surgery. However, uncoated stents still have a restenosis rate of about 15-30%[1,2]. Recently, drug-eluting stents were introduced as a means to lower restenosis rates even further. Since then drug eluting stents have been implanted in nearly 6 million patients worldwide[3]. To prevent early in-stent thrombosis all patients receiving a coronary stent are prescribed dual antiplatelet therapy for a certain period, depending on the type of stent used. However, there is an increased concern on late thrombosis in coronary stents, in particular in drug eluting stents, which might be attributable to interruption of antiplatelet therapy[4].

It is estimated that approximately 5% of patients who undergo coronary stenting requires some form of non-cardiac surgery within 1 year after stenting[5]. Since non-cardiac surgery is known to induce hypercoagulability, this causes increased concern on the effects of previous coronary stenting on postoperative cardiac outcome, in particular in-stent thrombosis. On the other hand, patients with multiple cardiac risk factors are at high risk for postoperative adverse cardiac events and might even benefit from preoperative prophylactic coronary revascularization.

This article will review recent literature on the topic of non-cardiac surgery in patients with coronary stents, in particular perioperative antiplatelet therapy and timing of surgery. Furthermore, recent evidence on the issue of preoperative prophylactic coronary revascularization in high-risk patients scheduled for non-cardiac surgery will be reviewed.

### Bare metal stents and non-cardiac surgery

The introduction of bare metal stents has reduced the incidence of restenosis, one of the major drawbacks of coronary angioplasty. However, initially stent placement causes complete denudation of the arterial endothelial surface and stent struts may damage the media or penetrate into the lipid core inducing inflammatory and coagulation activity. These factors temporarily increase the risk of in-stent thrombosis until a neo intima has been formed. Fortunately, the introduction of dual-antiplatelet therapy (aspirin and clopidogrel) has overcome this complication and reduced the rate of in-stent thrombosis to less than 1%. According to the guidelines of the ACC/AHA bare metal stents require at least one month of dual antiplatelet therapy for the prevention of early in-stent thrombosis and life-long aspirin therapy[6].

Several reports have been published on the influence of timing on the risk of non-cardiac surgery after bare metal coronary stent placement. In 2000 Kaluza et al. reported a shocking perioperative mortality rate of 32% in 25 patients who underwent non-cardiac surgery within 2 weeks after stent placement[7]. Importantly 75% of these deaths were attributable to cardiac complications. One additional patient experienced a myocardial infarction but survived because of an emergency PTCA. In contrast, no patient who underwent surgery after 2 weeks after stent placement died. Similar trends of high complication rates early after surgery were found in other studies. In the study of Sharma et al. a mortality rate of 26% was found in 27 patients undergoing surgery within 3 weeks after bare metal stent placement versus only 5% in 20 patients who underwent surgery after this period[8]. Recently Leibowitz et al confirmed the high mortality rate in patients with recent coronary stent placement; 24% of patients with surgery within 2 weeks died versus 9% of patients who had surgery after 2 weeks[9].

Other reports suggest that surgery after bare metal stenting should be postponed at least 6 weeks. The analysis of the Mayo Clinic database showed a mortality rate of 4% in 168 patients who underwent surgery within 6 weeks after bare metal stent placement versus no deaths in the group of 39 patients in whom surgery was performed at least 6 weeks after stent placement[10]. Reddy and Vaitkus found similar results: 25% mortality in patients operated within 6 weeks versus again no mortality in patients operated at least 6 weeks after bare metal stent placement[11].

A recent review of 10 studies encompassing a total of 980 patients who underwent non-cardiac surgery after coronary stent placement also showed that studies with a short median interval between stenting and non-cardiac surgery reported higher cardiac complication rates as compared to reports with longer median time interval. Importantly, when studies with a longer median interval between coronary stenting and non-cardiac surgery are evaluated in more detail, patients with early surgery experienced more cardiac events than those with late surgery (Schouten et al, in press).

Because of the complete denudation of the arterial endothelial surface and stent struts damaging the media or penetrating into the lipid core inducing inflammatory and coagulation activity, patients undergoing bare metal stenting are at increased risk for in-stent thrombosis within the first weeks after stent placement. As mentioned, the introduction of dual-antiplatelet therapy has overcome this complication. However in patients undergoing non-cardiac surgery antiplatelet therapy is often interrupted in the perioperative period because of the fear for excessive bleeding. Possibly, the interruption of antiplatelet therapy in the crucial first weeks after stent placement, while the patient is in a hypercoaguable state, is the explanation for the catastrophic outcome in most studies reporting on the outcome of patients undergoing non-cardiac surgery shortly after coronary stenting. Unfortunately, not all studies provided data on the number of patients that stopped antiplatelet therapy prior to surgery. However, if data were available, there was a clear trend towards a higher incidence of perioperative events after stopping antiplatelet therapy. In the report of Kaluza et al. 6 out of 8 patients who died in the perioperative period were without antiplatelet therapy[7]. The same trend was found by Sharma et al.; 86% of patients who discontinued antiplatelet therapy died perioperatively versus only 5% in the group of patients who continued antiplatelet therapy[8]. Recently data from the Erasmus MC database confirmed this finding in a study of 192 patients. In particular in patients with early non-cardiac surgery there was a marked difference in major adverse cardiac events between patients who discontinued antiplatelet therapy and those who continued; 30% vs. 0% respectively for patients who stopped and continued antiplatelet therapy[12].



### Drug eluting stents and non-cardiac surgery

Drug eluting stents have been introduced to lower the incidence of restenosis after coronary stent placement even more than bare metal stents. The use of these stents has grown exponentially over the last few years and over 6 million drug eluting stent have been used worldwide. As stated in an editorial by Shuchman in a recent issue of the New England Journal of Medicine, the Food and Drug Administration states that drug-eluting stents are safe and effective for discrete and relatively short lesions (up to 28 mm in the case of one approved stent and up to 30 mm in the other) in relatively small, native blood vessels (2.5 to 3.5 or 3.75 mm in diameter). However, drug-eluting stents are also widely used on an off-label basis for longer lesions, larger vessels, and multivessel lesions[3]. If indeed 5% of patients with a drug eluting stent require some form of non-cardiac surgery within 1 year after coronary stent placement, at least 300,000 patients with a drug eluting stent have underwent non-cardiac surgery. However in literature only little is known on the influence of drug eluting stents in patients undergoing non-cardiac surgery.

In a recent study of 192 patients, including 99 patients with drug eluting stents, undergoing non-cardiac surgery there was no difference in the incidence of perioperative major adverse cardiac events between patients with drug eluting stents and those with bare metal stents (2.2% vs. 3.0%, p=0.70)[12]. In line with reports of bare metal stents patients undergoing early surgery were at higher risk. In this study the definition of early surgery was based on the duration of which clopidogrel was required during the pivotal trials that led to approval of the devices and is contained in their labels (i.e. 3 months after sirolimus and 6 months after paclitaxel eluting stent placement). A report by Compton et al also suggested a low risk of complications in patients with drug eluting stents undergoing non-cardiac surgery in their study of 41 surgical procedures. In these patients aspirin and clopidogrel were continued during the perioperative period in 78% and 41%, respectively[13].

Recently concerns have risen on the optimal dual antiplatelet therapy after drug eluting stents. Though the above mentioned two small reports on drug eluting stent and non-cardiac surgery suggested a relatively low incidence of cardiac events after non-cardiac surgery, the concerns on the duration of dual antiplatelet therapy requires attention. What happens if clopidogrel is stopped early, i.e. within 3-6 months, after DES placement? The PREMIER registry showed that up to 1 in every 7 patients discontinues clopidogrel within 1 month after placement[14]. Importantly, those patients who stopped clopidogrel therapy prematurely had a 9-fold increased risk for mortality during the first 11 months after stent placement. Iakovou et al. found similar results in their analysis of 2229 patients; those who discontinued antiplatelet therapy too early had an 89-fold increased risk for in-stent thrombosis during a follow-up of 9 months[15]. Recent studies showed that even if clopidogrel is stopped after the recommended 3 to 6 months those who continue clopidogrel therapy have a better survival and less late in-stent thrombosis compared to those patients who discontinued clopidogrel and had only single (i.e. aspirin) antiplatelet therapy after this time period. These studies, including CREDO, support a prolonged therapy of at least 1 year of dual antiplatelet therapy, especially in patients with a recent acute coronary syndrome[16]. This observation has recently been confirmed by a study of Eisenstein et al.[17] They reported the results of a cohort of 1501 patients treated with DES and found that patients who were still on clopidogrel therapy at 6 and 12 months after stent placement had a significantly better cardiac event free survival and overall survival after up to 24 months of follow-up. This suggests that a prolonged or even life-long period of dual antiplatelet therapy might be necessary to prevent late in-stent thrombosis in DES. The devastating effects of late in-stent thrombosis were shown by the BASKET-LATE investigators: 88% of in-stent thrombosis presented as a myocardial infarction or death[18].

## Bleeding risk of continued perioperative antiplatelet therapy

Prolonged dual antiplatelet therapy might reduce the risk for in-stent thrombosis, especially in patients with a drug eluting stent. However, dual antiplatelet therapy in the perioperative period might be associated with an increased risk for bleeding complications.

In their extensive review on the impact of antiplatelet therapy on perioperative bleeding complications, Harder et al. concluded that monotherapy with aspirin or clopidogrel alone usually does not have to be discontinued in the perioperative period[19]. This conclusion was confirmed in the meta-analysis of Burger et al. In 41 studies including a total of 49,590 patients undergoing a variety of non-cardiac surgical procedures (14,981 on perioperative aspirin, and 34,609 not on aspirin) they found that aspirin continuation led to a 1.5 times increased risk of bleeding complication but not to a higher level of the severity of bleeding complications[20]. They concluded that based on their meta-analysis aspirin should only be discontinued perioperatively if "bleeding risks with increased mortality or sequels are comparable with the observed cardiovascular risks after aspirin withdrawal".

Since patients who undergo surgery early after coronary stent placement are at high risk for adverse cardiac events, the cardiovascular risk of these patients exceeds the risk for bleeding risk with increased mortality or sequels in the majority of non-cardiac surgical procedures. In fact vascular surgical procedures, such as carotid endarterectomy are performed while antiplatelet therapy is continued, without an increase in major bleeding complications.

Another issue of perioperative antiplatelet therapy in the perioperative period is the type of anesthesia to be used, in particular if neuraxial block is warranted. Several studies have shown that neuraxial block can be safely performed if a patient without a history of bleeding disorders is on aspirin[21,22]. Whether clopidogrel or even double antiplatelet therapy increases the risk of a neuraxial haematoma remains to be determined. As mentioned in the current guidelines of the American Society of Regional Anesthesia and Pain Medicine (ASRA), NSAIDs seem not to be associated with added significant risk for the development of spinal haematoma in patients having epidural or spinal anesthesia. However, the same guidelines suggest stopping clopidogrel 7 days prior to surgery[23].

In patients also receiving venous thrombosis prophylaxis by means of low-molecular weight heparin (LMWH) neuraxial block seems to be contra-indicated. As the majority of surgical procedures require thrombosis prophylaxis by means of LMWH, a neuraxial block is probably not feasible in most patients with a recent history of coronary stenting.

However, as with the interruption of perioperative antiplatelet therapy, the benefits and risks of each type of anesthesia should be considered and an individualized patient approach should be applied.



**Preoperative prophylactic coronary revascularization in high-risk patients scheduled for non-cardiac surgery.**

Patients with multiple cardiac risk factors scheduled for major surgery are at increased risk of perioperative cardiac complications. According to the guidelines of the American College of Cardiology /American Heart Association (ACC/AHA), it is highly recommended to refer these patients for non-invasive cardiac stress testing prior to surgery[24]. The guidelines also recommend coronary angiography for patients with high-risk noninvasive test results, and myocardial revascularization in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved. This recommendation was supported by the Coronary Artery Surgery Study that showed a reduced incidence of non-fatal myocardial infarctions after previous bypass surgery among vascular surgery patients compared to those treated medically, 8.5 vs. 0.6% ($p = 0.001$)[25]. More recently, the data from the Bypass Angioplasty Revascularization Investigation trial showed that bypass surgery and percutaneous coronary intervention had similar low rates of postoperative cardiac events in non-cardiac surgery[26]. However, these studies were not designed to assign the optimal strategy in severely ill patients with extensive coronary artery disease immediately prior to major non-cardiac surgery. In addition, these studies could not address the concern of delaying the non-cardiac surgical procedure because of testing, revascularization, and initiation of antiplatelet therapy since the time between revascularization and non-cardiac surgery in these studies was respectively 4.1 and 2.4 years.

The randomized Coronary Artery Revascularization Prophylaxis (CARP) trial was the first study that addressed the strategy of prophylactic revascularization compared to optimal medical therapy in patients with clinically stable coronary artery disease who were scheduled for major non-cardiac vascular surgery[27]. This trial showed that prophylactic revascularization was safe but did not improve perioperative or long-term outcome. The long-term (median follow-up 2.7 years) mortality was 22% in patients allocated to prophylactic coronary revascularization, compared to 23% in the medical only strategy, p=0.92. Also the incidence of perioperative non-fatal myocardial infarction was similar,

respectively 12 and 14%, p = 0.37. However, it must be noted that the majority of patients in the CARP trial had only 1 or 2 vessel disease. The recently conducted DECREASE V randomized pilot study in which the majority of patients had 3-vessel disease also showed no perioperative and long-term (follow-up 1 year) benefit of prophylactic coronary revascularization[28]. The findings of both CARP and DECREASE V support the current guidelines of the ACC/AHA on perioperative management in high-risk patients to reserve revascularization only for cardiac unstable patients. After successful non-cardiac surgery these patients should be regularly screened for the presence of ischemic complaints and aggressive anti-ischemic therapy, both medical and invasive, should be considered. In these patients at high risk scheduled for major non-cardiac vascular surgery prophylactic revascularization might be switched to late revascularization, preventing the delay of surgery.

Patients with unstable coronary artery disease or significant left main disease might still benefit from preoperative prophylactic revascularization. In this respect it should be noted that aside from the inclusion criteria from the pivotal randomized trials for drug eluting stents, the current guidelines of the European Society of Cardiology suggest that there are other applications for DES that might be associated with improved outcome compared to BMS; small vessels, chronic total occlusions, bifurcational/ostial lesions, bypass stenosis, insulin-dependent diabetes mellitus, multi-vessel disease, unprotected left main stenosis, and in-stent restenosis[29]. However, these indications are for patients with an ACS and are not specifically issued for prophylactic revascularization. Furthermore, it should be noted that DES requires a prolonged period of dual antiplatelet therapy and consequently, if one is not willing to operate under dual antiplatelet regimen, a postponement of the index surgical procedure.

### Conclusion

Early non-cardiac surgery after coronary stent placement is associated with an increased risk of major adverse cardiac events. The majority of these events are attributable to in-stent thrombosis. Antiplatelet therapy interruption in the perioperative period seems to be associated with an increase in adverse cardiac events, in particular in patients who undergo non-cardiac surgery early after coronary stenting. Furthermore, prophylactic coronary revascularization for high cardiac risk patients scheduled for major surgery seems not to be associated with an improved perioperative or long-term outcome.

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# Chapter 24

## Coronary artery stent placement immediately before non-cardiac surgery: a potential risk?

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*Anesthesiology. 2007;106(5):1067-9.*

Percutaneous coronary intervention (PCI), angioplasty with stenting is commonly used for treatment of symptomatic coronary artery disease. The introduction of stents has reduced the incidence of restenosis, one of the major drawbacks of coronary angioplasty, and proved to be an alternative treatment for bypass surgery. This strategy may be attractive compared to bypass surgery in patients scheduled for general surgery as the delay of the index surgical procedure is prevented. However, initially stent placement causes complete denudation of the arterial endothelial surface and stent struts may damage the media or penetrate into the lipid core inducing inflammatory and coagulation activity. These factors temporarily increase the risk of in-stent thrombosis until a neo intima has been formed. Fortunately, the introduction of dual-antiplatelet therapy (aspirin and clopidogrel) has overcome this complication and reduced the rate of in-stent thrombosis to less than 1%.

However, recent stent placement might be potentially harmful for patients undergoing non-cardiac surgery. Surgery increases the thrombosis risk due to a perioperative stress response including sympathetic activation promoting sheer stress on arterial plaques, enhanced vascular reactivity conducive to vasospasm, reduced fibrinolytic activity, platelet activation, and hypercoagulability. In addition, while the surgical patient is in a hypercoagulable state dual antiplatelet therapy is often interrupted because of the fear for excessive bleeding complications during surgery.

This double-edged sword of coronary stenting, prevention of cardiac complications on one hand and an excess of bleeding risk on the other, remains a controversial issue in perioperative management. Therefore we have reviewed the currently available evidence on stent related complications in the perioperative period in which timing of surgery and antiplatelet strategy seems to play a pivotal role.

A systematic electronic search of published reports on Medline was undertaken to identify studies published between January 1995 and October 2006 in English language that reported on perioperative cardiac outcome after non-cardiac surgery in patients with a history of PCI with stenting. To identify eligible studies the following Medical Subject Heading terms, or a combination of these, were used: stent; myocardial revascularization; surgery; postoperative complications; mortality; myocardial infarction, and perioperative care. Furthermore, we examined the reference lists of identified articles and published recommendations for perioperative cardiac risk management. Eventually, a total of ten relevant studies were identified[1-10]. Pertinent data from the selected studies were extracted independently by two investigators.

The ten studies encompass a total of 980 patients who underwent non-cardiac surgery after coronary stent placement. The median time from PCI to non-cardiac surgery ranged from 13 to 284 days. The majority of reports included bare metal stent use and only 2 recent studies reported the outcome of drug eluting stents[8,10]. Perioperative myocardial infarction and death were common complications, with myocardial infarction rates ranging from 2% to 28% and death from 3% to 20% (FIGURE 24.1). Studies with a short median interval between PCI and non-cardiac surgery reported higher cardiac complication rates as compared to reports with longer median time interval. Importantly, when studies with a longer median interval between PCI and non-cardiac surgery are evaluated in more detail, patients with early surgery experienced more cardiac events than those with late surgery (TABLE 24.1). Discontinuation of antiplatelet therapy is an important factor in this respect. Unfortunately, not all studies provided data on the number of patients that stopped antiplatelet therapy prior to surgery. However, if data were available, there was a clear trend towards a higher incidence of perioperative events after stopping antiplatelet therapy. In the report of Kaluza et al. 6 out of 8 patients who died in the perioperative period were without antiplatelet therapy[1]. The same trend was found by Sharma et

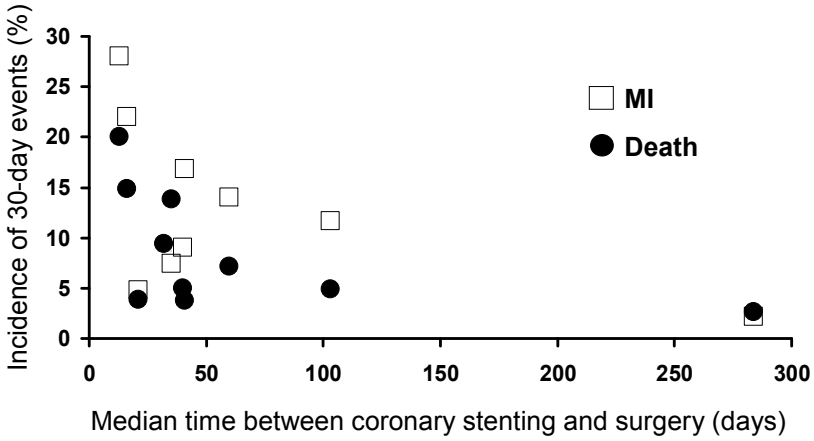


**FIGURE 24.1** Incidence of perioperative complications in studies with different median times between percutaneous transluminal coronary angioplasty plus stenting and non-cardiac surgery.[1–10]
MI = myocardial infarction.

**TABLE 24.1** Incidence of perioperative events in non-cardiac surgery after coronary stent placement.

| Study | Time to surgery | N | Mortality | Myocardial Infarction |
|---|---|---|---|---|
| Wilson et al. [4] | < 6 weeks | 168 | 4% | 6% |
| | > 6 weeks | 39 | 0 | 0 |
| Kaluza et al.[1] | < 2 weeks | 25 | 32% | 28% |
| | > 2 weeks | 15 | 0 | 0 |
| Sharma et al.[3] | < 3 weeks | 27 | 26% | 22% |
| | > 3 weeks | 20 | 5% | 10% |
| Reddy et al.[2] | < 6 weeks | 16 | 25% | 38% |
| | > 6 weeks | 40 | 0 | 0 |
| Brichon et al.[5] | < 3 months | 32 | 3% | 9% |
| Godet et al.[9] | 5-8 weeks | 78 | 5% | 9% |
| Schouten et al.[10] | Early* | 30 | 13% | 13% |
| | Late* | 162 | 2% | 0.6% |
| Leibowitz et al.[6] | < 2 weeks | 29 | 24% | 7% |
| | > 2 weeks | 65 | 9% | 8% |
| Vicenzi et al.[7] | < 35 days | 22 | | 72%** |
| | 35-90 days | 25 | | 44%** |
| | > 90 days | 56 | | 34%** |

* Early surgery was defined as within 1 month after bare metal stenting, within 3 months after sirolimus drug eluting stenting, and within 6 months after paclitaxel drug eluting stenting.
** Not only perioperative events but also events < 3 months within surgery are included. Events were defined as: cardiac death, myocardial infarction, re-percutaneous coronary interventions, congestive heart failure, unstable angina, significant arrhythmias, and myocardial cell injury.
The study of Ward et al. is not included in this table since they did not report the incidence of adverse events separately for PCI + stent procedures.



al.; 86% of patients who discontinued antiplatelet therapy died perioperatively versus only 5% in the group of patients who continued antiplatelet therapy[3]. Recently we confirmed this finding in a study of 192 patients. In particular in patients with early non-cardiac surgery there was a marked difference

in major adverse cardiac events (30% vs. 0% respectively for patients who stopped and continued antiplatelet therapy)[10].

The minimal period in which antiplatelet therapy should be prescribed prior to non-cardiac surgery is ill-defined. A period of four weeks seems to be too short as shown by the study of Brichon et al. In a group of 20 patients two experienced perioperative in-stent thrombosis, suggesting that a prolonged period of antiplatelet therapy may be required[5]. A period of six weeks is supported by the results of the studies of Wilson[4] and Reddy[2]. In a group of 79 patients undergoing non-cardiac surgery after an interval of six weeks no major cardiac events occurred. These results were questioned by the study of Vicenzi et al. In 56 patients who underwent non-cardiac surgery more than 90 days after PCI the cardiac event rate was as high as 34% within 3 months after surgery[7]. However, it should be taken into account that in a number of patients antiplatelet therapy was stopped 3 days prior to non-cardiac surgery which may be related to adverse outcome. Ferrari et al. showed that stopping antiplatelet therapy, even after a long period since stenting (mean time between stenting and withdrawal 15.5 ± 6.5 months), was a significant risk factor for adverse cardiac events[11].

In conclusion, the current available literature suggests that non-cardiac surgery after PCI with stenting should be delayed at least 6 weeks and dual antiplatelet therapy is associated with improved outcome.

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# Chapter 25

## A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study

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## ABSTRACT

**Background:** Prophylactic coronary revascularization in vascular surgery patients with coronary artery disease does not improve postoperative outcome. If a beneficial effect is to be expected, then at least those with extensive coronary artery disease should benefit from this strategy. The purpose of this research was to perform a feasibility study of prophylactic coronary revascularization in patients with preoperative extensive stress-induced ischemia.

**Methods:** One thousand eight hundred eighty patients were screened, and those with ≥ 3 risk factors underwent cardiac testing using dobutamine echocardiography (17-segment model) or stress nuclear imaging (6-wall model). Those with extensive stress-induced ischemia (≥ 5 segments or ≥ 3 walls) were randomly assigned for additional revascularization. All received beta-blockers aiming at a heart rate of 60 to 65 beats/min, and antiplatelet therapy was continued during surgery. The end points were the composite of all-cause death or myocardial infarction at 30 days and during 1-year follow-up.

**Results:** Of 430 high-risk patients, 101 (23%) showed extensive ischemia and were randomly assigned to revascularization (n = 49) or no revascularization. Coronary angiography showed 2-vessel disease in 12 (24%), 3-vessel disease in 33 (67%), and left main in 4 (8%). Two patients died after revascularization, but before operation, because of a ruptured aneurysm. Revascularization did not improve 30-day outcome; the incidence of the composite end point was 43% versus 33% (odds ratio 1.4, 95% confidence interval 0.7 to 2.8; p = 0.30). Also, no benefit during 1-year follow-up was observed after coronary revascularization (49% vs. 44%, odds ratio 1.2, 95% confidence interval 0.7 to 2.3; p = 0.48).

**Conclusions:** In this randomized pilot study, designed to obtain efficacy and safety estimates, preoperative coronary revascularization in high-risk patients was not associated with an improved outcome.

## INTRODUCTION

Patients with multiple cardiac risk factors scheduled for major vascular surgery are at increased risk of perioperative cardiac complications. According to the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA), it is highly recommended to refer these patients for noninvasive cardiac stress testing before surgery[1]. The guidelines also recommend coronary angiography for patients with high-risk noninvasive test results, and myocardial revascularization in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved.

However, noninvasive testing may delay surgery and run the risk of aortic aneurismal rupture or exacerbation of critical limb ischemia. Furthermore, coronary revascularization is commonly performed by percutaneous coronary intervention (PCI) with stent placement instead of bypass surgery (CABG). Although this approach prevents further delay of the index surgical procedure, it necessitates the prolonged use of extensive antiplatelet therapy, which may aggravate the risk of perioperative bleeding complications. But temporary discontinuation of antiplatelet therapy is potentially harmful, as it may lead to in-stent thrombosis[2,3].

The current ACC/AHA recommendations are based on small observational, noncontrolled studies and expert opinion[4,5]. The usefulness of the strategy of prophylactic revascularization was not confirmed by the recently completed CARP (Coronary Artery Revascularization Prophylaxis) randomized trial[6]. In this trial, the incidence of perioperative myocardial infarction was similar in patients allocated to prophylactic revascularization versus those allocated to optimal medical therapy (12% vs. 14% events). There was also no beneficial effect observed during long-term follow-up. However, it should be realized that the vast majority of patients included in the CARP trial had single- or 2-vessel disease with a preserved left ventricular function. Indeed, based on previous research from our group, sufficient cardioprotection by medical therapy can be expected in these patients, which may explain the CARP trial findings[7]. In contrast, patients with multiple cardiac risk factors and extensive stress-induced myocardial ischemia are insufficiently protected[7].

Hence, if a beneficial effect of the invasive strategy of prophylactic revascularization is to be expected, then at least patients with extensive coronary artery disease should benefit from this strategy. We therefore undertook the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo)-V pilot study to assess the feasibility and to obtain initial efficacy and safety estimates for the design of an adequately powered randomized controlled clinical trial in these patients.

## METHODS

### Patients

This study was conducted during 2000 to 2005 in 6 hospitals in Belgium (until 2001), Brazil (until 2001), the Netherlands, Italy, Serbia, and Montenegro. The early cessation in participation to the study of 2 centers was due to logistic reasons. A total of 1,880 patients undergoing elective open abdominal aortic or infrainguinal arterial reconstruction were screened for the prevalence of cardiac risk factors (FIGURE 25.1). These included age over 70 years, angina pectoris, prior myocardial infarction on the basis of history or a finding of pathologic Q waves on electrocardiography, compensated congestive heart failure or a history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction (serum creatinine >160 μmol/l), and prior stroke or transient ischemic attack[7]. Patients with at least 3 risk factors underwent cardiac stress testing before surgery. All patients who experienced

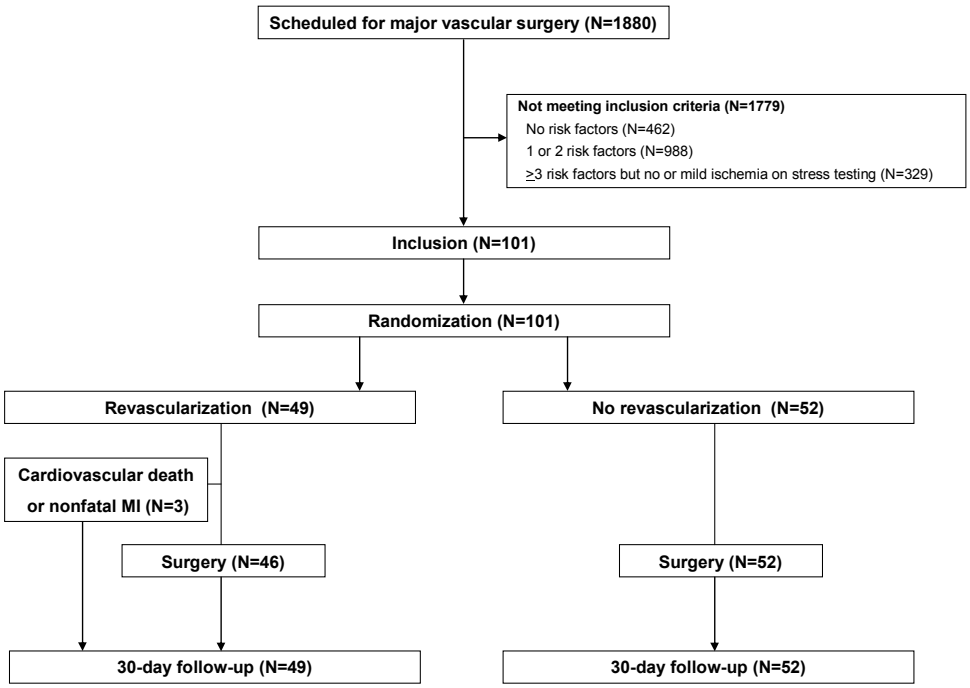


**FIGURE 25.1** Flowchart of the study.
Cardiac risk factors included age over 70 years, angina pectoris, prior myocardial infarction (MI) on the basis of history or a finding of pathologic Q waves on electrocardiography, compensated congestive heart failure or a history of congestive heart failure, current treatment for diabetes mellitus, renal dysfunction (serum creatinine >160 µmol/l), and prior stroke or transient ischemic attack. Patients with ≥3 risk factors and extensive ischemia were randomly (1:1) assigned to coronary revascularization.



extensive stress-induced ischemia were enrolled in the DECREASE-V pilot study. All patients provided informed consent, and the study was approved by the Erasmus Medical Center Medical Ethics Committee and local research ethics committees.

## Cardiac testing

Left ventricular ejection fraction (LVEF) was measured from resting echocardiographic images using the biplane Simpson's rule. Cardiac stress testing was performed by dobutamine echocardiography or dobutamine or dipyridamole perfusion scintigraphy, as previously described[8,9]. Test results were scored by the extent of stress-induced ischemia using a 17-segment model in dobutamine echocardiography and a 6-wall model in stress perfusion scintigraphy. Limited ischemia was defined by the presence of 1 to 4 ischemic segments or 1 to 2 ischemic walls, whereas extensive ischemia was defined by ≥ 5 ischemic segments or ≥ 3 ischemic walls.

## Allocated treatment

Perioperative beta-blocker therapy was installed in all patients at the screening visit, regardless of test results. A computer algorithm was used at each center to assign patients with extensive stress-induced ischemia randomly, in a 1:1 ratio, to 1 of the 2 strategies. The sealed envelope method was used to conceal treatment allocation, and it was assured that envelopes were opened in consecutive order. Patients were randomized to either an invasive approach followed by revascularization or a

noninvasive approach. Quantitative analysis of all coronary angiographies was reviewed centrally at Erasmus Medical Center, Rotterdam, the Netherlands, by 2 experienced cardiologists. They assessed independently the number of affected vessels. The mode of revascularization, CABG or PCI with stenting, was decided by the treating physicians, based on coronary anatomy and the possible delay of the index surgical procedure. Patients allocated to the medical-only strategy were referred for surgery without further delay.

### Beta-blocker therapy

Patients on chronic beta-blocker therapy continued their medication. Patients without beta-blockers started with bisoprolol 2.5 mg once a day at the screening visit. Beta-blocker dose was adjusted in all patients at admission to the hospital and on the day before surgery to achieve a resting heart frequency of 60 to 65 beats/min. The same dose of beta-blockers was continued postoperatively except in patients who were unable to take medication orally or by nasogastric tube postoperatively. In these patients, the heart rate was monitored continuously at the intensive care unit or hourly at the ward, and intravenous metoprolol was administered at a dose sufficient to keep the heart rate between 60 to 65 beats/min. The heart rate and blood pressure were measured immediately before each scheduled dose of beta-blockers. Beta-blockers were withheld if the heart rate was <50 beats/min or the systolic blood pressure was <100 mm Hg. After discharge, patients continued beta-blocker therapy, and dose adjustments were carried out during outpatient visits to achieve a resting heart frequency of 60 to 65 beats/min.

### Perioperative management

Anesthetic management, monitoring, and other aspects of perioperative management were at the discretion of the attending physician. Results of preoperative testing and coronary revascularization were discussed with the attending physicians, and hemodynamic management was implemented accordingly. Anticoagulant and antiplatelet therapy was continued after PCI and during the index surgical procedure. Intraoperative ischemia was treated at the discretion of attending physicians, and additional beta-blockers were permitted.

### End point definition

All patients were monitored for cardiac events after screening. Twelve-lead electrocardiogram (ECG) and serum troponin-T level were systematically determined 1, 3, 7, and 30 days after surgery. Outpatient follow-up was performed at 30 days if a patient had been discharged from the hospital. At the outpatient clinic, all patients were screened at 3-month intervals for cardiac events by clinical history and 12-lead ECG. All data were collected by the participating centers and evaluated in a blinded fashion by members of the adverse-events committee. The primary end point was the composite of all-cause death and nonfatal myocardial infarction that occurred between screening and 30-days after the index surgical procedure. Patients were followed-up during at least 1 year after surgery, and the composite of all-cause death and nonfatal myocardial infarction during this period was considered as secondary end point. Myocardial infarction within 48 h after CABG was defined as a creatine kinase (CK)-MB rise above 5× the local upper limit of normal. Myocardial infarction within 48 h after PCI was defined as a CK-MB rise above 3× the upper limit of normal. Myocardial infarction within 30 days after the index surgical procedure was defined as a positive troponin-T level in combination with new Q waves on the ECG lasting more than 0.03 s. In all other situations, myocardial infarctions were defined by new Q waves lasting more than 0.03 s.

### Sample size

The purpose of this pilot study was to assess the feasibility of prophylactic revascularization in high-risk patients scheduled for major vascular surgery, and to obtain initial efficacy and safety estimates needed for the design of an adequately powered randomized controlled clinical trial. We aimed for the enrollment of 100 patients, 50 in each strategy. Based on the DECREASE-I study[7], an incidence of 33% of the primary end point was expected in the patients allocated to optimal medical therapy only. It was recognized a priori that a modest, but clinically relevant, risk reduction by prophylactic revascularization would not be detectable given this sample size. However, if the beneficial effect of revascularization was similar to the observations in the CASS (Coronary Artery Surgery Study) registry (85% risk reduction associated with prior CABG in vascular surgery), then our study has 93% power (type II error of 7%), based on a 2-sided test with a type I error of 5%.

### Statistical analysis

All analyses were based on the intention-to-treat principle. Continuous data are presented as median values and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical and surgical characteristics between patients allocated to revascularization or no revascularization were evaluated by Wilcoxon nonparametric tests, chi-square tests, or Fisher exact tests, as appropriate. Differences in the incidence of the end points were evaluated by a chi-square test. The incidence of events over time was further examined by the Kaplan-Meier method, whereas a log-rank test was applied to evaluate differences between the allocated treatment strategies. Analyses were performed according to the intention-to-treat principle. All statistical tests were 2-sided, and a p-value <0.05 was considered significant.



## RESULTS

### Characteristics of patients

A total of 1,880 vascular surgery patients were enrolled and screened for cardiac risk factors (FIGURE 25.1), and 430 (23%) were classified as high risk, who were referred for cardiac testing. Testing showed extensive ischemia in 101 (22%). Dobutamine echocardiography was performed in 88 (88%), and stress scanning in 13 (13%). No serious side effects occurred during stress testing. Of 101 patients with extensive stress-induced ischemia, 49 patients were randomized for coronary revascularization. A reduced LVEF (<35%) was observed in 43 (43%) patients. No patient had significant valve disease such as aortic stenosis or mitral valve regurgitance. Coronary angiography, performed in patients allocated to the invasive strategy, showed 2-vessel disease in 12 (24%), 3-vessel disease in 33 (67%), and left main disease in 4 (8%). A PCI was performed in 32 patients, using a drug-eluting stent in 30 and a bare-metal stent in 2, and bypass surgery in 17. There were no differences in the presence of ischemic heart disease (i.e. previous myocardial infarction and angina pectoris) or other baseline characteristics between the randomized groups (TABLE 25.1). Complete revascularization was achieved in 42 (86%). Incomplete revascularization occurred in 7 (15%) patients initially scheduled for a percutaneous intervention. Bypass surgery was considered not feasible in these patients as the index procedure could not be further delayed. The median duration of revascularization to operation was 29 (13 to 65) days in the 17 patients undergoing bypass surgery and 31 (19 to 39) days in the 32 patients undergoing a percutaneous intervention.

Antiplatelet therapy, using aspirin and clopidogrel, was continued during surgery in all patients who underwent a PCI. The median perioperative blood transfusion requirement in patients with and without antiplatelet therapy was similar: 2 versus 3 U (p value = 0.25).

**TABLE 25.1** Baseline characteristics.

| | Revascularisation | No revascularisation |
|---|---|---|
| | N = 49 | N = 52 |
| Age, years – median (interquartile range) | 71 (64, 74) | 70 (63, 75) |
| Men – no. (%) | 42 (86) | 47 (90) |
| History of diabetes – no. (%) | 18 (37) | 15 (29) |
| Current angina pectoris – no. (%) | 25 (51) | 22 (42) |
| History of myocardial infarction – no. (%) | 49 (100) | 50 (96) |
| History of congestive heart failure – no. (%) | 23 (47) | 24 (46) |
| History of cerebrovascular accident – no. (%) | 20 (41) | 13 (25) |
| History of renal failure – no. (%) | 9 (18) | 11 (21) |
| Aspirin use – no. (%) | 37 (76) | 30 (58) |
| Beta-blocker – no. (%) | 34 (70) | 36 (69) |
| ACE-inhibitor use – no. (%) | 28 (57) | 22 (42) |
| Statin use – no. (%) | 34 (69) | 30 (58) |
| Type of surgery – no. (%) | | |
| Thoraco-abdominal | 5 (10) | 5 (10) |
| Tube graft | 11 (22) | 14 (27) |
| Bifurcated graft | 10 (20) | 15 (29) |
| Femoro-popliteal | 23 (47) | 18 (35) |
| Right coronary artery disease – no. (%) | 39 (80) | - |
| Left artery descending – no. (%) | 46 (94) | - |
| Left circumflex artery – no. (%) | 37 (76) | - |
| Left main disease – no. (%) | 4 (8) | - |
| Number of diseased vessels – no. (%) | | |
| 1 | 0 | - |
| 2 | 12 (24) | - |
| 3 | 33 (67) | - |

## Perioperative cardiac events

Two patients died before vascular surgery because of a ruptured aneurysm after successful bypass surgery. Their aortic diameters were, respectively, 62 and 73 mm. In 1 patient, a myocardial infarction occurred after an incomplete coronary revascularization. This precluded the proceeding of the scheduled vascular surgery. Revascularization did not improve 30-day outcome after vascular surgery. Troponin elevation was found in 38.8% in the noninvasive group versus 34.7% in the invasive group. The incidence of all-cause death or nonfatal myocardial infarction for patients with preoperative revascularization or medical treatment only was 43% versus 33%, respectively (odds ratio [OR] 1.4, 95% confidence interval [CI] 0.7 to 2.8; p = 0.30) (TABLE 25.2). Also, no difference was observed in the incidence of perioperative cardiac events between patients treated by prophylactic bypass surgery or percutaneous intervention (41.1% vs. 43.8%, respectively).

## Late cardiac events

The incidence of the 1-year end point all-cause death or nonfatal myocardial infarction in high-risk patients was 47%. In high-risk patients, no long-term benefit was observed after coronary revascularization; respectively, 49% versus 44% of patients with preoperative revascularization or medical treatment only died or experienced a nonfatal myocardial infarction (OR 1.2, 95% CI 0.7 to 2.3; p = 0.48) (FIGURE 25.2). No patients initially randomized for medical therapy underwent revascularization

| **TABLE 25.2** Patient outcome. | | | | | | |
|---|---|---|---|---|---|---|
| | Revascularisation N=49 | | No revascularisation N=52 | | HR and 95% CI | P-value |
| Events prior to surgery | | | | | | |
| All cause mortality – no. (%) | 2 | (4.1) | 0 | | - | 0.23 |
| Myocardial infarction – no. (%) | 1 | (2.1) | 0 | | - | |
| Composite – no. (%) | 3 | (6.1) | 0 | | - | 0.11 |
| Events up to 30 days post surgery | | | | | | |
| All cause mortality – no. (%) | 11 | (22.5) | 6 | (11.5) | 2.2 (0.74-6.6) | 0.14 |
| Myocardial infarction – no. (%) | 17 | (34.7) | 16 | (30.8) | - | |
| Composite – no. (%) | 21 | (42.9) | 17 | (32.7) | 1.4 (0.73-2.8) | 0.30 |
| Events up to 365 days post surgery | | | | | | |
| All cause mortality – no. (%) | 13 | (26.5) | 12 | (23.1) | 1.3 (0.55-2.9) | 0.58 |
| Myocardial infarction – no. (%) | 18 | (36.7) | 19 | (36.5) | - | |
| Composite – no. (%) | 24 | (49.0) | 23 | (44.2) | 1.2 (0.68-2.3) | 0.48 |

within 1 year of follow-up. One patient randomized to the invasive strategy underwent a redo PCI because of myocardial infarction in the first year of follow-up.

### Implications for a study design

Assuming that the event rates in the 101 studied patients are representative of what would occur in the planned study, the required sample size for a randomized study to establish definitively that coronary revascularization is superior to medical therapy to improve postoperative outcome in high-risk patients by 20% (relative risk) compared to optimal medical therapy would be over 300 patients per arm. This would require a sample size of 9,000 major vascular surgery patients, of which 2,000 patients have 3 or more cardiac risk factors at screening.



## DISCUSSION

The concept of a beneficial effect of prophylactic coronary revascularization before major vascular surgery is based on the assumption that perioperative myocardial infarctions arise at locations in coronary arteries with hemodynamically critical stenosis, elicited by the stress of surgery. Preoperative coronary revascularization might prevent this devastating event and, in addition, improve long-term outcome. This hypothesis was supported by the CASS study that showed a reduced incidence of non-fatal myocardial infarctions after previous bypass surgery among vascular surgery patients compared to those treated medically (8.5% vs. 0.6%, p = 0.001)[4]. More recently, the data from the BARI (Bypass Angioplasty Revascularization Investigation) trial showed that bypass surgery and PCI had similar low rates of postoperative cardiac events in non-cardiac surgery[5]. However, these studies were not designed to assign the optimal strategy in severely ill patients with extensive coronary artery disease immediately before major vascular surgery. In addition, these studies could not address the concern of delaying the vascular surgical procedure because of testing, revascularization, and initiation of antiplatelet therapy since the time between revascularization and non-cardiac surgery in these studies was, respectively, 4.1 and 2.4 years.

The randomized CARP trial was the first study that addressed the strategy of prophylactic revascularization compared with optimal medical therapy in patients with clinically stable coronary artery disease who were scheduled for major vascular surgery[6]. This trial showed that prophylactic

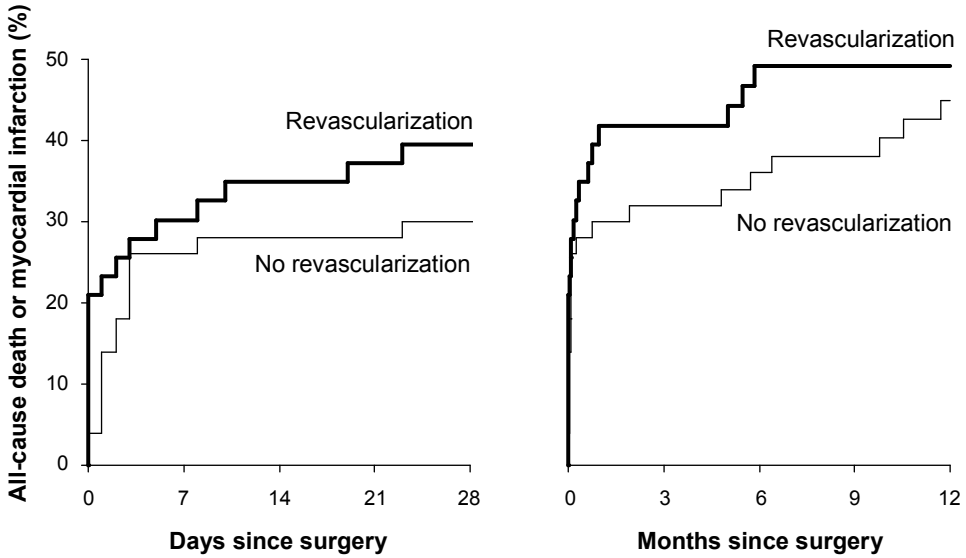


**FIGURE 25.2** Incidence of all-cause death or myocardial infarction during 1-year follow-up according to the allocated strategy in patients with 3 or more cardiac risk factors with extensive stress-induced ischemia.

revascularization was safe but did not improve perioperative or long-term outcome. The long-term mortality was 22% in patients allocated to prophylactic coronary revascularization, compared with 23% in the medical only strategy (p = 0.92). Also, the incidence of perioperative nonfatal myocardial infarction was similar, respectively, 12% and 14% (p = 0.37). In the present study, the effect of prophylactic revascularization was comparable to the effect reported by McFalls et al.[6], although the study population is different. The current study population consisted of 12% women, 43% of the patients had a reduced left ventricular function (LVEF <35%), and the vast majority of patients, 75%, had 3-vessel or left main disease compared with 33% in the CARP trial. In a subgroup of 37 comparable patients of the CARP trial (i.e. 3 or more cardiac risk factors and extensive stress-induced ischemia assessed by noninvasive testing), prophylactic coronary revascularization was associated with a favorable, nonsignificant trend for long-term survival (OR 4.0, 95% CI 0.8 to 19). If a beneficial effect of revascularization was to be expected, this should have occurred in the selected population with high-risk anatomy. However, this was not observed, although the current study was not powered to test this strategy. A study to establish the effect of coronary revascularization would require, based on the findings of this pilot study, a screening population of 9,000 patients, of which 2,000 would have 3 or more risk factors, and of these 600 would have extensive stress-induced ischemia during cardiac testing and be eligible for randomization to revascularization.

Our findings support the current guidelines of the ACC/AHA on perioperative management in high-risk patients to reserve revascularization only for cardiac unstable patients. After successful vascular surgery, these patients should be regularly screened for the presence of ischemic complaints, and aggressive anti-ischemic therapy, both medical and invasive, should be considered. As shown in FIGURE 25.2, a trend was observed for a "catch up" of late cardiac events in patients treated medically. In these patients at high risk scheduled for major vascular surgery, prophylactic revascularization might be switched to late revascularization, preventing the delay of surgery.

The apparent lack of benefit of coronary revascularization of the present study is not fully understood. Most likely, patients with stress-induced ischemia not only suffer from a blood flow-limiting coronary lesion but also from (multiple) nonsignificant lesions that are vulnerable to rupture due to the stress of surgery[10]. The perioperative stress response, which includes a cytokine response, catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability, triggers coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion[11,12]. Autopsy results have shown that this mechanism is responsible for at least half of all perioperative infarctions[10,12]. These findings are in line with dobutamine echocardiography results that show a correlation between the assessment of the preoperative culprit coronary lesion and the location of the perioperative myocardial infarction in only half of all cases[13]. Surgical or percutaneous treatment of the culprit coronary lesion(s) apparently provides insufficient protection for rupture of these instable lesions.

The optimal perioperative evaluation and management of patients with multiple risk factors and extensive stress-induced ischemia remains controversial. Success will depend on careful collaboration between cardiologists, anesthesiologists, and surgeons. In patients with aortic aneurysms, a surgical repair is performed to reduce the chance of aneurysm-related death. It might be hypothesized that abdominal aortic aneurysm repair should not be performed in this high-risk group. As the current trial shows, open repair poses an unacceptable 30-day cardiac event rate of approximately 30%, whereas the chance of aneurysm rupture is around 9 per 100 person-years. Endovascular treatment modalities may be an alternative for these high-risk patients. Although the EVAR (Endovascular Aneurysm Repair)-2 trial showed no benefit of elective endovascular repair in patients deemed unfit for open repair because of comorbidities[14], these findings were not confirmed in the recently conducted study by the Society for Vascular Surgery Outcomes Committee. In a group of 565 high-risk patients, matched for the EVAR-2 inclusion criteria, undergoing endovascular repair, perioperative mortality was 2.9%. These promising results need to be confirmed in a large study population. Importantly, in all cases, an individualized strategy should be performed, weighing the chances of future aneurysms rupture or limb salvage instead of amputation and short-term perioperative events.



### Conclusions

In this small randomized pilot study, designed to obtain initial efficacy and safety estimates for the design of an adequately powered randomized controlled clinical trial, preoperative coronary revascularization in high-risk vascular surgery patients with extensive stress-induced ischemia was not associated with an improved postoperative and long-term outcome.

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# Chapter 26

## Non-cardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events

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Non-cardiac surgery early after percutaneous coronary intervention (PCI) with stenting has been associated with adverse cardiac events in the perioperative period[1,2]. However, these reports were on patients with bare-metal stents, did not include drug-eluting stents, and did not compare patients who continued their antiplatelet therapy during surgery with those who interrupted this therapy. Therefore, we conducted the current study.

Patients who underwent non-cardiac surgery between 1999 and 2005 and had a successful PCI because of unstable coronary artery disease within the 2 years before surgery were enrolled. The data on PCI procedures were part of a prospectively maintained registry including a total of 574 procedures. Data on the surgical procedure, as well as 30-day cardiovascular outcome, were retrospectively collected by screening of medical charts. The medical ethics committee of our hospital approved the study. All patients underwent PCI using either bare-metal or drug-eluting stents (paclitaxel or sirolimus). Patient characteristics included the indication for PCI, the number of affected and stented coronary arteries, whether the procedure was successful, left ventricular function, and medication use during and after PCI. In addition, cardiac risk factors were scored. Patients with bare-metal stents were prescribed lifelong aspirin and clopidogrel for at least 1 month at the discretion of the treating physician (median 30 days, interquartile range 30 to 90 days). Patients with drug-eluting stents usually received lifelong aspirin as well as clopidogrel for at least 3 months (sirolimus, median 90 days, interquartile range 60 to 180 days) to 6 months (paclitaxel, median 180 days, interquartile range 180 to 180 days), or longer at the discretion of the treating physician.

The surgical procedures were categorized according to surgical risk, based on the definition of the Revised Cardiac Risk Index[3]. Furthermore, the cardiac risk factors and medication use assessed during the initial PCI procedures were updated at the time of operation and were used to assess the Revised Cardiac Risk Index for each patient[3]. Importantly, there was no protocol for perioperative antiplatelet use in the population studied. Consequently, some patients received aspirin and/or clopidogrel throughout the surgical procedure, whereas in other patients aspirin and clopidogrel were stopped 1 week before operation.

Medical charts were reviewed for the composite end point of 30-day major adverse cardiac events (MACE), defined as nonfatal myocardial infarction and/or cardiac death as previously defined according to guidelines of the American College of Cardiology/European Society of Cardiology[4]. Patients with an increased cardiac risk (i.e. previous PCI) were routinely screened for postoperative cardiac end points using serial troponin T and electrocardiographic monitoring on days 1, 3, and 7 after surgery. Additional tests were performed at the discretion of the treating physician. Blood loss during operation and the necessity and quantity of perioperative transfusion requirements were noted in all patients.

In total, 192 patients underwent surgery within 2 years after the initial PCI procedure (TABLE 26.1). Patients were arbitrarily divided in an early-surgery group (defined as non-cardiac surgery during which clopidogrel was required during the trials that led to approval of these devices and according to their labels: bare-metal stents 1 month, sirolimus-eluting stents 3 months, paclitaxel-eluting stents 6 months) and a late-surgery group. Thirty patients underwent early surgery according to this classification.

During the first 30 postoperative days, 5 patients (2.6%) experienced a MACE (all fatal, see TABLE 26.2 for characteristics of these patients). In the early-surgery group, 4 MACEs (13.3%) occurred, whereas in the late-surgery group, only 1 MACE (0.6%) occurred (Fisher exact test $p = 0.002$) (TABLE 26.3). In 91

| **TABLE 26.1** | Baseline characteristics of all patients. |
|---|---|
| | **N=192** |
| **Medical history – no (%)** | |
| Ischemic heart disease | 192 (100) |
| Congestive heart failure | 5 (3) |
| Diabetes mellitus | 47 (25) |
| Renal impairment | 29 (15) |
| History of CVA or TIA | 23 (12) |
| **Revised Cardiac Risk Index – no (%)** | |
| 1 risk factor | 65 (34) |
| 2 risk factors | 74 (39) |
| 3 or more risk factors | 53 (28) |
| **Medical therapy – no (%)** | |
| Beta-blockers | 131 (68) |
| Statins | 136 (71) |
| Calcium antagonists | 50 (26) |
| Nitrates | 20 (10) |
| Diuretics | 24 (13) |
| ACE-inhibitors | 47 (24) |
| Antiplatelet therapy during surgery | 101 (53) |
| **Coronary stenting – no (%)** | |
| Bare metal | 93 (48) |
| Drug eluting | 99 (52) |
| Number of vessels dilated | |
| 1 | 91 (47) |
| 2 | 60 (31) |
| 3 | 41 (21) |
| Stenting successful | 192 (100) |
| **Type of non-cardiac surgery – no (%)** | |
| Abdominal | 31 (16) |
| Vascular peripheral | 30 (16) |
| Eye | 23 (12) |
| Urologic | 24 (13) |
| Orthopedic | 23 (12) |
| Renal transplantation | 12 (6) |
| ENT | 10 (5) |
| Aortic | 9 (5) |
| Reconstructive | 9 (5) |
| Gynaecologic | 5 (3) |
| Neurologic | 4 (2) |
| Carotid | 3 (2) |
| Other | 9 (5) |



patients (47%), antiplatelet medication was interrupted during the perioperative period. There was no significant difference in surgical risk between patients in whom antiplatelet therapy (both clopidogrel and aspirin) was interrupted versus those in whom antiplatelet therapy was continued. The interruption was associated with a significantly higher incidence of MACE in patients who stopped versus those who continued (5.5% vs. 0%, Fisher exact test $p = 0.023$). In the group of patients with a MACE, all 5 patients discontinued antiplatelet therapy, whereas in the group without a MACE, only

**TABLE 26.2** Characteristics of patients with perioperative MACE.

| Patient | Age | Gender | Type of surgery | Time from PCI | Target vessel | Type of stent | Aspirin withheld | Clopidogrel withheld |
|---|---|---|---|---|---|---|---|---|
| A | 58 | M | Abdominal | 1 | LAD | Bare metal | Yes | Yes |
| B | 69 | M | Esophagectomy | 28 | RCA, LCx | Bare metal | Yes | Yes |
| C | 64 | M | Abdominal | 30 | RCA | Paclitaxel | Yes | Yes |
| D | 47 | M | ENT | 80 | RCA, LAD | Sirolimus | Yes | Yes |
| E | 65 | M | Urologic | 253 | LAD, RCA, LCx | Paclitaxel | Yes | N/A |

| Patient | Complication |
|---|---|
| A | MI, thrombosis LAD stent (angiography) |
| B | MI, thrombosis RCA stent (autopsy) |
| C | MI, left main thrombosis, no stent thrombosis (autopsy) |
| D | MI, thrombosis LAD stent (ECG) |
| E | MI, thrombosis LAD stent (angiography) |

**TABLE 26.3** Incidence of nonfatal MI or cardiac death within 30 days after non-cardiac surgery.

| | Late Surgery (n = 162) | Early Surgery (n = 30) |
|---|---|---|
| No MACE | 161 (99.4%) | 26 (86.7%) |
| MACE | 1 (0.6%) | 4 (13.3%) |

MACE = major adverse cardiac events; MI = myocardial infarction.

**TABLE 26.4** Incidence of nonfatal MI or cardiac death within 30 days after non-cardiac surgery in patients with early (n = 30) surgery after PCI who either continued or discontinued antiplatelet therapy.

| | Late Surgery (n = 162) | Early Surgery (n = 30) |
|---|---|---|
| No MACE | 17 (100%) | 9 (69.3%) |
| MACE | 0 (0%) | 4 (30.7%) |

MACE = major adverse cardiac events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

46% (86 of 187) patients discontinued their antiplatelet therapy. In particular, in patients in whom antiplatelet therapy was stopped before the required time for clopidogrel use (early-surgery group), the discontinuation of antiplatelet therapy had a detrimental effect: an incidence of MACEs of 30.7% in the discontinuation group versus 0% in patients who continued antiplatelet therapy (Fisher exact test p = 0.026) (TABLE 26.4). Again, all 4 patients with a MACE discontinued antiplatelet therapy, whereas only 35% (9 of 26) of the patients without a MACE discontinued antiplatelet therapy.

There was no difference in the incidence of MACE between patients with drug-eluting stents and those with bare-metal stents (2.2% vs. 3.0%, p = 0.70); neither was there a significant difference within the early-surgery group (28.6% for bare-metal stents and 8.7% for drug eluting stents, p = 0.23). Remarkably, in 57% of the patients with bare-metal stents, antiplatelet therapy was interrupted in the early-surgery group, whereas antiplatelet therapy was interrupted in 39.1% of the drug-eluting stent group.

Excessive blood loss during surgery was noted in the medical charts of 2 patients (1 receiving antiplatelet therapy). Blood transfusion was required in 44 patients (24% vs. 20% for those who continued vs. those who discontinued antiplatelet therapy, respectively, p = 0.50). In patients requiring blood

transfusion, the number of units of homologues' blood did not differ between those who continued versus those who discontinued antiplatelet therapy (median 2 vs. 3 U, p = 0.51).

This study showed an association between early non-cardiac surgery after coronary artery stenting and perioperative adverse cardiovascular events. Importantly, in patients undergoing early surgery, discontinuation of antiplatelet therapy during the perioperative period may be a major cause of the increase in MACE. The type of stent (i.e. bare-metal or drug-eluting) did not influence cardiovascular outcome in this cohort of patients.

In recent studies, an association between early non-cardiac surgery after PCI and adverse cardiac outcome has been reported as well[1,2,5]. However, these reports did not include the use of drug-eluting stents. The excessive risk of early surgery after PCI might be attributable to the high risk of in-stent thrombosis during the perioperative period. This thrombosis risk is possibly increased by the stress response to major surgery. The stress response includes sympathetic activation promoting shear stress on arterial plaques, enhanced vascular reactivity conducive to vasospasm, reduced fibrinolytic activity, platelet activation, and hypercoagulability. Because procoagulant clotting factors increase while fibrinolysis decreases, the surgical patient is in a hypercoaguable state. Furthermore, coronary stenting results in denudation of the endothelial surface. This might also contribute to the high risk of patients with early surgery because re-endotheliazation takes up to 8 weeks. This hypothesis is supported by our finding that all MACEs in the early-surgery group occurred in patients in whom antiplatelet therapy was discontinued, including 3 events in the 17 patients with bare-metal stents in whom antiplatelet therapy was discontinued and 2 events in 9 patients with drug-eluting stents without antiplatelet therapy. In contrast to our findings, Reddy et al.[5] did not show an association between discontinuation of antiplatelet therapy and perioperative MACEs in 56 patients with prior bare-metal stenting. This might have been attributable to the small number of events in their study.



The small number of events is also a limitation of the current study. Multivariate analysis could not be performed because of this small number. However, the difference found between those patients who continued their antiplatelet therapy and those who did not deserves attention, and, until more evidence is available, antiplatelet therapy during surgery should be continued unless there is an absolute contraindication.

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# Chapter 27

## Perioperative and long-term cardiovascular outcomes in patients undergoing endovascular treatment compared with open vascular surgery for abdominal aortic aneurysm or iliaco-femoro-popliteal bypass

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## ABSTRACT

**Background:** The aim of the present study was to determine the perioperative and long-term cardiac outcomes of patients who underwent elective open or endovascular major vascular surgery corrected for cardiac risk factors and dobutamine stress echocardiography.

**Methods:** Patients who underwent either endovascular (n = 123) or open (n = 560) vascular surgery from 1996 to 2004 at Erasmus Medical Center were enrolled. Patients were screened for cardiac risk factors (advanced age, gender, angina pectoris, myocardial infarction, heart failure, diabetes, stroke, renal failure), cardioprotective medication, and the presence of stress-induced ischemia by dobutamine stress echocardiography. Postoperative data on troponin release, CK-MB, and electrocardiography were routinely collected on days 1, 3, and 7 and before discharge. After discharge, patients were regularly screened at the outpatient clinic. The main outcome measures were perioperative and long-term cardiac death and myocardial infarction.

**Results:** The incidence of perioperative cardiac events was significantly less in endovascular-treated patients compared with conventionally treated patients, also after adjustment for clinical risk factors, dobutamine stress echocardiography, and medication (hazard ratio [HR] 0.19, 95% confidence interval [CI] 0.07 to 0.53). In contrast, during long-term follow-up (median 3.8 years, range 0 to 8.4), the incidence of long-term cardiac mortality and myocardial infarction were similar in the 2 groups (HR 0.89, 95% CI 0.52 to 1.52).

**Conclusion:** Endovascular stent grafting is associated with a reduced incidence of perioperative complications compared with open vascular surgery. Despite the initial perioperative survival benefit, patients who undergo endovascular surgery remain at high risk for late cardiac events.

## INTRODUCTION

A major limitation of nonrandomized comparative studies between open and endovascular surgical procedures conducted so far is the difference in baseline characteristics[1]. Endovascular therapy is reserved for patients with distinct vascular anatomy and may be preferred for patients at high cardiac risk. These factors may bias perioperative and long-term mortality. Apart from differences in surgical techniques, a number of other factors have been associated with perioperative and late adverse cardiac events, including stress-induced myocardial ischemia during dobutamine stress echocardiography and cardioprotective medication use[2-10]. Because these issues have not been addressed previously, the present study was conducted to determine the perioperative and long-term cardiac outcomes of patients who underwent elective open or endovascular major vascular surgery adjusted for differences in clinical and surgical characteristics.

## METHODS

The study population was composed of patients who underwent elective abdominal aneurysm or iliacofemoropopliteal bypass surgery from January 1996 to January 2004 at Erasmus Medical Center, Rotterdam, The Netherlands. Hence, it was a retrospective study of prospectively collected data. The medical ethics committee of our hospital approved the study protocol.

### Preoperative cardiac risk assessment

All patients were routinely screened for cardiac risk factors, including age, hypertension, angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure (serum creatinine >2 mg/dl), and diabetes mellitus. Routinely, all patients underwent dobutamine stress echocardiography before surgery, evaluating wall motion at rest as a marker of left ventricular function and stress-induced new wall motion abnormalities as a marker of ischemia. Dobutamine stress echocardiography was performed as previously described, and test results were considered positive if stress-induced ischemia occurred[11]. Perioperative and long-term medication use was noted, including angiotensin-converting enzyme inhibitors, platelet aggregation inhibitors, β-blockers, calcium antagonists, coumarin derivatives, diuretics, nitrates, and statins. Patients unable to take medications orally perioperatively were switched to intravenous formulas. If no intravenous formulas were available (i.e. statins and angiotensin-converting enzyme inhibitors), oral medications were restarted as soon as possible after surgery.

### Procedure

The site of procedure was classified as abdominal aneurysm repair and procedures involving the iliacofemoropopliteal arteries. All abdominal aneurysms were infrarenal aneurysms, and no suprarenal cross clamping was necessary in the open group. The choice of procedure (i.e. open or endovascular) was left to the discretion of the treating vascular surgeon and was mainly based on anatomic considerations. For endovascular procedures, locoregional anesthesia was used, and for open procedures, a combination of locoregional and general anesthesia was used. During the postoperative period, blood and plasma samples for cardiac troponin T, creatinine phosphokinase levels, creatinine phosphokinase-MB levels, and electrocardiography were routinely collected on days 1, 3, and 7 and before discharge. After discharge, all patients were followed up at the outpatient clinic every 6 months.

### Outcome

The primary outcome of the study was the incidence of perioperative and late cardiovascular events, including cardiac death and nonfatal myocardial infarction. Myocardial infarction was defined as the presence of 2 of the following 3 criteria: (1) characteristic ischemic symptoms lasting >20 minutes; (2) electrocardiographic changes, including acute ST elevation followed by the appearance of Q waves or the loss of R waves, new left bundle branch block, new persistent T-wave inversion for ≥ 24 hours, or new ST-segment depression persisting >24 hours; and (3) positive troponin T results (i.e. >0.10 ng/ml) or peak creatine kinase-MB ≥ 8% of elevated total creatinine phosphokinase, with characteristic increases and decreases[12]. Cardiovascular death was defined as any death with a cardiovascular cause, including those deaths following cardiac procedures, cardiac arrest, myocardial infarction, pulmonary embolus, or stroke, or sudden deaths not ascribed to other causes.

### Statistical analysis

Continuous variables are described as mean value (range) and categorical variables as percentage frequencies. Univariate differences between patient subgroups were evaluated using Student's t test or the chi-square test as appropriate. Kaplan-Meier survival curves were constructed to assess perioperative and long-term cardiac event–free and reintervention-free survival. Multivariate (Cox) regression was used to compare cardiac event–free survival after endovascular and open vascular surgery. The number of outcome events in the study was limited. Therefore, to avoid overfitting and to enable the assessment of the relation between clinical risk factors and the perioperative composite end point, we used the Revised Cardiac Risk Index[13]. Odds ratios and corresponding 95% confidence intervals (CIs) are reported. The limit of statistical significance was set at $p = 0.05$ (2-sided). All analysis was performed using the statistical software SPSS for Windows version 10.1 (SPSS, Inc., Chicago, Illinois).



## RESULTS

A total of 683 vascular surgery patients were included in the study; 123 patients underwent endovascular procedures, and 560 underwent conventional open vascular surgery. Cardiac risk factors and dobutamine stress echocardiographic results for all patients are listed in TABLE 27.1. In total, 25 patients (3.6%), 21 (3.8%) in the open group and 4 (3.3%) in the endovascular group, underwent preoperative coronary revascularization because of extensive stress-induced myocardial ischemia during dobutamine stress echocardiography.

### Perioperative cardiac outcome

Perioperative cardiac events occurred in 4 (3.1%) patients treated by endovascular procedures and in 122 (21.8%) patients treated conventionally. The hazard ratio (HR), corrected for cardiac risk factors, dobutamine stress echocardiography results, cardioprotective medication, and site of procedure was 0.19 (95% confidence interval 0.07 to 0.53) in favor of the endovascular treated patients. This improved outcome however was only observed in patients undergoing abdominal aortic procedures (HR 0.20, 95% confidence interval 0.06-0.63, FIGURE 27.1A), while the difference in peripheral procedures was not significantly different (HR 0.40, 95% confidence interval 0.05 to 3.22, FIGURE 27.1B). Multivariate analysis showed that both beta-blocker use (HR 0.66, 95% confidence interval 0.46-0.95) and statin use (HR 0.58, 95% confidence interval 0.39-0.87) were associated with an improved outcome (TABLE 27.2). In particular for the open group this association was significant. For the endovascular group no multivariate analysis could be performed because of the low number of events, i.e. 4 cardiovascular complications.

**TABLE 27.1** Baseline characteristics of the analyzed patients.

| | Total (N = 683) | Open (N = 560) | Endovascular (N = 123) |
|---|---|---|---|
| Men – no. (%) | 532 (77) | 423 (76) | 106 (86) |
| Age, years – mean (range) | 68 (30-97) | 68 (30-93) | 69 (40-97) |
| Peripheral procedure – no. (%) | 260 (38) | 194 (35) | 66 (54)* |
| Abdominal procedure – no. (%) | 423 (62) | 366 (65) | 57 (46)* |
| Previous angina pectoris – no. (%) | 164 (24) | 138 (25) | 25(20) |
| Previous myocardial infarction – no. (%) | 252 (37) | 224 (40) | 28 (22)* |
| Previous heart failure – no. (%) | 66 (10) | 56 (10) | 10 (8) |
| CVA or TIA – no. (%) | 90 (13) | 83 (15) | 6 (6) |
| Diabetes Mellitus – no. (%) | 85 (12) | 70 (13) | 15 (12) |
| Systemic hypertension – no. (%) | 351 (51) | 283 (51) | 65 (53) |
| Renal Failure – no. (%) | 53 (8) | 46 (8) | 7 (6)* |
| COPD – no. (%) | 171 (25) | 142 (25) | 28 (23) |
| ACE-inhibitor therapy – no. (%) | 193 (28) | 165 (30) | 27 (22) |
| Aspirin therapy – no. (%) | 225 (33) | 191 (34) | 34 (28) |
| Beta-blocker therapy – no. (%) | 366 (53) | 303 (54) | 61 (50) |
| Ca-antagonist therapy – no. (%) | 179 (26) | 153 (27) | 25 (20) |
| Warfarin derivates – no. (%) | 140 (20) | 117 (21) | 22 (18) |
| Diuretic therapy – no. (%) | 114 (17) | 101 (18) | 13 (11)* |
| Nitrate therapy – no. (%) | 96 (14) | 88 (16) | 8 (7)* |
| No new wall motion abnormalities – no. (%) | 546 (80) | 437 (78) | 109 (89) |
| New wall motion abnormalities – no. (%) | 137* (20) | 123 (22) | 14 (11)‡ |
| Rest wall motion score (mean) – no. (%) | 1.32 | 1.33 | 1.26 |

‡ = 58% of patients with new wall motion abnormalities on DSE were on β-blocker therapy. * = p<0.05; COPD = chronic obstructive pulmonary disease; ACE = angiotensin converting enzyme; CVA = cerebrovascular accident; TIA = transient ischemic attack

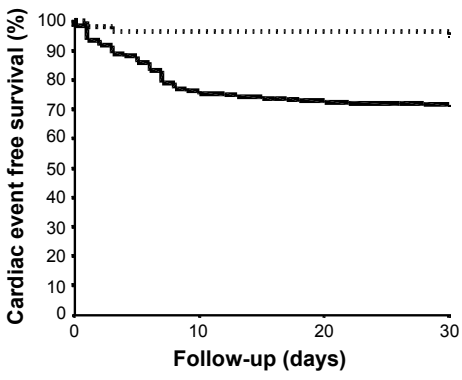


**FIGURE 27.1A** Perioperative cardiovascular death or myocardial infarction in open abdominal vascular surgery (solid line) and endovascular abdominal surgery (dotted line).

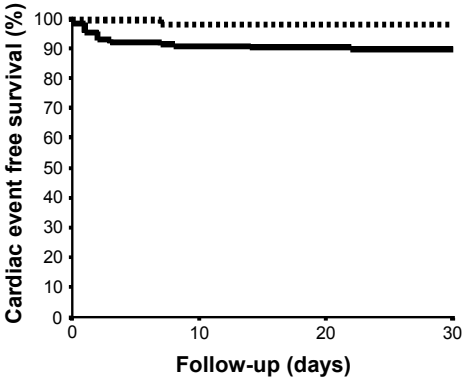


**FIGURE 27.1B** Perioperative cardiovascular death or myocardial infarction in open peripheral surgery (solid line) and endovascular peripheral surgery (dotted line).

| **TABLE 27.2** | Multivariable predictors and estimated risk of perioperative cardiovascular events, i.e. cardiovascular death and mortality. | |
|---|---|---|
| | HR (95% Confidence interval) | P-value |
| Endovascular | 0.19 (0.07-0.53) | 0.001 |
| Abdominal procedure | 3.79 (2.29-6.28) | <0.001 |
| Revised cardiac risk index | | |
| 1 risk factor | 1.0 | |
| 2 risk factors | 1.75 (1.03-2.97) | 0.037 |
| 3 or more risk factors | 2.72 (1.72-4.29) | <0.001 |
| Beta-blocker use | 0.66 (0.46-0.95) | 0.025 |
| Statin use | 0.58 (0.39-0.87) | 0.008 |

HR = Hazard ratio

### Long-term outcome

Cardiovascular events occurred in 125 patients during a median of 3.8 years (range 0 to 8.4). In the endovascular group, 20 events occurred, and in the open group, there were 105 events (16% vs. 19%). In univariate analysis, there was no difference in survival rates between the endovascular and conventionally treated patients (FIGURE 27.2). After correction for cardiac risk factors, cardioprotective medication use, dobutamine stress echocardiographic results, and site of procedure, there was no significant difference between the open and endovascular groups (HR 0.89, 95% CI 0.52 to 1.52).

Neither aortic nor iliacofemoral procedures had a cardiovascular event–free survival benefit after endovascular treatment (HR 0.31, 95% CI 0.72 to 2.90, and HR 0.59, 95% CI 0.28 to 1.25, respectively). Also, the results of the multivariate analysis showed that β-blocker and statin users had significantly reduced incidence of long-term cardiac events irrespective of clinical risk factors and type of surgery (TABLE 27.3). Stress-induced myocardial ischemia during dobutamine stress echocardiography was also associated with late adverse cardiac events (HR 2.63, 95% CI 1.87 to 3.71). During long-term



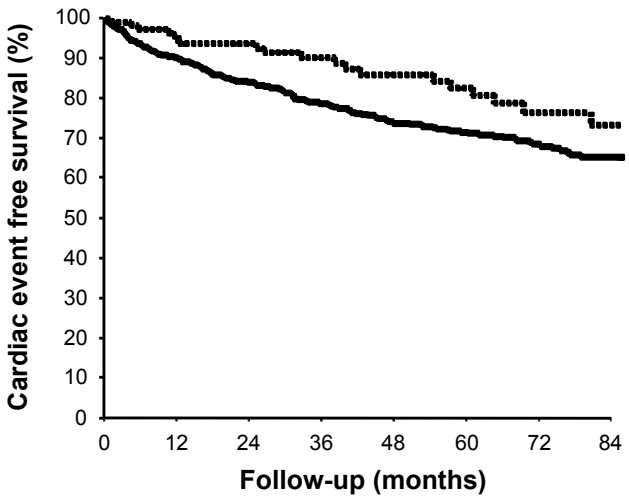


**FIGURE 27.2** Long-term cardiovascular death or myocardial infarction in open (solid line) and endovascular (dotted line) vascular surgery patients who survived the first 30 postoperative days.

**Table 27.3** Multivariable predictors and estimated risk of long term cardiovascular death.

| | HR (95% Confidence interval) | P-value |
|---|---|---|
| Endovascular | 0.89 (0.52-1.52) | 0.267 |
| Positive dobutamine stress echocardiography | 2.63 (1.87-3.71) | <0.001 |
| Beta-blocker use | 0.63 (0.45-0.86) | 0.004 |
| Statin use | 0.62 (0.43-0.88) | 0.008 |

HR = Hazard ratio

follow-up, the number of reinterventions due to technical failure was significantly greater in the endovascular-treated patients compared with the conventional group (3% vs. 25%, p <0.001). This was mainly due to persistent type II endoleaks. This high incidence of reinterventions was not associated with a higher mortality rate related to the new operative procedures.

## DISCUSSION

This study showed that endovascular therapy for the exclusion of an abdominal aortic aneurysm was associated with improved perioperative outcomes compared with patients who underwent open abdominal aortic aneurysm repair, even after corrections were made for significant cardiac risk factors and dobutamine stress echocardiographic results. However, no difference in perioperative outcome was observed in patients who underwent either open or endovascular peripheral vascular procedures. Patients who underwent endovascular surgery had a lower perioperative cardiac event rate, but during long-term follow-up, the cardiac event rate significantly increased and became similar to the long-term cardiac event rate of conventionally treated patients.

The results of our study showed that the incidence of perioperative cardiac complications was less often observed in patients who underwent endovascular procedures compared with conventional vascular procedures. This reduced incidence of perioperative cardiac events is likely to be associated with reduced myocardial stress during endovascular procedures[2,3,14,15]. In patients who undergo endovascular procedures, no aortic clamping and declamping are performed; the procedure is done under locoregional anesthesia, and in combination with reduced blood loss, a more hemodynamic stable condition is achieved[16-20]. Cuypers et al[16] also confirmed these assumptions in an observational study of 120 vascular patients. The incidence of perioperative myocardial ischemia was compared between 49 patients who underwent endovascular treatment and 71 patients who underwent conventional aortic surgical procedures using transesophageal echocardiography and electrocardiography. During aortic clamping and declamping in the conventional surgery group, hemodynamic instability occurred, which was associated with a higher incidence of myocardial ischemia[16].

The perioperative cardiac event rate of patients who underwent peripheral endovascular procedures was also lower compared with the cardiac event rate of patients who underwent conventional surgery. However, after adjustment was made for significant clinical characteristics and cardioprotective medications, this association was no longer significant. There are no studies of the perioperative outcomes of patients who undergo endovascular or conventional peripheral vascular surgery. The lack of a significant association observed in our study is most likely associated with a relatively small number of events in these groups of patients. Therefore, future studies are necessary to test these findings.

Although the perioperative cardiac complication rate was significantly lower in patients who underwent endovascular procedures, surprisingly, the incidence of long-term cardiac mortality was similarly high in patients who underwent endovascular or open procedures. Our study period from 1996 to 2004 was long with regard to endovascular abdominal aneurysm repair, considering that endovascular devices have improved substantially. Although this might influence the number of required reinterventions, it will probably not change the rate of long-term adverse cardiac events. There is considerable research on the late survival of patients who undergo conventional vascular surgery, but there are only limited data available about the long-term survival of patients who undergo endovascular procedures. May et al[21] found that endovascular abdominal aortic aneurysm repair was associated with a significantly better 3-year event-free survival rate compared with open abdominal aortic aneurysm repair. In contrast, Moore et al[22] reported higher and similar long-term cardiac mortality rates during an average 5-year follow-up period in patients who underwent endovascular treatment compared with patients who underwent conventional surgery. In agreement with these findings, in our study, we also found that the incidence of long-term cardiac mortality was similar between the endovascular and conventional surgery groups. This finding also highlights the importance of using preoperative cardiac risk evaluation and subsequent long-term cardiac risk assessment and management in patients who undergo endovascular procedures. Patients who undergo endovascular surgery identified at increased cardiac risk may benefit from the use of long-term cardioprotective medication, such as β-blockers and statins[23,24].

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# Chapter 28

## Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair

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## ABSTRACT

**Objective:** Dobutamine stress echocardiography (DSE) provides an objective assessment of the presence and extent of coronary artery disease. Therefore we compared cardiac outcome in patients at high-cardiac risk undergoing open or endovascular repair of infrarenal AAA using preoperative DSE results.

**Methods:** Consecutive patients with ≥ 3 cardiac risk factors (age >70 years, angina pectoris, myocardial infarction, heart failure, stroke, renal failure, and diabetes mellitus) undergoing infrarenal AAA repair were reviewed retrospectively. All underwent cardiac stress testing using DSE. Postoperatively data on troponin release and ECG were collected on day 1, 3, 7, before discharge, and on day 30. The main outcome measures were perioperative myocardial damage and myocardial infarction or cardiovascular death.

**Results:** All 77 patients (39 endovascular, 38 open) had a history of cardiac disease. The number and type of cardiac risk factors were similar in both groups. Also DSE results were similar: 55 vs. 56%, 24 vs. 28%, and 21 vs. 18% had no, limited, or extensive stress induced myocardial ischemia respectively. The incidence of perioperative myocardial damage (47% vs. 13%, $p = 0.001$) and the combination of myocardial infarction or cardiovascular death (13% vs. 0%, $p = 0.02$) was significantly lower in patients receiving endovascular repair.

**Conclusion:** In patients with similar high cardiac risk, endovascular repair of infrarenal aortic aneurysms is associated with a reduced incidence of perioperative myocardial damage.

## INTRODUCTION

Patients scheduled for abdominal aortic aneurysm repair with multiple cardiac risk factors are at increased risk of perioperative cardiac events. The incidence of adverse perioperative cardiac complications ranges from 1.1% to 2.4% and 9.9% for patients with no, 1 or 2, and ≥ 3 clinical cardiac risk factors[1]. While cardioprotective medication, i.e. beta-blocker and statin therapy, reduces the incidence of adverse perioperative cardiac events in most vascular surgery patients, those at highest risk do not seem to benefit[1]. In addition, more aggressive therapy, i.e. prophylactic coronary revascularization, did not show a reduction in perioperative adverse cardiac events in those at high-risk[2].

A major improvement for these patients at high cardiac risk might be expected from endovascular aneurysm repair. However, no randomized trials comparing open and endovascular treatment have been reported on patients at high cardiac risk. Less than half of the patients in the DREAM trial (44%) and EVAR-1 trial (43%) had a history of cardiac disease[3,4]. A major limitation of non-randomized comparative studies between open and endovascular surgical procedures conducted so far is the lack of objective criteria for baseline cardiac condition[5]. Preoperative cardiac stress testing such as dobutamine stress echocardiography (DSE) and nuclear imaging provide an objective assessment of the presence and extent of coronary artery disease[6]. Therefore we conducted the present study, in which patients with an infrarenal aortic aneurysm were assessed preoperatively by cardiac stress testing, to compare cardiac outcome in high-risk patients treated by either open or endovascular repair.

## METHODS

### Patients

The study population was composed of consecutive patients with 3 or more cardiac risk factors, retrospectively identified by screening of medical charts, who underwent elective abdominal aneurysm repair between January 2000 and January 2006 at a tertiary referral center, Erasmus University Medical Center Rotterdam, the Netherlands. The choice for either repair method was at the discretion of the treating vascular surgeon and was based mainly on anatomical considerations. Open repair requiring suprarenal aortic clamping or renal artery bypass were not included in this analysis. The study was approved by the Erasmus MC medical ethics committee.

### Preoperative cardiac risk assessment

All patients were routinely screened for cardiac risk factors, including age over 70 years, history of or presence of angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure (serum creatinine >2 mg/dl), and diabetes mellitus[1]. The presence of hypertension and chronic obstructive pulmonary disease (COPD) was noted. A patient was classified as having COPD at the preoperative screening visit according to symptoms and pulmonary function test (i.e. FEV1 <70% of maximal age and gender predictive value). According to the ACC/AHA guidelines all patients with 3 or more risk cardiac risk factors underwent cardiac stress testing prior to surgery[7].

Perioperative medication use was noted including ACE-inhibitors, platelet aggregation inhibitors, beta-blockers, calcium antagonists, oral anticoagulants, diuretics, nitrates, and statins. Patients unable to take medication orally perioperatively were switched to intravenous formula. If no intravenous formula was available, i.e. statins and ACE-inhibitors, oral medication was restarted as soon as possible after surgery.

Patients on chronic beta-blocker therapy continued their medication. Patients without beta-blockers started with bisoprolol 2.5 mg once a day at the preoperative screening visit. Beta-blocker dose was adjusted in all patients at admission to the hospital and on the day prior to surgery to achieve a resting heart frequency of 60–65 beats per minute. The same dose of beta-blockers was continued postoperatively except in patients who were unable to take medication orally. In these patients, the heart rate was monitored continuously at the intensive care unit or hourly at the ward, and intravenous metoprolol was administered at a dose sufficient to keep the heart rate between 60–65 beats per minute.

### Cardiac stress testing

Resting echocardiography was used to estimate the left ventricular ejection fraction using the Simpson rule. Cardiac stress testing was performed by dobutamine echocardiography as previously described[8]. Myocardial stress induced ischemia was assessed using a semi-quantitative evaluation; a 5-point score in a 17-segement model. Limited ischemia was defined by the presence of 1–4 ischemic segments, while extensive ischemia was defined by ≥ 5 ischemic segments. The overall sensitivity of this technique for the detection of significant coronary artery disease (diameter stenosis greater than or equal to 50%) is reported to be 95%; specificity 82% and accuracy 92%[9].

### Outcome

All patients were monitored for cardiac events after abdominal aortic aneurysm repair. Twelve-lead ECG and serum troponin-T level were systematically determined one, three, seven, and 30 days after surgery. Outpatient follow-up was performed at 30 days if a patient had been discharged from the hospital. All patients had a follow-up at 30 days after surgery, except for patients who died within 30 days.



The primary outcome of the study was the incidence of perioperative myocardial damage defined as a rise and fall in serum levels of cardiac troponin T. Secondary outcomes included the incidence of myocardial infarction and the combination of myocardial infarction and cardiovascular death were assessed. Myocardial infarction was defined as the presence of 2 out of the following 3 criteria: (1) Characteristic ischemic symptoms lasting >20 minutes, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists >24 hours, and (3) a positive troponin T, i.e. >0.10 ng/ml, or peak CK-MB ≥ 8% of an elevated total creatinine phosphokinase with characteristic rise and fall[10]. Cardiovascular death was defined as any death with a cardiovascular cause, including those deaths following a cardiac procedure, cardiac arrest, myocardial infarction, pulmonary embolus, stroke, or sudden deaths not ascribed to other causes[11].

### Statistical analysis

Continuous data are presented as median values with interquartile range, whereas dichotomous data are presented as percentages. Differences in clinical characteristics between patients undergoing endovascular repair or open repair were evaluated by Wilcoxon non-parametric tests, Chi-square tests or Fisher's exact tests, as appropriate. Differences in the incidence of the endpoints were evaluated by a Chi-square test. The limit of statistical significance was set at $p = 0.05$ (two-sided). All analysis was performed using the statistical software SPSS for Windows 12.0.1 (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

### Patient characteristics

A total of 77 patients were identified with ≥ 3 cardiac risk factors who underwent either endovascular (n = 39) or open (n = 38) infrarenal aortic aneurysm repair. The number and type of cardiac risk factors did not differ significantly between the treatment groups (TABLE 28.1). The majority of patients (97%) received perioperative beta-blocker therapy. Other cardioprotective medication use was similar in patients with open or endovascular repair (TABLE 28.2).

**TABLE 28.1** Baseline characteristics (all patients ≥ 3 risk factors).

| | Open N=38 | Endovascular N=39 |
|---|---|---|
| Male – no. (%) | 35 (92) | 38 (97) |
| Age, years – mean (SD) | 73.6 (5.6) | 73.3 (6.8) |
| Cardiac risk factors – no. (%) | | |
| Myocardial infarction | 31 (82) | 32 (82) |
| Angina pectoris | 25 (66) | 27 (69) |
| Congestive heart failure | 5 (13) | 10 (25) |
| Diabetes mellitus | 6 (16) | 5 (13) |
| Renal insufficiency | 6 (16) | 7 (18) |
| CVA or TIA | 13 (34) | 9 (23) |
| Age >70 years | 30 (79) | 32 (82) |
| Other risk factors | | |
| Hypertension – no. (%) | 16 (42) | 16 (41) |
| Previous CABG or PCI – no. (%) | 14 (37) | 17 (44) |
| COPD – no. (%) | 17 (45) | 15 (39) |
| BMI, kg/m$^2$ – mean (SD) | 25.9 (3.9) | 25.9 (3.7) |
| AAA size, mm - median | 60 | 61 |
| Dobutamine stress echocardiography – no. (%) | | |
| Left ventricular ejection fraction < 35% | 23 (61) | 22 (56) |
| No ischemia | 21 (55) | 21(54) |
| Limited ischemia | 9 (24) | 11(28) |
| Extensive ischemia | 8 (21) | 7 (18) |

CVA = cerebrovascular accident, TIA = transient ischemic attack, CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention, COPD = chronic obstructive pulmonary disease, BMI = body mass index, AAA = abdominal aortic aneurysm

**TABLE 28.2** Perioperative medication use.

| | **Open** N=38 | **Endovascular** N=39 |
|---|---|---|
| **Medical therapy – no. (%)** | | |
| Statin | 25 (66) | 22 (56) |
| Beta-blocker | 37 (97) | 38 (97) |
| Aspirin | 23 (61) | 23 (59) |
| Warfarin | 4 (11) | 7 (18) |
| ACE-inhibitor | 14 (37) | 13 (34) |
| Calcium antagonists | 10 (26) | 11 (29) |
| Diuretics | 16 (42) | 13 (33) |

Forty-five (58%) patients had a left ventricular ejection fraction of <35%, 61% in the open group and 56% in the endovascular group (p = 0.82). Almost half (45%) of the patients had stress inducible myocardial ischemia during stress testing, 45% in the open group and 46% in the endovascular group. Also the extent of myocardial ischemia did not differ significantly between the open and endovascular group, 55 vs. 54%, 24 vs. 28%, and 21 vs. 18% had no, limited, or extensive stress- inducible myocardial ischemia respectively. Based on these test results and at the discretion of the treating physician 6 patients underwent pre-operative cardiac revascularization to optimize cardiac condition (2 in the open group and 4 in the endovascular group).

### Outcome

Myocardial damage, i.e. a rise in serum levels of cardiac troponin T, was found in 18 (47%) patients undergoing open repair and in 5 (13%) patients undergoing endovascular repair (p = 0.001, TABLE 28.3). Five patients with elevated cardiac troponin T levels had renal dysfunction. Importantly all of these patients had troponin concentrations of >0.10 ug/l. When these patients are excluded, patients undergoing open repair still had a significantly higher incidence of myocardial ischemia compared to those undergoing endovascular repair (44% vs. 12%, p = 0.006).

**TABLE 28.3** 30-day cardiac outcome.

| | Open | Endovascular | P-value |
|---|---|---|---|
| | N=38 | N=39 | |
| Positive Troponin T – no. (%) | 18 (47) | 5 (13) | 0.001 |
| Myocardial Infarction – no. (%) | 5 (13) | 0 | 0.02 |
| All-cause death – no. (%) | 3 (8) | 0 | 0.11 |
| CV death or MI – no. (%) | 5 (13) | 0 | 0.02 |
| Length of stay (median, range) | 11 (3-123) | 3 (1-32) | <0.001 |

CV = cardiovascular, MI = myocardial infarction



Three (8%) patients in the open repair group died within 30 days after surgery whereas in the endovascular group all patients survived. Five (13%) in the open group experienced a myocardial infarction versus none in the endovascular group (p = 0.02). The incidence of the combined endpoint of cardiovascular death or nonfatal MI for patients in the open group was 13% versus 0% in the endovascular group (p = 0.02). Importantly, patients with no, or only limited, stress-induced myocardial ischemia at preoperative testing had a lower incidence of perioperative MI than patients with extensive stress induced ischemia (3% vs. 21%, p = 0.03).

## DISCUSSION

Perioperative cardiac complications are a major cause for morbidity and mortality in patients with multiple cardiac risk factors undergoing abdominal aortic aneurysm repair. The optimal treatment for these patients is not well defined. Perioperative beta-blocker use reduces the incidence of perioperative cardiac complications in patients with no or limited stress inducible myocardial ischemia at preoperative testing[1,12]. However, patients with extensive stress inducible ischemia remain at high cardiac risk despite beta-blocker use with a perioperative event rate of approximately 30%[1]. It was hypothesized that prophylactic revascularization might provide sufficient protection in this patient group. Unfortunately, a recently conducted study on prophylactic coronary revascularization failed to show an improvement in perioperative cardiac outcome in 510 patients undergoing major vascular

surgery[2]. The current study showed that, in patients at high-risk with similar extent of coronary artery disease, endovascular treatment reduces the incidence of perioperative myocardial complications as compared to open repair.

The low incidence of myocardial damage in endovascular aneurysm repair has been described previously. Abraham et al. found a 10% incidence of myocardial ischemia in endovascular treated patients[13]. Interestingly, in our group of patients with a higher risk profile we found a similar incidence of myocardial ischemia. The extent of coronary artery disease as assessed by the number of stress inducible ischemic segments correlated well with the extent of perioperative myocardial damage in the open repair group, 5%, 11%, 38% myocardial infarctions for patients with no, limited, and extensive stress inducible ischemia respectively. In the endovascular repair group no such correlation was found. This difference might be explained by the reduced myocardial stress during an endovascular procedure[14]. In patients undergoing an endovascular procedure no aortic clamping and declamping are performed, the procedure is done under loco-regional anesthesia, and in combination with a reduced blood loss a more hemodynamic stable condition is achieved[15-18]. Cuypers et al. also confirmed these assumptions in an observational study of 120 vascular patients[15]. The incidence of perioperative myocardial ischemia was compared between 49 patients who underwent endovascular treatment and 71 patients who underwent conventional aortic surgical procedures using transesophageal echocardiography and electrocardiography. During aortic clamping and declamping in the conventional surgery group hemodynamic instability occurred, which was associated with a higher incidence of myocardial ischemia.

Unfortunately endovascular repair can only be performed in patients with a distinct aortic anatomy. Endovascular repair of juxtarenal and suprarenal aortic aneurysms is not common practice so far. However, technological development continues apace and the first results of branched endografts are promising. Recently O'Neill described the results of 119 patients with an AAA anatomy unsuitable for conventional endovascular repair[19]. These patients were treated with fenestrated stents. Only one (0.8%) patient died (due to a non-cardiac cause) within 30 days after the procedure.

In contrast, the results of the EVAR 2 trial, in which patients deemed unfit for open repair were randomized for endovascular or no aneurysm repair, showed a 30-day mortality of 9% after endovascular repair[20]. The main difference between the patients in the EVAR-2 trial and the current analysis is that patients in our analysis were not deemed unfit for open surgery. It is of interest that in contrast to the 100% of patients with a history of cardiac disease in the current analysis, only 69% of the patients in EVAR-2 had a history of cardiac disease. Despite that, in the current study we found no myocardial infarction or death in the endovascular treated patients. It might be argued that more patients in our study received cardioprotective medication; statin use 61% vs. 39% in EVAR-2 and 97% of patients were on beta-blocker therapy.

Another important aspect of the comparison between endovascular and open repair of abdominal aortic aneurysms is the long-term outcome after repair. Though the DREAM trial and EVAR-1 trial showed a perioperative benefit for patients treated endovascularly, both trials failed to show a benefit in overall survival after a median follow-up of respectively 1.8 and 2.9 years[3,21]. In DREAM and EVAR-1 approximately 30 to 40% of late mortality was attributable to cardiovascular causes, not including aneurysm related causes. This is not surprising since more than 60% of vascular surgery patients have documented coronary artery disease which will mainly determine adverse late outcome[22]. In addition, previously asymptomatic patients may further progress during follow-up and subsequently increase late mortality. Importantly, the EVAR-2 trial results indicate that high-risk patients who undergo

endovascular repair have the same rate of cardiovascular related deaths as patients randomized to no repair of their aneurysm during a median follow-up of 2.4 years[20]. Open abdominal aneurysm repair might be considered the ultimate cardiac stress test. If a patient survives the operation, the overall cardiac prognosis might be not that bad. On the other hand, this "selection" of frail patients does not occur in patients who undergo endovascular repair. Consequently, it might be argued that survivors of endovascular aneurysm repair are generally in worse cardiac health than survivors of open repair. Since long-term outcome after successful repair of an abdominal aortic aneurysm (open or endovascular) is related to underlying coronary artery disease, aggressive treatment is of critical importance[23].

The main limitation of the current study is that it is not a randomized study. Patients were selected for open or endovascular repair based on surgeon's preference and anatomical features. It might be so that if patients would have been randomized for open or endovascular repair, thereby reducing the extent of surgery in the conventional group (less challenging anatomy), the difference in cardiac outcome might be slightly less pronounced. However, the results of the preoperative cardiac stress tests showed that the two groups had similar prevalence and extent of coronary artery disease.

In conclusion, endovascular therapy seems to be associated with less perioperative adverse cardiac events compared to open surgery in patients with 3 or more cardiac risk factors, irrespective of the extent of underlying coronary artery disease.



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# Chapter 29

## Endovascular repair of abdominal aortic aneurysm

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The long-term prognosis after successful repair of an abdominal aortic aneurysm is related to the presence and extent of underlying coronary artery disease[1]. Blankensteijn et al.[2] showed that the favorable response to endovascular repair, as compared with open surgery, at 30 days dissipated after one year.

We analyzed 396 patients with an abdominal aortic aneurysm (57 who had undergone endovascular repair and 339 who had undergone open repair) for long-term prognosis with regard to the presence or absence and the extent of coronary artery disease (FIGURE 29.1), as assessed by the number of stress-induced ischemic wall-motion abnormalities determined with the use of a 16-segment model during dobutamine echocardiography. During a median follow-up of 2.8 years, 74 deaths from cardiac causes and 109 myocardial infarctions occurred. Multivariate Cox regression analysis, correcting for the type of surgery and cardiac risk factors (age and the presence or absence of angina, myocardial infarction, diabetes, heart failure, and stroke) showed that prognosis was related to the presence of ischemic wall-motion abnormalities (hazard ratio, 2.54; 95 percent confidence interval, 1.70 to 3.79) and to the increasing extent of such abnormalities (hazard ratio, 3.37; 95 percent confidence interval, 2.11 to 5.40), whereas the type of aneurysm repair was not related to long-term survival (hazard ratio, 0.82; 95 percent confidence interval, 0.45 to 1.50). Since the long-term outcome after successful repair of an abdominal aortic aneurysm is related to underlying coronary artery disease, aggressive treatment is of critical importance[3].

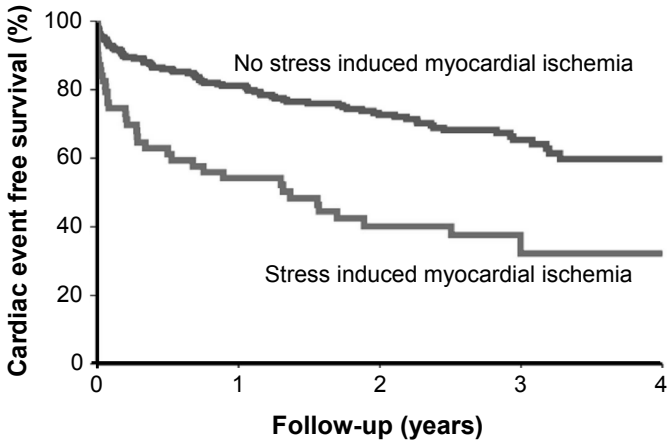


**FIGURE 29.1** Long-term prognosis after repair of abdominal aortic aneurysm, according to the presence or absence of coronary artery disease.
Among 396 patients with an abdominal aortic aneurysm, the preoperative presence of stress-induced myocardial ischemia during dobutamine echocardiography was associated with a worse long-term prognosis ($p<0.001$).

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# Part III

## Long-term Risk Reduction

# Chapter 30

## Preoperative cardiac risk assessment in vascular surgery patients: seeing beyond the perioperative period

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Patients scheduled for non-cardiac vascular surgery are at significant risk of cardiovascular morbidity and mortality due to underlying symptomatic or asymptomatic coronary artery disease (CAD). As was shown by Hertzer et al. in their landmark study in 1984 using coronary angiography in 1000 patients undergoing non-cardiac vascular surgery, 61% of all patients did have at least one significant lesion[1]. In fact, only 8% of all patients had no abnormalities. More recent studies using functional tests for CAD such as dobutamine stress echocardiography confirmed these findings. In a study population of 1097 vascular surgical patients, the incidence of rest wall motion abnormalities was nearly 50%, while one-fifth of patients had stress-induced myocardial ischaemia[2].

The high prevalence of CAD in vascular surgical patients explains the adverse outcome in this patient population. The incidence of perioperative myocardial infarction, defined as the presence of two out of three of the following markers: (i) the presence of typical chest pain complaints; (ii) ECG abnormalities; and (iii) increased troponin levels, is 5%. Importantly, 75% of the perioperative myocardial infarctions remain asymptomatic and may therefore be difficult to assess. This might be attributable to the disguising effects of sedation and the simultaneous occurrence of symptoms directly related to surgery such as nausea. The incidence of troponin release is even up to 25% in the vascular surgery population. However, the impact of perioperative asymptomatic myocardial ischemia on long-term outcome is not fully appreciated.

The preoperative evaluation offers a unique opportunity to identify patients at increased perioperative risk and initiate appropriate lifestyle changes and risk reduction therapy, as these will also improve long-term outcome. Importantly, patients should live long enough to enjoy the benefits of surgery. The preoperative evaluation of high-risk patients is hampered by the complex pathophysiology of a perioperative myocardial infarction (MI). Both coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, and a sustained oxygen supply–demand mismatch contribute equally to the incidence of a perioperative MI[3,4]. The former is related to the inflammatory status of the coronary artery tree. This has important implications on perioperative and long-term risk reduction strategies. A single intervention, for instance aiming at restoration of the supply–demand mismatch, may offer insufficient protection for coronary plaque instability. Therefore, treatment of the coronary culprit lesion only offers limited protection as the disseminated inflammatory disease of the coronary artery tree progresses.

Recently Kertai et al. used a total of 2310 patients to develop a Bayesian model for the prediction of all-cause mortality in patients undergoing all types of open vascular surgery[5]. The type of surgery was a strong risk factor; patients with a ruptured abdominal aortic aneurysm had the worst outcome, followed by elective thoracoabdominal and abdominal aortic surgery, lower extremity arterial bypass surgery, and carotid surgery. Risk factors based on medical history, in order of descending risk, were: renal dysfunction, congestive heart failure, ischemic heart disease, cerebrovascular event, hypertension, and pulmonary disease. The data of the Coronary Artery Revascularization Prophylaxis (CARP) study of McFalls et al.[6] confirm these preoperative risk factors and offer the clinician hints for long-term outcome. Recently biomarkers such as high sensitive C-reactive protein (hsCRP) have also emerged as potential predictors of adverse cardiovascular events after vascular surgery. As shown by Owens et al. in a group of 91 vascular surgery patients, a preoperative hsCRP level >5 mg/L was associated with a 2.3-fold increased risk for adverse cardiovascular events during a mean follow-up of 12 months[7].

Another well known biomarker, in the CARP study assessed after the stress of surgery, is troponin release. In line with these findings, Landesberg et al. showed in 2003 that patients with a perioperative

troponin T release >0.03 ng/mL and/or a troponin I release >0.6 ng/mL had a significant 2-fold increased risk for long-term mortality during a mean follow-up of 32 months, irrespective of the type of vascular surgery and clinical risk factors[8]. This was also confirmed in a study of 393 vascular surgery patients by Kertai et al.: an increase in troponin T level >0.1 ng/mL was associated with a 1.9-fold increased risk for all-cause mortality during a median follow-up of 4 years[9].

Although the combination of clinical cardiac risk factors and biomarkers offers a unique opportunity to stratify patients according to the long-term risk, outcome in patients with peripheral arterial disease (PAD) remains poor. The 5-year event rate of cerebrocardiovascular events is 20%, with mortality rates of up to 30%. The Reduction of Atherothrombosis for Continued Health (REACH) Registry, including 55 814 patients with known atherosclerotic disease (CAD, PAD and cerebrovascular disease) showed that patients with polyvascular disease, i.e. the combination of PAD and CAD, have a significantly worse outcome compared with patients with CAD only[10]. An explanation for the high event rate is the medical undertreatment of patients with PAD. Recently a report from Denmark confirmed the undertreatment of PAD patients as compared with CAD patients. Patients with PAD were less likely to receive antiplatelet therapy, statins, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers. For all of these therapies there is substantial evidence that they are associated with an improved event-free survival. In fact, current guidelines recommend the aggressive use of statins, antiplatelet therapy, and blood pressure lowering in these patients[11]. The investigators of CARP are to be congratulated for their effort in giving their patients so-called best medical treatment; 80% were on β-blockers during 2 years of follow-up, 85% were on antiplatelet therapy, 70% on statins, and 60% on ACE inhibitors.

For the improvement of the long-term prognosis of patients with PAD it is advisable that current guidelines on lifestyle changes and treatment targets of cardiac risk factors are fully disseminated among physicians involved in care of these patients. The recent results of the Euro Heart Survey underscore the importance of continuous education and surveillance of guideline implementation.



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# Chapter 31

## Long-term prognosis of patients with peripheral arterial disease: a comparison in patients with coronary artery disease

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## ABSTRACT

**Background:** The presence of peripheral arterial disease (PAD) is considered to be a risk factor for adverse late outcome. This study was designed to compare the long-term outcomes of patients with PAD with a risk factor matched population of coronary artery disease (CAD) patients, but without PAD.

**Methods:** A total of 2,730 PAD patients undergoing vascular surgery were categorized into groups: 1) carotid endarterectomy (n = 560); 2) elective abdominal aortic surgery (AAA) (n = 923); 3) acute AAA surgery (r-AAA) (n = 200), and 4) lower limb reconstruction procedures (n = 1,047). All patients were matched using the propensity score, with 2,730 CAD patients who underwent coronary angioplasty. Survival status of all patients was obtained. In addition, the cause of death and complications after surgery in PAD patients were noted. The Kaplan-Meier method was used to compare survival between the matched PAD and CAD population and the different operation groups. Prognostic risk factors and perioperative complications were identified with the Cox proportional hazards regression model.

**Results:** The PAD patients had a worse long-term prognosis (hazard ratio 2.40, 95% confidence interval 2.18 to 2.65) and received less medication (beta-blockers, statins, angiotensin-converting enzyme inhibitors, aspirin, nitrates, and calcium antagonists) than CAD patients did ($p < 0.001$). Cerebro-cardiovascular complications were the major cause of long-term death (46%). Importantly, no significant difference in long-term survival was observed between the AAA and lower limb reconstruction groups (log rank $p = 0.70$). After vascular surgery, perioperative cardiac complications were associated with long-term cardiac death, and non-cardiac complications were associated with all-cause death.

**Conclusions:** Long-term prognosis of vascular surgery patients is significantly worse than for patients with CAD. The vascular surgery patients receive less cardiac medication than CAD patients do, and cerebro-cardiovascular events are the major cause of late death.

## INTRODUCTION

Atherosclerosis is a systemic disease affecting numerous vascular beds. In patients with peripheral arterial disease (PAD), coronary artery disease (CAD) has a prevalence of 46% to 71%[1,2]. Post-operative and long-term prognosis after vascular surgery is predominantly determined by underlying CAD[3]. Furthermore, cardiac death accounts for approximately 40% of 30-day mortality, and the 1-year mortality has been estimated at 6% to 10%[4-7]. To improve outcomes of patients with PAD requiring surgery, assessment and aggressive therapy of atherosclerotic risk factors is recommended. Hence, the secondary prevention for subjects with PAD is similar to the measures for patients with CAD[8,9]. However, data are scarce about the survival and treatment of patients with PAD compared with patients with CAD.

In addition, long-term outcomes in vascular surgery patients with PAD are ill-defined and often not considered in the immediate pre-operative workup. To provide information on long-term prognosis after open vascular surgery repairs among an entire stratum of procedures, it would be important to understand the relationship between pre-operative characteristics and nonfatal perioperative complications with long-term all-cause mortality and cardiac events in a large cohort of patients with PAD. Therefore, in this analysis, we compared survival and treatment of patients with PAD scheduled for open vascular surgery procedures with a risk factor matched large cohort of patients with documented severe myocardial ischemia referred for coronary angioplasty in the same clinical setting, without signs or symptoms of PAD.

## METHODS

### Study design and patient selection

Between January 1993 and June 2006, 2,730 PAD patients underwent major vascular surgery at the Erasmus Medical Center, Rotterdam, the Netherlands, and were entered into a computerized database. All patients underwent open surgery and were categorized into 4 groups, respectively: 1) carotid endarterectomy (CEA); 2) elective infrarenal abdominal aortic surgery (AAA); 3) acute infrarenal AAA surgery (r-AAA); and 4) lower limb arterial reconstruction procedures (LLR). The medical ethics committee of the Erasmus Medical Center was informed about the study protocol, and per institutional practice, no official approval was requested.

### Operation groups

Patients in the CEA group underwent an elective reconstruction or desobstruction of the carotid artery. The AAA group underwent open infrarenal AAA repair (aortic-to-aortic or aortic-bifurcation prostheses procedures, removal of infected prostheses, and other operations of the abdominal aorta). Those with a rupture of the infrarenal abdominal aorta were classified as r-AAA. Finally, patients of the LLR group underwent iliac-femoral, femoral-popliteal, or femoral-tibial artery bypass procedures; removal of infected prostheses; peripheral desobstruction; and other elective peripheral arterial surgical reconstructions.

### Propensity score risk factor matched CAD population

To compare the risk of underlying vascular disease (PAD or CAD) on long-term mortality, we compared the prognosis of patients undergoing vascular surgery (PAD patients) with the survival of a separate group of 15,993 patients diagnosed with severe myocardial ischemia (CAD patients), who were referred to the Erasmus Medical Center in the same period (1993 to 2006) for coronary

**TABLE 31.1** Propensity score risk factor matched peripheral arterial disease (PAD) and coronary artery disease (CAD) population.

| | Before matching | | | After matching‡ | | |
|---|---|---|---|---|---|---|
| | PAD n=2,730 | CAD n=15,993 | p-value | PAD n=2,730 | CAD N=2,730 | p-value |
| Age (yr ± SD) | 66 (± 11) | 61 (± 13) | <0.001 | 66 (± 11) | 66 (± 12) | 1.0 |
| Male (%) | 75 | 72 | <0.001 | 75 | 75 | 1.0 |
| Hypertension (%) | 45 | 33 | <0.001 | 44 | 45 | 0.9 |
| Diabetes mellitus (%) | 15 | 11 | <0.001 | 14 | 12 | 0.8 |
| Smoking (%) | 23 | 24 | 0.008 | 23 | 21 | 0.8 |
| Prior PCI† (%) | 10 | 11 | 0.02 | 10 | 11 | 0.9 |
| Prior CABG* (%) | 19 | 27 | <0.001 | 19 | 22 | 0.4 |
| Prior myocardial infarction (%) | 25 | 38 | <0.001 | 25 | 25 | 1.0 |

*Prior coronary artery bypass graft and prior myocardial infarction; †prior percutaneous coronary intervention; ‡matched for age, gender, year of operation, hypertension, diabetes mellitus, smoking status, prior percutaneous coronary intervention

angioplasty without signs or symptoms of PAD obtained from review of medical records. Because of the differences in baseline characteristics between the PAD and CAD populations, propensity score methodology was used to identify comparable patients with the same risk. First, a propensity score for each patient was constructed, providing an estimate of the propensity toward belonging to 1 patient group versus the other using multivariate logistic regression with the type of population as end point (PAD coded as 0, CAD coded as 1). Included in the analysis were the following available cardiovascular risk factors: age, gender, year of operation, hypertension, diabetes mellitus, smoking status, prior percutaneous coronary intervention, prior coronary artery bypass graft, and prior myocardial infarction (MI). Then, each PAD patient was matched with 1 CAD patient with the same propensity score, rounded off at 2 deciles. The graphical method of examination by box plots showed a balance of the estimated propensity score between PAD and CAD patients within each decile of the propensity score. As a result, the matched CAD population resembled the PAD cohort after matching for cardiovascular risk factors (TABLE 31.1). Finally, a total of 2,730 PAD patients were matched with 2,730 CAD patients.

In addition, medication use (statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors), aspirin, nitrates, and calcium antagonists) of the CAD population was recorded to attempt to explain differences in survival between the PAD and CAD populations.

### Patients' characteristics

For all PAD patients, we recorded age, gender, hypertension (defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, and/or use of antihypertensive medication), diabetes mellitus (the presence of a fasting blood glucose ≥ 140 mg/dl or requirement for insulin or oral hypoglycemic agents), smoking status, hypercholesterolemia (total cholesterol of >200 mg/dl and/or the requirement of lipid-lowering medication), chronic obstructive pulmonary disease according to symptoms and pulmonary function tests (i.e. forced expiratory volume in 1 s <70% of maximal age and gender predictive value), body mass index, renal dysfunction (baseline serum creatinine >1.5 mg/dl), the presence of ischemic heart disease (prior MI, prior coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention) and angina pectoris), heart failure (defined according the New York Heart Association functional classification), and medication (statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, beta-blockers, aspirin, and anticoagulants). All prescription and over-the-counter medications were noted on the day of admission.

### Clinical follow-up and end points

Post-operative clinical information was retrieved from an electronic database of patients followed in our hospital. On occasion, missing data were abstracted retrospectively by reviewing patients' medical records. Routinely, all vascular surgery patients are screened for adverse post-operative outcome by repeated cardiac isoenzyme measurements and electrocardiographic recording. Additional tests are performed at the discretion of the attending physician. After surgery, patients visit the outpatient clinic regularly and are screened for late cardiac events. From the municipal civil registries, we obtained the survival status. At the reference date, January 2007, follow-up was complete in 99.3% of cases. The mean follow-up of the PAD patients was 6.37 ± 4.08 years, the mean follow-up of the CAD patients was 9.17 ± 4.14 years. The primary end point was long-term all-cause mortality in the PAD and CAD populations. The secondary end point was the composite of perioperative mortality and nonfatal events in the PAD population.

### Perioperative and long-term mortality

Perioperative all-cause mortality was defined as death occurring during 30-day in-hospital stay or as death occurring after hospital discharge but within the first 30 days after surgery. Cardiac death was defined as death secondary to MI, heart failure, or arrhythmias. Long-term all-cause mortality was defined as death beyond 30 days after surgery; deaths that occurred in the 30-day period were thus excluded from the long-term period.

The cause of death in the PAD population was grouped into a cerebro-cardiovascular (CCV), a non-CCV, and an unknown cause of death. A CCV death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and included deaths following MI, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular accident or transient ischemic attack), surgery-related bleeding complications (only a post-operative cause of death), and others. Sudden unexpected death was classified as a CCV death. An MI was defined as the presence of 2 out of the following 3 criteria: 1) typical chest pain complaints; 2) electrocardiographic changes including acute ST-segment elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 h, or new ST-segment depression that persisted >24 h; and 3) a positive troponin T (i.e. >0.10 ng/ml) or peak creatinine phosphokinase myocardial band ≥ 8% of an elevated total creatinine phosphokinase with characteristic rise and fall[10]. Non-CCV death was defined as any death with a principal non-CCV cause, including infection, malignancy, respiratory insufficiency, and others. The cause of death was ascertained by reviewing medical records, the computerized hospital database, autopsy reports, or by contacting the referring physician or general practitioner.

### Nonfatal perioperative events in the PAD population

We recorded the following nonfatal complications within 30 days after surgery: infection (such as wound infection, pneumonia, sepsis, and urinary tract infection), MI, arrhythmias, heart failure, stroke, reoperation (percutaneous revascularization or bypass surgery to a vessel that has been treated during the index procedure), hemorrhage (arterial bleeding leading to hypotension (systolic pressure of <100 mm Hg) requiring blood transfusion), thrombectomy, amputation (excluded toe amputation), perioperative renal dysfunction (peak post-operative serum creatinine >+0.5 mg/dl within 3 days after surgery compared with pre-operative serum creatinine), and the requirement of hemodialysis (excluding pre-operative hemodialysis).

## Statistical analysis

Continuous data are described as mean values and standard deviations, and dichotomous data are described as percentage frequencies. The chi-square test was used for categorical variables, and the analysis of variance test was used for continuous variables. Kaplan-Meier survival analysis was used to compare survival times between the PAD and CAD patients and the 4 PAD subgroups, stratified by type of surgery. To test for differences between the resulting curves, the log-rank test was used. For the long-term survival analysis using the Kaplan-Meier method, we included those who died within 30 days after surgery. A univariate Cox proportional hazard regression model was used to explore the association of underlying vascular disease on long-term survival. We used univariate and not multivariate analysis because we matched all PAD and CAD patients for the available baseline cardiovascular risk factors. For this long-term analysis, we included all survivors within 30 days after vascular surgery. Multivariate logistic regression and Cox proportional hazard regression models were used to explore the relationship of major baseline risk factors of all PAD patients undergoing vascular surgery and perioperative all-cause and cardiac death, respectively. Risk factors entered in the risk model were type of operation, age >70 years, gender, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, smoking status, hypercholesterolemia, prior MI, prior heart failure, prior coronary revascularization, prior angina, and renal dysfunction. For the long-term all-cause

**Table 31.2** Baseline characteristics of all patients with peripheral artery disease, according to type of operation.

| Number of patients | All patients 2,730 (100%) | CEA‡ 560 (21%) | AAA* 923 (34%) | r-AAA# 200 (7%) | LLR‖ 1,047 (38%) | p-value |
|---|---|---|---|---|---|---|
| **Demographics** | | | | | | |
| Mean age (± SD) | 66 (± 11) | 65 (± 10) | 66 (± 11) | 71 (± 9) | 65 (± 12) | <0.001 |
| Male (%) | 75 | 73 | 78 | 88 | 72 | <0.001 |
| **Cardiovascular risk factor (%)** | | | | | | |
| Body mass index (± SD) | 25.0 (± 5) | 25.8 (± 3) | 24.9 (± 5) | 25.4 (± 3) | 24.7 (± 4) | 0.006 |
| Current smoker | 24 | 11 | 28 | 14 | 29 | <0.001 |
| Hypertension | 45 | 34 | 53 | 43 | 46 | <0.001 |
| Diabetes Mellitus | 15 | 10 | 13 | 10 | 20 | <0.001 |
| Hypercholesterolemia | 29 | 28 | 37 | 33 | 26 | <0.001 |
| COPD§ | 18 | 7 | 26 | 20 | 17 | <0.001 |
| Renal dysfunction** | 12 | 5 | 13 | 20 | 14 | <0.001 |
| **Disease history (%)** | | | | | | |
| Angina | 15 | 7 | 17 | 14 | 19 | <0.001 |
| Myocardial Infarction | 24 | 9 | 30 | 27 | 31 | 0.01 |
| Coronary revascularization | 24 | 19 | 26 | 20 | 28 | <0.001 |
| Heart failure | 5 | 1 | 6 | 5 | 7 | <0.001 |
| **Medication use (%)** | | | | | | |
| Statins | 26 | 26 | 33 | 19 | 23 | <0.001 |
| Diuretics | 18 | 10 | 18 | 19 | 23 | <0.001 |
| ACE-inhibitors† | 31 | 21 | 35 | 25 | 34 | <0.001 |
| Calcium antagonists | 34 | 27 | 43 | 22 | 32 | <0.001 |
| Nitrates | 19 | 13 | 21 | 14 | 20 | <0.001 |
| Beta-blockers | 33 | 26 | 45 | 22 | 29 | <0.001 |
| Aspirin | 40 | 73 | 33 | 28 | 32 | <0.001 |
| Anti-coagulation | 20 | 6 | 17 | 10 | 33 | <0.001 |

*AAA= elective infrarenal abdominal aortic surgery; †ACE-inhibitors= angiotensin-converting-enzyme inhibitors; ‡CEA= carotid endarterectomy; §COPD= chronic obstructive pulmonary disease; ‖LLR= lower limb arterial reconstruction procedures; #r-AAA= acute infrarenal abdominal aortic surgery; **renal dysfunction= baseline serum creatinine >1.5 mg/dl

and cardiac mortality, multivariate Cox proportional hazards regression analysis was performed and included also all nonfatal perioperative complications.

All univariate risk factors with a p value of <0.10 were entered in the perioperative and long-term multivariate analysis, resulting in an adjusted significant odds and hazard ratios (ORs and HRs) or as not significant. Unadjusted and adjusted ORs and HRs were reported with corresponding 95% confidence intervals (CIs). A p value of <0.05 was considered to be significant. All computations were performed with SPSS software version 12.0.1 (SPSS Inc., Chicago, Illinois), running under Windows 2000 Professional (Microsoft, Redmond, Washington).

## RESULTS

### Patient characteristics

The mean age of all patients with PAD (n = 2,730) was 66 ± 11 years and 76% were male. A total of 560 patients (20%) underwent CEA surgery; 923 patients (34%) underwent AAA surgery (aortic-to-aortic n = 206, aortic bifurcation n = 624, infected prostheses n = 51, and others n = 42); 200 patients (7%) had a r-AAA; and 1,047 patients (38%) underwent LLR surgery (iliac-femoral n = 208, femoral-popliteal n =6 03, femoral-tibial n = 203, and infected prostheses n = 33). Patient's characteristics are presented in TABLE 31.2.

### Primary end point

Compared with CAD patients, patients with PAD had a significantly worse long-term prognosis (unadjusted HR 2.40, 95% CI 2.18 to 2.65) (FIGURE 31.1). Annual mortality rates of the PAD and CAD populations were 5.7% and 3.0% per year (p < 0.001). Importantly, patients with CAD received more cardiac medications than the PAD patients did (beta-blockers 74% vs. 34%, calcium antagonists 52% vs. 33%, aspirin 88% vs. 40%, nitrates 37% vs. 19%, statins 67% vs. 29%, and ACE inhibitors 57% vs. 31%, respectively) (FIGURE 31.2).

### Secondary end point

Within 30 days after surgery, a total of 153 PAD patients (5.6%) died. The overall mortality of the CEA, AAA, r-AAA, and LLR groups was 8 (1.4%), 58 (6.3%), 57 (28.5%), and 30 (2.9%) (p<0.001), respectively. The leading causes of death were CCV events (76%) (TABLE 31.3). Specified according to the type of surgery, the leading cause of death at 30 days for CEA patients was stroke (38%), for AAA was MI (24%), for r-AAA was fatal bleeding (40%), and for LLR was infection (33%). Outcomes at 30 days of patients undergoing CEA or LLR were superior to patients undergoing AAA surgery (FIGURE 31.3). Patients scheduled for r-AAA surgery had the worst 30-day outcome. Also, in the multivariate Cox proportional hazards regression analysis, the type of operation was an important independent risk factor for perioperative all-cause mortality and cardiac events (TABLE 31.4).

A total of 1,353 (52.5%) patients with PAD died during 6.37 ± 4.08 years of follow-up, excluding the 153 patients who died within 30 days post-operatively. Mortality rates among the different surgical procedures were 216 (39.1%), 470 (54.3%), 87 (60.8%), and 580 (57.0%) for CEA, AAA, r-AAA, and LLR, respectively. Annual mortality rates of CEA, AAA, LLR, and r-AAA are 5.0%, 5.9%, 5.9%, and 6.8% per year (log rank p < 0.001), respectively. The leading cause of death was CCV (46%). Myocardial infarction accounts for 19% of all causes of long-term mortality. During long-term follow-up, patients of the LLR group had a similar prognosis compared with the AAA group (log rank p = 0.70), but patients of the r-AAA group had the worst outcome (FIGURE 31.1). However, the multivariate Cox

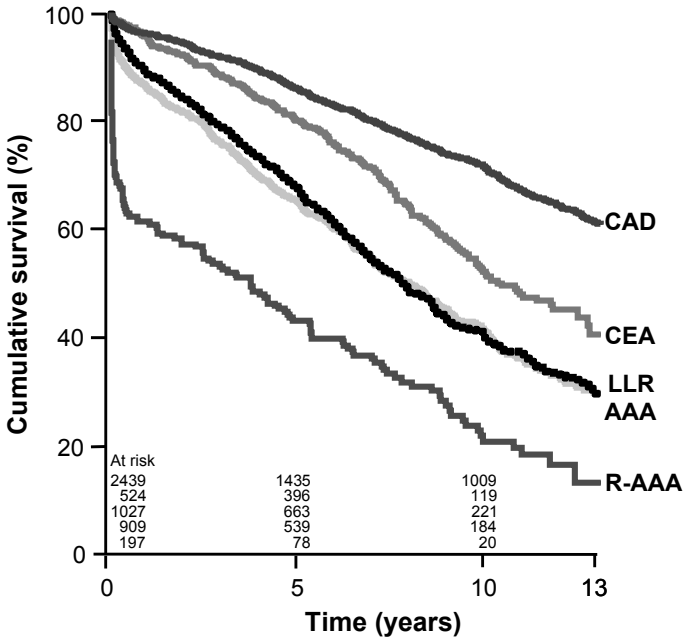


**FIGURE 31.1** Kaplan-Meier estimate of long-term survival of CAD and different types of peripheral surgical patients. To test for differences between the resulting curves, the log-rank test was used. AAA = elective infrarenal abdominal aortic surgery; CAD = coronary artery disease; CEA = carotid endarterectomy; LLR = lower limb arterial reconstruction; r-AAA = acute infrarenal AAA.



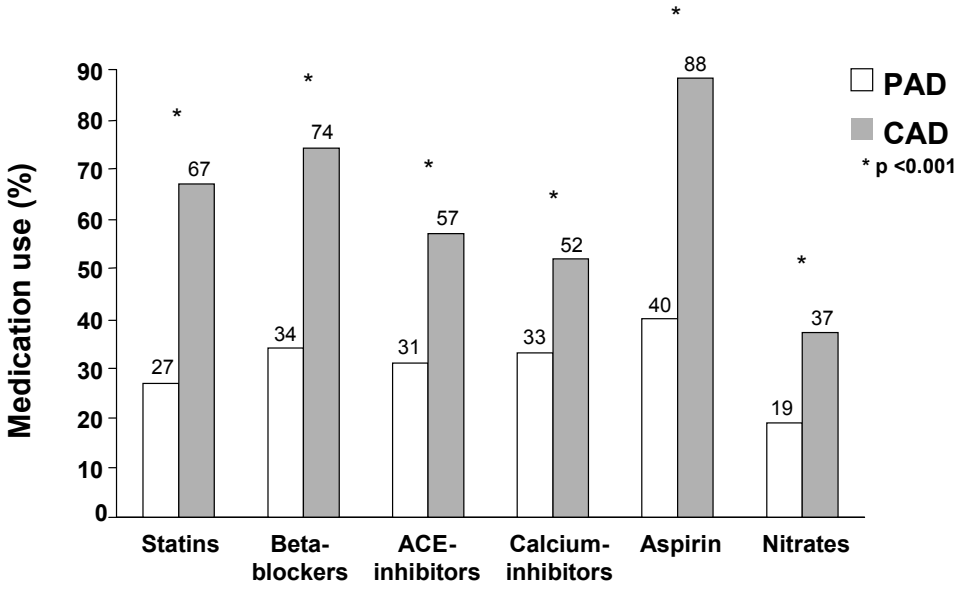


**FIGURE 31.2** Medication use according to PAD and CAD patients.
ACE = angiotensin-converting enzyme; PAD = peripheral arterial disease; other abbreviation as in figure 31.1.

**TABLE 31.3** Cause of death during the perioperative and long-term period.

| Number of patients | All patients 2,730 (100%) | CEA‡ 560 (21%) | AAA* 923 (34%) | r-AAA# 200 (7%) | LLR§ 1,047 (38%) | p-value |
|---|---|---|---|---|---|---|
| **Perioperative mortality** | **153 (6)** | **8 (1)** | **58 (6)** | **57 (29)** | **30 (3)** | |
| Total CCV† death – no. (%) | 116 (76) | 6 (75) | 45 (78) | 46 (81) | 19 (63) | 0.3 |
| Myocardial infarction | 28 (18) | 2 (25) | 14 (24) | 6 (11) | 6 (20) | 0.3 |
| Congestive heart failure | 15 (10) | 0 (0) | 7 (12) | 4 (7) | 4 (13) | 0.5 |
| Arrhythmia | 15 (10) | 0 (0) | 4 (7) | 7 (12) | 4 (13) | 0.5 |
| Stroke | 9 (6) | 3 (38) | 3 (5) | 3 (5) | 1 (3) | 0.001 |
| Fatal bleeding | 40 (26) | 1 (13) | 13 (22) | 23 (40) | 3 (10) | 0.01 |
| Other | 9 (6) | 0 (0) | 5 (9) | 3 (5) | 1 (3) | 0.6 |
| Total n-CCV‖ death – no. (%) | 37 (24) | 2 (25) | 13 (22) | 11 (19) | 11 (37) | 0.3 |
| Infection | 22 (14) | 0 (0) | 4 (7) | 8 (14) | 10 (33) | 0.005 |
| Malignancy | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | NA |
| Respiratory insufficiency | 9 (6) | 2 (25) | 4 (7) | 2 (4) | 1 (3) | 0.1 |
| Others | 6 (4) | 0 (0) | 5 (9) | 1 (2) | 0 (0) | 0.1 |
| Unknown – no. (%) | 0 (0) | NA | NA | NA | NA | NA |
| **Long-term mortality**** | **1,353 (53)** | **216 (39)** | **470 (54)** | **87 (61)** | **580 (57)** | |
| Total CCV death – no. (%) | 625 (46) | 91 (42) | 203 (43) | 36 (41) | 295 (51) | 0.03 |
| Myocardial infarction | 250 (19) | 31 (14) | 85 (18) | 15 (17) | 119 (21) | 0.2 |
| Congestive heart failure | 168 (12) | 28 (13) | 41 (9) | 10 (12) | 89 (15) | 0.01 |
| Arrhythmia | 26 (2) | 2 (1) | 11 (2) | 3 (3) | 10 (2) | 0.4 |
| Stroke | 96 (7) | 22 (10) | 33 (7) | 5 (7) | 35 (6) | 0.2 |
| Others | 85 (6) | 8 (4) | 33 (7) | 2 (2) | 42 (7) | 0.1 |
| Total n-CCV death – no. (%) | 412 (31) | 66 (31) | 150 (32) | 30 (35) | 166 (29) | 0.6 |
| Infection | 78 (6) | 4 (2) | 26 (6) | 7 (8) | 41 (7) | 0.03 |
| Malignancy | 153 (11) | 32 (15) | 54 (12) | 7 (8) | 60 (10) | 0.2 |
| Respiratory insufficiency | 85 (6) | 9 (4) | 31 (7) | 10 (12) | 35 (6) | 0.1 |
| Others | 96 (7) | 21 (10) | 39 (8) | 6 (7) | 30 (5) | 0.09 |
| Unknown – no. (%) | 316 (23) | 59 (27) | 117 (25) | 21 (24) | 119 (21) | 0.2 |

*AAA= elective infrarenal abdominal aortic surgery; †CCV=cerebro-cardiovascular; ‡CEA= carotid endarterectomy; §LLR= lower limb arterial reconstruction procedures; ‖nCCV= non-cerebro-cardiovascular; #r-AAA= acute infrarenal abdominal aortic surgery; **Excluding those patients who died within the postoperative period (n=153)

proportional hazards regression analysis illustrated that, converse to the perioperative outcome, the type of surgery was not related to outcome during long-term follow-up (TABLE 31.5). The proportional hazards assumptions were tested by constructing interaction terms between the variables and time to each end point. The Cox proportional hazards regression analyses showed no statistically significant interaction with time (each p value >0.05).

Long-term all-cause outcome was affected by age, smoking, chronic obstructive pulmonary disease, MI, renal dysfunction, and non-cardiac complications (infection, stroke, and amputation). Preoperative cardiac risk factors (age >70 years, diabetes mellitus, prior MI, coronary revascularization, heart failure) and perioperative nonfatal cardiac complications (MI, heart failure, arrhythmia) were the primary determinants of long-term adverse cardiac outcome.

**TABLE 31.4** Multivariate associations of baseline characteristics with all-cause and cardiac mortality in the perioperative period.

| | Perioperative all-cause mortality | | Perioperative cardiac death[†] | |
|---|---|---|---|---|
| Risk factor | OR Univariate (95% CI) | OR Multivariate (95% CI) | OR Univariate (95% CI) | OR Multivariate (95% CI) |
| Operation group | | | | |
| LLR[‖] (reference) | 1.0 | 1.0 | 1.0 | 1.0 |
| r-AAA[#] | 13.51 (8.40 – 21.74) | 12.22 (7.46 – 20.04) | 6.86 (3.32 – 14.15) | 6.21 (2.94 – 13.12) |
| AAA[*] | 2.27 (1.45 – 3.57) | 2.00 (1.27 – 3.16) | 2.05 (1.06 – 3.97) | 1.89 (1.01 – 3.68) |
| CEA[‡] | 0.49 (0.22 – 1.07) | NS | 0.26 (0.06 – 1.17) | NS |
| Sex | 1.19 (0.80 – 1.77) | NS | 1.40 (0.72 – 2.72) | NS |
| Age >70 year | 2.31 (1.66 – 3.21) | 1.55 (1.09 – 2.21) | 2.57 (1.50 – 4.39) | 1.95 (1.12 – 3.39) |
| Hypertension | 1.50 (1.08 – 2.09) | 1.55 (1.08 – 2.22) | 1.72 (1.02 – 2.92) | NS |
| COPD[§] | 2.39 (1.68 – 3.40) | 2.05 (1.40 – 3.01) | 2.06 (1.17 – 3.62) | NS |
| Diabetes Mellitus | 1.13 (0.73 – 1.76) | NS | 1.20 (0.60 – 2.40) | NS |
| Hypercholesterolemia | 0.71 (0.40 – 1.23) | NS | 0.83 (0.36 – 1.96) | NS |
| Current Smoker | 1.10 (0.73 – 1.68) | NS | 0.88 (0.43 – 1.81) | NS |
| Myocardial infarction | 1.22 (0.80 – 1.89) | NS | 1.41 (0.80 – 2.47) | NS |
| Coronary revascularization | 0.54 (0.34 – 0.84) | NS | 0.65 (0.33 – 1.28) | NS |
| Heart failure | 1.26 (0.65 – 2.34) | NS | 2.50 (1.12 – 5.61) | NS |
| Angina | 1.11 (0.60 – 2.03) | NS | 1.27 (0.55 – 2.96) | NS |
| Renal dysfunction[**] | 2.61 (1.77 – 3.84) | 2.09 (1.38 – 3.18) | 2.88 (1.60 – 5.19) | 2.11 (1.15 – 3.88) |

[*]AAA= elective infrarenal abdominal aortic surgery; [†]cardiac death= death because of mycardial infarction, heart failure and arrhythmia; [‡]CEA= carotid endarterectomy; [§]COPD= chronic obstructive pulmonary disease; [‖]LLR= lower limb arterial reconstruction procedures; [#]r-AAA= acute infrarenal abdominal aortic surgery; [**]renal dysfunction=baseline serum creatinine >1.5 mg/dl



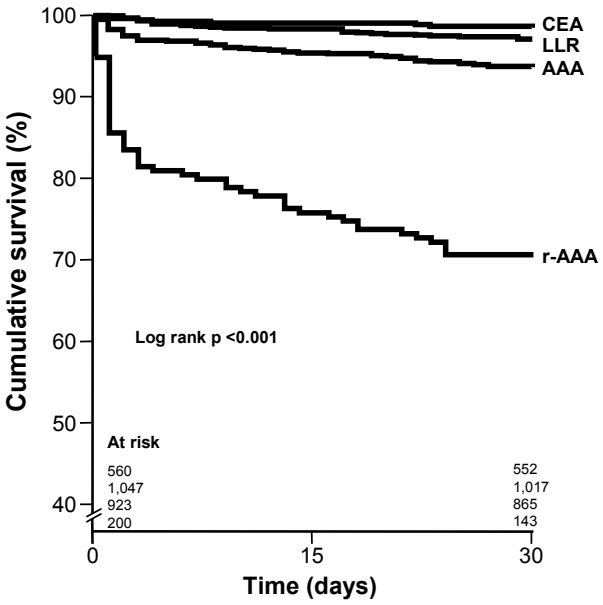


**FIGURE 31.3** Kaplan-Meier estimate of overall perioperative (30-day) survival of different types of surgical patients. To test for differences between the resulting curves, the log-rank test was used. Abbreviations as in figure 31.1.

**TABLE 31.5** Multivariate associations of baseline characteristics and non-fatal perioperative complications with long-term all-cause and cardiac mortality.

| | Long-term all-cause mortality | | Long-term cardiac death[†] | |
|---|---|---|---|---|
| | HR Univariate (95% CI) | HR Multivariate (95% CI) | HR Univariate (95% CI) | HR Multivariate (95% CI) |
| **Baseline risk factors** | | | | |
| Operation group | | | | |
| LLR[‖] (reference) | 1.0 | 1.0 | 1.0 | 1.0 |
| r-AAA[#] | 1.29 (1.03 – 1.62) | NS | 1.11 (0.75 – 1.64) | NS |
| AAA[*] | 0.97 (0.86 – 1.09) | NS | 0.75 (0.61 – 0.93) | NS |
| CEA[‡] | 0.66 (0.57 – 0.78) | NS | 0.50 (0.38 – 0.67) | NS |
| Sex | 1.15 (1.01 – 1.30) | NS | 1.13 (0.91 – 1.41) | NS |
| Age > 70 year | 2.18 (1.96 – 2.43) | 2.11 (1.88 – 2.36) | 2.00 (1.65 – 2.41) | 2.02 (1.66 – 2.47) |
| Hypertension | 1.15 (1.03 – 1.28) | NS | 1.18 (0.98 – 1.42) | NS |
| COPD[§] | 1.60 (1.41 – 1.81) | 1.49 (1.29 – 1.71) | 1.29 (1.02 – 1.63) | NS |
| Diabetes Mellitus | 1.32 (1.14 – 1.52) | NS | 1.87 (1.50 – 2.34) | 1.47 (1.16 – 1.87) |
| Hypercholesterolemia | 1.06 (0.93 – 1.22) | NS | 1.38 (1.10 – 1.72) | NS |
| Current Smoker | 1.30 (1.16 – 1.46) | 1.20 (1.06 – 1.36) | 1.44 (1.18 – 1.76) | NS |
| Myocardial infarction | 1.43 (1.28 – 1.62) | NS | 2.59 (2.15 – 3.13) | 1.59 (1.26 – 2.01) |
| Coronary revascularization | 1.08 (0.96 – 1.22) | NS | 2.17 (1.80 – 2.62) | 1.61 (1.30 – 1.99) |
| Heart failure | 1.74 (1.41 – 2.14) | NS | 2.94 (2.19 – 3.94) | 1.45 (1.04 – 2.01) |
| Angina | 1.26 (1.10 – 1.45) | NS | 2.22 (1.81 – 2.73) | 1.21 (1.01 – 1.59) |
| Renal dysfunction[**] | 2.23 (1.83 – 2.47) | 1.72 (1.47 – 2.02) | 2.31 (1.80 – 2.96) | 1.60 (1.22 – 2.09) |
| **Postoperative complications** | | | | |
| Non-fatal myocardial infarction | 1.45 (1.19 – 1.76) | NS | 4.07 (2.17 – 7.63) | 2.22 (1.15 – 4.28) |
| Heart failure | 2.20 (1.47 – 3.29) | NS | 3.36 (1.89 – 5.96) | 1.86 (1.01 – 3.43) |
| Arrhythmia | 2.04 (1.41 – 2.98) | 1.65 (1.12 – 2.43) | 2.41 (1.33 – 4.40) | 1.86 (1.00 – 3.52) |
| Infection | 1.75 (1.52 – 2.02) | 1.51 (1.31 – 1.76) | 1.51 (1.17 – 1.96) | NS |
| Stroke | 2.05 (1.55 – 2.72) | 1.98 (1.47 – 2.67) | 1.57 (0.90 – 2.73) | NS |
| Amputation | 2.03 (1.58 – 2.61) | 1.74 (1.33 – 2.29) | 1.50 (0.84 – 2.68) | NS |
| Hemorrhage | 1.24 (0.99 – 1.57) | NS | 0.95 (0.60 – 1.50) | NS |
| Trombectomy | 1.14 (0.87 – 1.48) | NS | 1.45 (0.96 – 2.19) | NS |
| Re-operation | 1.30 (0.98 – 1.74) | NS | 1.49 (0.93 – 2.39) | NS |
| Acute Renal failure[††] | 1.81 (1.54 – 2.12) | 1.44 (1.21 – 1.73) | 1.73 (1.31 – 2.29) | 1.39 (1.01 – 1.92) |
| Hemodialysis[‡‡] | 2.95 (1.98 – 4.38) | 1.67 (1.06 – 2.63) | 3.13 (1.61 – 6.06) | NS |

[*]AAA= elective infrarenal abdominal aortic surgery; [†]cardiac death= death because of myocardial infarction, heart failure and arrhythmia; [‡]CEA= carotid endarterectomy; [§]COPD= chronic obstructive pulmonary disease; [‖]LLR= lower limb arterial reconstruction procedures; [#]r-AAA= acute infrarenal abdominal aortic surgery; [**]renal dysfunction=baseline serum creatinine >1.5 mg/dl; [††]renal failure= peak post-operative serum creatinine > + 0.5 mg/dl (> 44 umol/L) within three days after surgery compared with preoperative serum creatinine [‡‡]Excluding patients who were on preoperative dialysis

## DISCUSSION

Our main finding of this study is that patients with PAD, compared with a matched population for cardiac risk factors and year of treatment with CAD, are at increased risk for long-term mortality. In addition, PAD patients receive less cardiovascular medical therapy (e.g. beta-blockers, statins, ACE inhibitors, calcium antagonists, nitrates, and aspirin) than CAD patients do.

Furthermore, we conclude that CCV death is the major cause of perioperative and long-term mortality among vascular surgical patients with PAD (76% and 46%, respectively). Cardiac risk factors and perioperative cardiac complications are associated with long-term cardiac death, but non-cardiac complications including infection, stroke, amputation, acute renal failure, and dialysis dependency are mainly related with all-cause mortality.

The type of vascular surgery was found to be an independent risk factor for an adverse outcome in the perioperative period but not during the long-term follow-up. The long-term prognosis of patients undergoing acute repair of the ruptured abdominal aorta is similar to patients undergoing elective AAA surgery, contrary to the perioperative period. Similar results were observed by Soisalon-Soininen et al.[11] among 1,070 patients undergoing repair of ruptured and nonruptured abdominal aorta aneurysms.

Aggressive treatment of atherosclerotic risk factors (i.e. hypertension, diabetes mellitus, smoking, and hypercholesterolemia) and usage of cardioprotective medications (i.e. beta-blockers, statins, aspirin, and ACE inhibitors) are recommended for PAD patients, because they are associated with improved long-term survival[12-14]. However, in our matched PAD and CAD population for cardiovascular risk factors, we clearly observed an underuse of cardiac medication among patients with PAD. McDermott et al.[8] reported that patients with CAD, compared with PAD patients, are treated more frequently with aspirin and lipid-lowering medication (82% vs. 37% and 56% vs. 40%, respectively). Overall, the undertreatment of PAD patients can explain their worse long-term outcome when compared with CAD patients.



Peripheral atherosclerotic disease is becoming an increasingly important health issue in Western society; it affects between 8 to 12 million adults[15]. The introduction of endovascular repair has the potential to improve the outcome for PAD patients undergoing non-cardiac surgery because of its reduced perioperative myocardial stress[16]. This technique is currently considered as a promising alternative, especially in high-risk cardiac patients. In addition, new cardioprotective strategies, including medical therapy[17] and prophylactic coronary interventions[18], are currently being evaluated in these patients. Though the preliminary results of endovascular repair are promising and associated with improved immediate post-operative outcome, the beneficial effect on long-term survival remains controversial[3,19,20]. We described the results of open surgery in a tertiary hospital in relation to long-term outcome of patients undergoing different types of vascular surgery. The results of this study will provide useful information to compare long-term outcome between open and endovascular surgery.

We do think that propensity matching is appropriate in this study setting. In this study, we deal with patients with the same underlying disease, namely generalized atherosclerosis. However, patients with PAD present themselves with different clinical symptoms (e.g. claudication), compared with the more cardiac-related complications (e.g. angina) observed in CAD patients. We used the propensity score to compare survival of patients with generalized atherosclerosis with the same risk profile with 2 different treatments (PAD or CAD).

*Study limitations*

First, the study is not a randomized clinical trial but an observational study of a propensity-matched cohort. Despite using propensity to adjust as much as possible for the bias inherent in the decision about being PAD or CAD patients, we cannot exclude the possibility of residual confounding. As can be seen in TABLE 31.1, the PAD and CAD populations differed significantly, and by using the propensity

score matching procedure, the resulting matched CAD cohort ultimately reassembled the PAD cohort. We did not match the PAD and CAD database with the risk factor hypercholesterolemia, because of the inconsistency of the CAD database regarding the reporting of hypercholesterolemia during the early stage of our study period. Second, although data were prospectively collected, this analysis is retrospective. Because of the acute setting of r-AAA patients, not all the baseline characteristics were completely recorded in the admission data, which might result in an underdiagnosis of some risk factors. Third, changes in the perioperative management have evolved markedly over time and were not taken into account in our analysis. These include multiple factors ranging from preoperative management, such as drug therapy, to anesthesiological and surgical techniques to intensive post-surgical care management. We tried to adjust for this confounding by adding the year of operation in our multivariate analysis (as a categorical variable per 2 years). We did not investigate our results across different time periods, because we did not observe different perioperative (30-day) outcomes in the PAD database over time. Finally, in our cohort, we found a remarkably low incidence of diabetes mellitus (15%). The diagnosis of diabetes mellitus was based on the requirement for insulin therapy, hypoglycemic agents, or as fasting blood glucose ≥ 140 mg/dl. In patients qualified as nondiabetics with PAD, fasting glucose levels may be normal, and the diagnosis of diabetes is only made after a glucose loading test. Unfortunately, we did not routinely perform a loading test for patients with a normal fasting glucose. Therefore, the number of diabetics might be underestimated.

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# Chapter 32

## Temporary worsening of renal function after aortic surgery is associated with higher long-term mortality

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## ABSTRACT

**Background:** Little is known about acute changes of renal function in the postoperative period, and outcome of patients undergoing major vascular surgery. Specifically, data are scarce in patients in whom renal function is temporarily decreased and returns to baseline at 3 days after surgery.

**Methods:** 1324 patients who underwent elective open abdominal aortic aneurysm surgery in a single center were studied. Renal function (creatinine clearance, CrCl) was measured preoperatively and on days 1, 2 and 3 after surgery. Patients were divided into 3 groups: (1) improved or unchanged (ΔCrCl ± 10% function compared to baseline value); (2) temporary worsening (worsening >10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3); (3) persistent worsening (>10% decrease compared to baseline value). Outcome measure was all-cause mortality.

**Results:** 30-day mortality was 1.3%, 5.0% and 12.6% in the three groups, respectively. Adjusted for baseline characteristics and postoperative complications, 30-day mortality was the highest in patients with a persistent worsening of renal function (hazard ratio [HR]: 7.3, 95% confidence interval [CI]: 2.7-19.8), followed by those with temporary worsening (HR: 3.7, 95%CI: 1.4-9.9). During 6.0 ± 3.4 years follow-up, 348 (36.5%) patients died. The risk of late mortality was 1.7 (95%CI: 1.3-2.3) in the persistent worsening group followed by those with temporary worsening (HR: 1.5, 95%CI: 1.2-1.4).

**Conclusions:** Although renal function may recover completely after aortic surgery temporary decreased renal function was associated with an increased long-term mortality.

## INTRODUCTION

Atherosclerosis is a generalized disease with symptoms ranging from angina pectoris, myocardial infarction, stroke to claudication. The major cause of abdominal aortic aneurysm [AAA] is atherosclerosis and is frequently associated with impaired organ function, a true determinant of long-term survival following surgery[1]. Renal dysfunction with or without symptoms is often present, and is considered to be a marker for the presence and severity of underlying vascular disease[2-4]. Postoperative decreased renal function is a well known feared complication after major vascular surgery and associated with increased long-term mortality[5,6]. The incidence rate varies between 2 to 45% (ranging from mild renal dysfunction to chronic hemodialysis)[6-9]. The pathogenesis of postoperative decreased renal function is multifactorial[10]. Poor baseline renal function, perioperative blood loss, use of nephrotoxic agents, suprarenal aortic cross-clamping time, high intraabdominal pressure, systemic or regional hypoperfusion, temporary hypotension and ligation of renal veins during surgery all negatively affect postoperative renal function. All these factors combined can cause acute renal failure with a high periprocedural mortality rate of 50–80%[11-13]. In patients with abnormal kidney function at baseline, postoperative chronic renal dysfunction requiring renal replacement therapy is common. In order to prevent this devastating complication, it is recommended to take every possible measure to minimize the risk[5,11,14]. Importantly, even subtle changes in postoperative renal function might identify patients at risk.

However, little is known about acute changes of renal function in the postoperative period, and its short and long-term outcome of patients undergoing major vascular surgery. Specifically, data are scarce in patients in whom renal function is temporarily decreased and returns to baseline value within three days after surgery; i.e. temporary worsening of renal function. Hence, the purpose of this observational study was to describe the predictive value of postoperative renal function changes, especially in those with temporary worsening of renal function, of patients undergoing AAA surgery.

## METHODS

### Study design and patient selection

Between January 1995 and June 2006, 1 324 patients underwent open infrarenal abdominal aortic aneurysm [AAA] repair at the Erasmus Medical Centre, Rotterdam, the Netherlands and were entered into a computerized database. Exclusion criteria were patients with a baseline creatinine clearance of <30 mL/min (0.5 mL/s), those on chronic hemodialysis, patients who died within three days after surgery, endovascular surgery and patients who required additional renal revascularization.

### Renal function assessment

Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method[15]. The renal function or creatinine clearance [CrCl] was computed with the Cockcroft and Gault formula from serum creatinine, age, gender and body weight. The following equation was used: Creatinine clearance (CrCl, mL/min/1.73m$^2$) = (140 – age/years) * (body weight/kg)/72 * serum creatinine (mg/dL), multiplied by 0.85 in women[16].
This equation gives a more accurate assessment of renal function than serum creatinine alone[17-19].

### Renal function groups

The serum creatinine (mg/dL) was measured preoperatively at baseline, and postoperatively at day 1, day 2 and day 3. Patients were divided into three groups, based on changes in estimated CrCl from baseline to day 1 or 2 and from day 1 or 2 to day 3: group 1: improved or unchanged renal function (ΔCrCl between -10% to +10% function compared to baseline value); group 2: temporary worsening of renal function (temporary worsening of >10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3); group 3: persistent worsening of renal function (>10% decrease compared to baseline value). Baseline creatinine clearance was defined as the value recorded just before surgery, when data were not available, the measurements in the preceding days before surgery were used.

### Clinical follow-up and end points

Perioperative clinical information was retrieved from an electronic database of patients maintained in our hospital. On occasion, missing data were abstracted retrospectively by reviewing patients' medical records. From the municipal civil registries, we obtained the survival status. The follow-up was complete in 98.2%. The primary outcome was overall 30-day and long-term all-cause mortality after AAA surgery, verified by contacting the patient's primary physician and reviewing medical records. Mortality at 30 days was defined as all deaths occurring during postoperative in-hospital stay or after hospital discharge but within the first 30 days after surgery. Long-term mortality was defined as death occurring in the first ten years after surgery. The causes of death were grouped into 3 different categories: (1) cerebro-cardiovascular death [CCVD], (2) non-cerebrocardiovascular death [non-CCVD] and (3) unknown cause of death. Cerebro-cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and included deaths following myocardial infarction (MI), serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke [cerebro vascular accident (CVA) or transient ischemic attack (TIA)], surgery-related fatal bleeding complications and others. Sudden unexpected death was classified as a CCVD. Non-CCVD was defined as any death with a principal non-cerebro-cardiovascular cause, including infection, malignancy, respiratory insufficiency and others. The cause of death was ascertained by reviewing medical records, the computerized hospital database, autopsy reports, or by contacting the referring physician or general practitioner. The secondary outcome was short-term complications (perioperative and during postoperative in-hospital stay within 30 days or after hospital discharge but within the first 30 days after surgery). The complications noted are infection, stroke, coronary revascularization [coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)], heart failure, limb amputation, limb necrosis, hemorrhage (vascular bleeding leading to a hypotensive state (systolic pressure of <100 mmHg) and requirement of blood transfusions) and new postoperative dialysis (temporary or persistent).

### Statistical analyses

Continuous data are described as mean values and its standard deviation (±SD) or as median (and corresponding interquartile range), and dichotomous data are described as percentage frequencies. The analysis of variance (ANOVA) with Bonferroni test was used for continuous variables and chi-square test was used for categorical variables. The probability of all-cause mortality was calculated by the Kaplan-Meier method and the resulting curves were compared by the log rank test. We performed multivariate Cox regression analyses to investigate the independent value of CrCl for perioperative and long-term mortality, after adjustment for age, gender, cardiovascular risk factors [e.g. hypertension (defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or use of cardiovascular medication), diabetes mellitus (the presence of a fasting blood glucose ≥ 140 mg/dl (≥ 7.8 mmol/L) or requirement for insulin or oral hypoglycemic agents), smoking status, hypercholesterolemia [total cholesterol of > 200 mg/dl (> 5.2 mmol/L)], chronic obstructive pulmonary

disease (COPD), according to symptoms and pulmonary function tests (i.e. forced expiratory volume in one second (FEV1) <70% of maximal age and gender predictive value), body mass index (BMI) and medication usage (statins, diuretics, angiotensin-converting-enzyme inhibitors, calcium antagonists, nitrates, beta-blockers, digitalis and aspirin), presence of ischemic heart disease (prior myocardial infarction, prior coronary revascularization and angina pectoris), heart failure (defined according to the New York Heart Association classification), baseline creatinine clearance and short-term complications (infection, stroke, coronary intervention, heart failure, amputation, limb necrosis, hemorrhage and dialysis requirement). All prescription and over-the-counter medications were noted on the day of admission. Data are presented as Hazard Ratios [HRs] with 95% confidence intervals [CIs]. A p value of <0.05 was considered significant. The proportional hazards assumptions were tested by constructing interaction terms between the variables and time to each end-point. Cox regression analyses showed no statistically significant interaction with time (each p value >0.05). All computations were performed with SPSS software version 12.0.1 (SPSS Inc., Chicago, Illinois, USA), running under Windows 2000 Professional.

## RESULTS

### Patient characteristics

A total of 1 324 patients underwent AAA surgery. After exclusion of patients with a preoperative creatinine clearance of <30 mL/min (0.5 mL/s) (n=86), those on chronic hemodialysis (n=8), endovascular surgery (n=236), those patients who died within three days after surgery (n=31) and patients who required additional renal revascularization (n=11), the population included in the analysis was 952 patients. Of 28 (2.9%) patients, missing data were abstracted by reviewing patients' medical records. Mean age was 66 ± 14 years and 80% were men. Improved or unchanged renal function, temporary worsening of renal function and persistent worsening of renal function were present in 56%, 27% and 17% of the patient's population, respectively. In the whole population, a slight decrease in CrCl was observed within three days after surgery (mean CrCl day 1 or 2 after surgery is 76 ± 40 ml/min (1.27 ± 0.67 mL/s), on day 3 it was noticed to be 77 ± 44 ml/min (1.28 ± 0.73 mL/s), compared with a preoperative CrCl of 81 ± 34 ml/min (1.35 ± 0.57 mL/s). Mean changes in CrCl on day 1 or 2 and on day 3 for the temporary and persistent worsening of renal function groups were -30%/-7% and -35%/-46% compared with baseline value, respectively (FIGURE 32.1). The baseline characteristics in

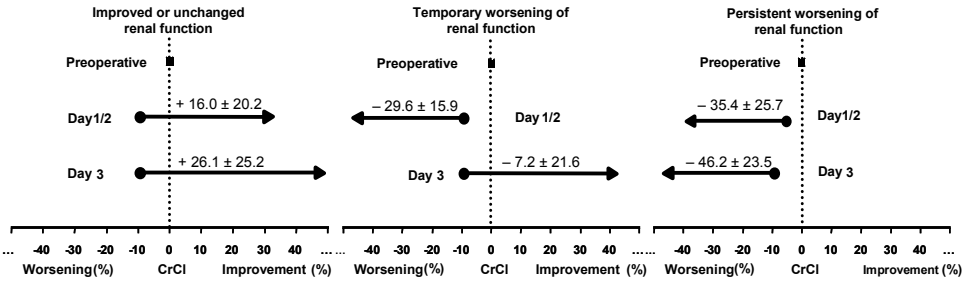


**FIGURE 32.1** Subdivision of the renal function groups, based on the creatinine clearance [CrCl] response, with mean changes of CrCl (% ± SD).
Improved or unchanged renal function: Δ creatinine clearance between –10% to +10% function compared to baseline value; temporary worsening of renal function: temporarily worsening >10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3; persistent worsening of renal function:>10% decrease compared to baseline value.

the three groups were similar for renal function and cerebro-cardiovascular risk factors (TABLE 32.1). Only a higher incidence of hypertension was observed in the temporary and persistent worsening renal function groups. A significant association between total perioperative blood loss and suprarenal aortic cross-clamping time was found with worsening of renal function (p <0.001). No significant difference in aortic cross-clamping time between the temporary and persistent worsening renal function group was observed (p=0.3).

**TABLE 32.1** Baseline characteristics of the abdominal aortic aneurysm group.

| | All patients 952 (100%) | Improved or unchanged renal function 535 (56%) | Temporary worsening of renal function 258 (27%) | Persistent worsening of renal function 159 (17%) | p-value |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Mean age (± SD) | 66 (± 14) | 65 (± 14) | 67 (± 14) | 66 (± 14) | 0.1 |
| Male (%) | 79 | 80 | 76 | 83 | 0.2 |
| **Cardiovascular risk factor (%)** | | | | | |
| Hypertension | 41 | 36 | 47 | 50 | <0.001 |
| Diabetes Mellitus | 6 | 6 | 5 | 9 | 0.3 |
| Current smoker | 31 | 30 | 33 | 31 | 0.8 |
| Elevated cholesterol | 23 | 23 | 28 | 16 | 0.1 |
| COPD† | 21 | 19 | 23 | 26 | 0.1 |
| Body mass index (± SD) | 25 (± 4) | 25 (± 4) | 25 (± 4) | 26 (± 3) | 0.1 |
| Baseline serum creatinine (mg/dl) (± SD) | 1.0 (± 0.3) | 1.0 (± 0.3) | 1.0 (± 0.3) | 1.1 (± 0.3) | 0.5 |
| Baseline creatinine clearance (mL/min) (± SD) | 81 (± 34) | 80 (± 30) | 80 (± 36) | 83 (± 41) | 0.7 |
| **Disease history (%)** | | | | | |
| Previous MI‡ | 30 | 28 | 31 | 37 | 0.3 |
| Previous CABG* | 14 | 14 | 16 | 12 | 0.5 |
| Previous PCI° | 6 | 6 | 7 | 5 | 0.8 |
| Previous heart failure | 5 | 5 | 4 | 6 | 0.6 |
| Angina | 15 | 15 | 12 | 16 | 0.6 |
| **Medication use (%)** | | | | | |
| Statins | 23 | 22 | 27 | 23 | 0.3 |
| Diuretics | 12 | 10 | 14 | 13 | 0.2 |
| ACE-inhibitors¯ | 24 | 22 | 25 | 29 | 0.2 |
| Calcium antagonists | 30 | 27 | 35 | 33 | 0.07 |
| Nitrates | 15 | 16 | 13 | 17 | 0.4 |
| Beta-blockers | 34 | 34 | 33 | 37 | 0.7 |
| Digitalis | 3 | 2 | 4 | 3 | 0.6 |
| Aspirin | 21 | 22 | 22 | 18 | 0.6 |
| **Surgery parameters (median ± SD)** | | | | | |
| Total blood loss (ml) | 2250(± 2720) | 2000(± 1946) | 2500(± 2449) | 3200(± 4356) | <0.001 |
| SACCT (min)ˆ | 51 (± 29) | 40 (± 21) | 54 (± 28) | 63 (± 30) | <0.001 |

†COPD= Chronic Obstructive Pulmonary Disease; ‡MI= Myocardial Infarction; *CABG= Coronary Artery Bypass Graft; °PCI= Percutaneous Coronary Intervention; ¯ACE-inhibitors= angiotensin-converting-enzyme inhibitors; ˆSACCT= suprarenal aortic cross-clamping time Creatinine clearance (ml/min/1.73m$^2$) estimated by Cockcroft and Gault formula; Improved or unchanged renal function: Δ creatinine clearance between –10% to +10% function compared to baseline value; temporary worsening of renal function: temporarily worsening >10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3; persistent worsening of renal function: >10% decrease compared to baseline value. NOTE. To convert serum creatinine in mg/dl to umol/L, multiply by 88.4; creatinine clearance in ml/min to mL/s, multiply by 0.01667.

### Short-term outcome

Overall 30-day mortality was 1.3%, 5.0% and 12.6% in the three renal function groups, respectively. The survival was significantly worse in the temporary and persistent worsening renal function group, compared with those with an improved or unchanged renal function (p <0.001), as shown in the Kaplan-Meier (FIGURE 32.2). Both the unadjusted and adjusted regression analysis showed a significant difference in risk of 30-day mortality (TABLE 32.2). The Hazard Ratios of the temporary and persistent worsening of renal function groups were compared with the improved or unchanged renal function group. The unadjusted HRs were 4.0 (95% CI: 1.6–10.2) followed with 10.9 (95% CI: 4.5–26.2). After adjustment, they were 3.7 (95% CI: 1.4–9.9) and 7.3 (95% CI: 2.7–19.8), respectively. The adjusted HR for baseline creatinine clearance was 0.975 (95% CI: 0.958–0.993, p=0.007) per 1 ml/min increase in CrCl. Other important risk factors were hemorrhage (HR 3.3, 95%CI: 1.3–8.3), COPD (HR 3.0, 95%CI: 1.4–6.4), myocardial infarction (HR 7.5, 95%CI: 2.1–27.1) and dialysis (HR 6.3, 95%CI: 1.9–21.3). Beta-blocker use was associated with improved short-term outcome (HR 0.3, 95%CI: 0.1–0.9). Patients with a persistent worsening of renal function had more frequently hemorrhages (p <0.001) and required postoperative initiation of dialysis more often, compared with the other two renal function groups (TABLE 32.3).

### Long-term outcome

A total of 348 (36.5%) patients died within the 10 years follow-up (mean 6.0 ± 3.4 years). In the improved or unchanged renal function group 30.8% patients died, followed with 43.4% and 46.5%

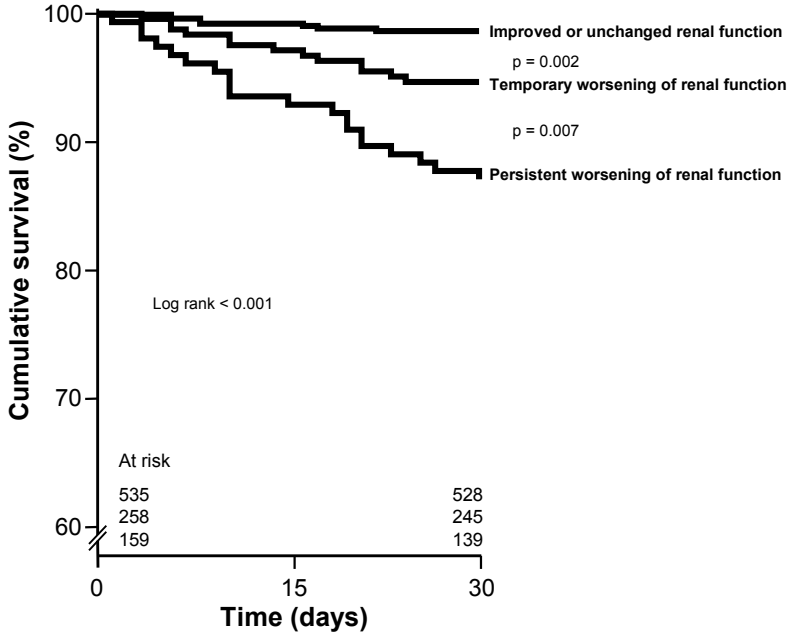


**FIGURE 32.2** All cause short-term mortality in 952 patients who underwent abdominal aortic aneurysm surgery, according to three renal function groups.
Improved or unchanged renal function: Δ creatinine clearance between –10% to +10% function compared to baseline value; temporary worsening of renal function: temporarily worsening >10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3; persistent worsening of renal function>10% decrease compared to baseline value.

**Table 32.2** Unadjusted and adjusted predictors of estimate risk of short and long-tem mortality in the abdominal aortic aneurysm group (n=983).

| | Unadjusted HRs (95% CI) | Adjusted* HRs (95% CI) |
|---|---|---|
| 30-day outcome | | |
| Improved or unchanged renal function | 1.0 | 1.0 |
| Temporary worsening of renal function | 4.0 (1.6 – 10.2) | 3.7 (1.4 – 9.9) |
| Persistent worsening renal function | 10.9 (4.5 – 26.2) | 7.3 (2.7 – 19.8) |
| 10-year outcome | | |
| Improved or unchanged renal function | 1.0 | 1.0 |
| Temporary worsening of renal function | 1.7 (1.3 – 2.1) | 1.5 (1.2 – 1.9) |
| Persistent worsening renal function | 2.1 (1.6 – 2.7) | 1.7 (1.3 – 2.3) |

*Adjusted for age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, BMI, prior myocardial infarction, prior coronary revascularization (percuntaneous coronary intervention and coronary artery bypass grafting), angina pectoris, heart failure, baseline creatinine clearance, medication (statins, diuretics, angiotensin-converting-enzyme inhibitors, calcium antagonists, nitrates, beta-blockers, digitalis and aspirin) and short-term complications (infection, stroke, coronary intervention, hart failure, amputation, limb necrosis, hemorrhage and dialysis). Improved or unchanged renal functionΔ creatinine clearance between –10% to +10% function compared to baseline value; temporary worsening of renal function: temporarily worsening >10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3; persistent worsening of renal function: >10% decrease compared to baseline value.

**Table 32.3** Short-term complications after abdominal aortic aneurysm surgery.

| | All patients 952 (100%) | Improved or unchanged renal function 535 (56%) | Temporary worsening of renal function 258 (27%) | Persistent worsening of renal function 159 (17%) | p-value |
|---|---|---|---|---|---|
| **Complications n (%)** | | | | | |
| Infection | 177 (19) | 88 (16) | 57 (22) | 32 (20) | 0.1 |
| Wound | 25 (3) | 14 (3) | 8 (3) | 3 (2) | 0.7 |
| Pneumonia | 91 (10) | 39 (7) | 32 (14) | 20 (13) | 0.02 |
| Sepsis | 11 (1) | 4 (1) | 2 (1) | 5 (3) | 0.05 |
| Urinary tract infection | 32 (3) | 22 (4) | 10 (4) | 0 (0) | 0.03 |
| Rest | 18 (2) | 9 (2) | 5 (2) | 4 (3) | 0.8 |
| Stroke | 21 (2) | 8 (2) | 6 (2) | 7 (4) | 0.1 |
| Coronary intervention | 13 (1) | 5 (<1) | 3 (1) | 5 (3) | 0.2 |
| Heart failure | 20 (2) | 9 (2) | 5 (2) | 6 (4) | 0.3 |
| Amputation | 12 (1) | 4 (1) | 3 (1) | 5 (3) | 0.06 |
| Limb necrosis | 23 (2) | 10 (2) | 7 (3) | 6 (3) | 0.5 |
| Hemorrhage | 60 (6) | 24 (4) | 14 (5) | 22 (14) | <0.001 |
| Dialysis† | 26 (3) | 1 (<1) | 3 (1) | 22 (14) | <0.001 |
| Temporary dialysis | 23 (2) | 1 (<1) | 3 (1) | 19 (12) | <0.001 |
| Persistent dialysis | 3 (1) | 0 (0) | 0 (0) | 3 (2) | 0.001 |

Coronary intervention=coronary artery bypass grafting or percutaneous coronary intervention; hemorrhage= vascular bleeding leading to a hypotensive state (systolic pressure of <100 mmHg) and requirement of packet cells; dialysis=requirement of new postoperative temporary or persistent dialysis. Improved or unchanged renal functionΔ creatinine clearance between –10% to +10% function compared to baseline value; temporary worsening of renal function: temporarily worsening >10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3; persistent worsening of renal function: >10% decrease compared to baseline value.† excluding 8 patients on chronic haemodialysis

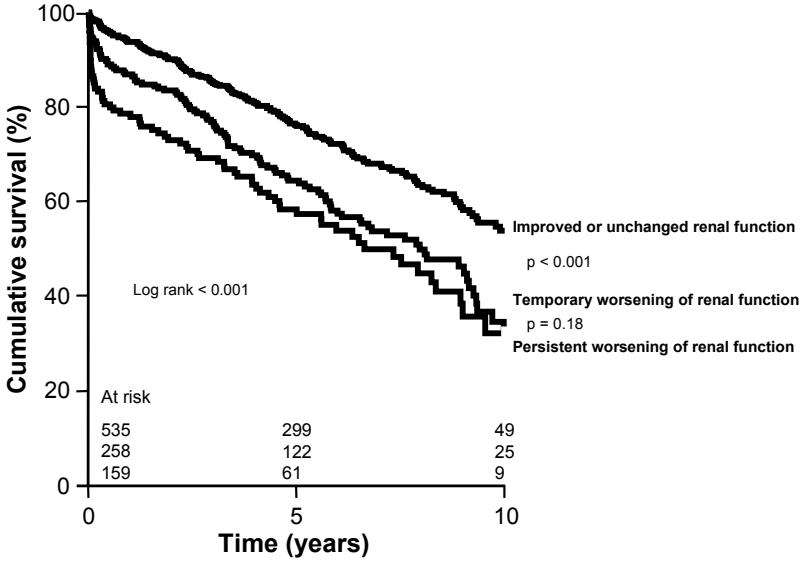


**FIGURE 32.2** All cause long-term mortality in 952 patients who underwent abdominal aortic aneurysm surgery, according to three renal function groups.
Improved or unchanged renal function: Δ creatinine clearance between –10% to +10% function compared to baseline value; temporary worsening of renal function: temporarily worsening >10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3; persistent worsening of renal function: >10% decrease compared to baseline value.

in the temporary and persistent worsening of renal function groups. During the long-term follow-up, patients with temporary worsening of renal function had the same long-term prognosis as patients with persistent worsening of renal function (log rank p=0.18) (FIGURE 32.3).

In adjusted analysis, significant risk factors for long-term all-cause mortality included age (HR 1.02, 95%CI: 1.006–1.03, per 1 year increase in age), COPD (HR 1.8, 95%CI: 1.4–2.3), baseline CrCl (HR 0.992, 95%CI: 0.988–0.997 per 1 ml/min increase in CrCl), stroke (HR 1.5, 95%CI: 1.1–2.0), dialysis (HR 2.6, 95%CI: 1.5–4.6) and hemorrhage (HR 1.5, 95%CI: 1.01–2.2). Statin use was associated with improved long-term outcome (HR 0.69, 95%CI: 0.5–0.96).

Cerebro-cardiovascular events (157 (45%)) were the major cause of death which included: MI 19%, congestive hart failure 9%, arrhythmia 2%, stroke 7%, fatal bleeding 5% and others 3%. The non-cerebro-cardiovascular (115 (33%)) events included: infection 7%, malignancy 9%, respiratory insufficient 7% and others 10%. An unknown cause of death was only determined in 76 (22%) patients.

## DISCUSSION

The main finding of our study is that renal function changes within the first three days after abdominal aortic aneurysm (AAA) surgery is a predictor for perioperative and long-term mortality. Although, renal function may recover completely after aortic surgery with a more or less favorable 30-day outcome, they are at high risk for long-term mortality, while patients with a persistent worsening of renal function are most likely to have a poor 30-day and long-term prognosis.

The temporary and persistent worsening renal function groups have a higher incidence of hypertension, compared with the improved or unchanged group. Also the total blood loss and suprarenal aortic cross-clamping time as postoperative complications are significantly higher. All these risk factors combined, indicate that these two groups are predisposed for a higher risk of postoperative renal failure and thereby mortality[11,20-22].

As mentioned before, the etiology of developing postoperative renal failure after aortic surgery is multifactorial. Renal function prior to surgery, total blood loss, the use of nephrotoxic agents, preexisting atherosclerosis, hypertension, suprarenal aortic cross-clamping time and ligation of renal veins during the operation all negatively affect postoperative renal function and, in turn, leads to death[20,23-25].

Suprarenal aortic cross-clamping is required in about 15% of operations for infrarenal vascular disease resulting in renal hypoxia reperfusion injury, which is an inevitable consequence. When limb ischemia is also present, muscle necrosis and myoglobinuria might also be present, all negatively affecting renal function[26]. A safe renal ischemia time has been determined to be between 45–50 minutes[20,27]. The median cross-clamping times of the temporary and persistent worsening renal groups are higher than the above cutoff, however there was no significant differences in clamping time between these groups. An intraoperative blood loss exceeding 2000 ml has also been found to be an independent predictor of 30-day mortality in patients with a ruptured AAA[22]. Since the temporary and persistent worsening of renal function groups have a total blood loss higher than 2000 ml, they were at high risk for an increase 30-day mortality.



Lassnigg, et al. suggested that patients who survived the first 30 days after cardiothoracic surgery and had sufficient recovery of renal functions regained the same long-term prognosis as patients without temporary impaired renal function[21]. In our study, patients with temporary renal function changes had a worse 30-day survival than patients without renal function changes (log rank $p = 0.002$), but they never regain the same long-term (10 years) prognosis (log rank $p < 0.001$). Actually, the trend is that patients with temporary renal function changes have even a worse long-term outcome than those with persistent worsening of renal function. The high-risk patients, with persistent worsening of renal function, die mainly within the first 30 days, so the diluting effect of renal function changes is less for the long-term mortality outcome. The risk of developing severe non-renal complications that might lead to death, is increased further by renal injury itself and can be explained by the extent and pattern of preexisting co morbidities.

The effect of acute changes (within the first three days) on renal function after AAA surgery was also investigated by Ellenberger, et al[6]. They reported the highest mortality rate within 30-days of patients with serum creatinine increases of > 0.5 mg/dl (> 44 umol/L) compared with baseline, again indicating that renal function changes within three days after surgery, is a strong predictor for perioperative mortality. However, long-term mortality was not evaluated and serum creatinine was used as a marker for renal function. Even though serum creatinine is considered to be a practical and reasonable approach to use for the evaluation of renal dysfunction, we chose CrCl as a more accurate measurement of renal function, as recommended by the recent National Kidney Foundation guidelines[28].

In our cohort, we found a remarkably low incidence of diabetes mellitus (6%). Earlier cohorts of AAA repair reported an incidence of 12-13%[29,30]. The diagnosis of diabetes mellitus was based on requirement for insulin therapy, hypoglycemic agents or as fasting blood glucose ≥ 140 mg/dl (≥ 7.8

mmol/L). However, fasting glucose concentrations were not routinely assessed and may have caused an under diagnosis of diabetes.

A major limitation of our study is the retrospective analysis of the data. In addition, not all perioperative data (duration of aortic cross clamping, transfusion requirements, need for additional surgical interventions, time to extubation, admission in intensive care unit, use of medication) were available to implement these parameters in our analysis. Furthermore, changes in the perioperative management have evolved markedly over time and were not taken into account in our analysis. These include multiple factors ranging from preoperative management, such as drug therapy, anesthesiological and surgical techniques to intensive post-surgical care management.

It is well established that a key impediment in the field of Acute Renal Failure [ARF], is a lack of uniform definition in the changes of kidney function. Current definitions that relay on changes in serum creatinine and urine output are neither sensitive nor specific. In a recent publication[31], the authors were able to describe 19 different definitions of ARF (ranging from –20% to –100% changes in serum creatinine or an increase in serum creatinine ranging from ≥ 0.3 mg/dl (≥ 27 umol/L) to ≥ 1.0 mg/dl (≥ 88 umol/L)). Although none of these cutoffs were evaluated, when comparing our arbitrary definition of change of kidney function with most other published definitions we found that our cutoff is extremely conservative. As the main objective of this study was to evaluate the association between small changes of renal function in relation to outcome, we have chosen a cutoff of 10% change. Furthermore, kidney function estimating equations (e.g. Cockcroft Gault) are derived in patients who were in a steady state. Since we reported perioperative estimated creatinine clearance changes (within three days after surgery) by definition, such a steady state is difficult to establish, which might underestimate true changes in kidney function. Unfortunately, there are no practical ways to readily measure kidney function in the acute setting. The strength of our study is that this retrospective study covers a long time period (6.0 ± 3.4 years) and includes a large number of patients. Few studies have focused on the long-term outcome of a temporary decrease in renal function shortly after surgery.

In conclusion, patients with temporary worsening of renal function are at high risk for poor long-term outcome suggesting that these patients might need more close medical follow-up than suggested previously.

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# Chapter 33

## Statins are associated with a reduced infrarenal abdominal aortic aneurysm growth

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## ABSTRACT

**Objective:** To evaluate the effect of statins on aneurysm growth in a group of consecutive patients under surveillance for infrarenal aortic aneurysms (AAA).

**Methods:** All patients (59 statin users, 91 non-users) under surveillance between January 2002 and August 2005 with a follow-up for aneurysm growth of at least 12 months and a minimum of three diameter evaluations were retrospectively included in the analysis. Multiple regression analysis, weighted with the number of observations, was performed to test the influence of statins on AAA growth rate.

**Results:** During a median period of 3.1 (1.1–13.1) years the overall mean aneurysm growth rate was 2.95±2.8 mm/year. Statin users had a 1.16 mm/year lower AAA growth rate compared to non-users (95% CI 0.33–1.99 mm/year). Increased age was associated with a slower growth (–0.09 mm/year per year, p=0.003). Female gender (+1.82 mm/year, p=0.008) and aneurysm diameter (+0.06 mm/year per mm, p=0.049) were associated with increased AAA growth. The use of non-steroidal anti-inflammatory drugs, chronic lung disease, or other cardiovascular risk factors were not independently associated with AAA growth.

**Conclusions:** Statins appear to be associated with attenuation of AAA growth, irrespective of other known factors influencing aneurysm growth.

## INTRODUCTION

Abdominal aortic aneurysm (AAA) occurs frequently in the elderly population, i.e. a prevalence of 5–7% in males between 65 and 74 years, increasing to over 10% in males over 74 years of age[1-3]. The overall mortality from ruptured AAA remains high, i.e. up to 75%, and preventive elective repair of large AAAs appears to be the best option[4]. Screening for AAA in populations at increased risk, i.e. elderly males, to detect those who will benefit from elective repair seems to be safe and cost-effective[1-5]. However, perioperative complications of elective AAA repair remain a significant problem despite recent advances such as cardioprotective medication[6,7] and endovascular repair[8,9].

Therefore, an attractive option would be the slowing of AAA growth, thereby preventing the AAA to reach a size requiring surgical intervention. However, the pathogenesis of AAA growth and factors that determine this growth, leading eventually to rupture, remain ill-defined. Recently, several studies were performed to identify risk factors that were associated with aneurysmal growth on the level of the human aorta itself using cell cultures obtained by aortic wall biopsies. Important factors in this respect are inflammation markers such as interleukin-6[10,11] and specific matrix metalloproteinases (MMPs) inducing collagen and elastin degradation in the aortic wall[12]. Importantly, drugs with an anti-inflammatory action such as prostaglandin synthetase inhibitors reduce the inflammatory response and are associated, in a case–control study in humans, with a reduced aneurysm growth rate[13].

Statins (3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors) are known to be highly effective drugs for reducing LDL–cholesterol levels and improve long-term outcome in patients with or at risk for coronary artery disease. Recently other, so-called 'pleiotropic', effects of statins were described[14]. Statins alter the inflammatory status, e.g. a reduction of IL-6 release, and may modulate the release of several substances in the arterial wall, including MMPs[15]. Recently, results of animal studies suggested an association between statin use and suppression of the development of aortic aneurysms due to these pleiotropic effects[16].

However, so far no data are available on the influence of statins on growth of abdominal aneurysms in humans. Therefore, we conducted the present study with the aim to evaluate the effect of statins on aneurysm growth in a group of consecutive patients under surveillance for infrarenal aortic aneurysms.

## METHODS

### Patient population

The study population was composed of patients who were under surveillance for infrarenal abdominal aortic aneurysm at two hospitals, Erasmus Medical Center in Rotterdam and Reinier de Graaf Gasthuis in Delft, in The Netherlands between January 2002 and August 2005. Patients were retrospectively identified by screening of surgical medical charts. Patients with an inflammatory (n=12) or mycotic aneurysm (n=1) were excluded from analysis. All patients had a follow-up for aneurysm growth of at least 12 months. A minimum of three separate diameter evaluations was required to calculate aneurysm growth rates. The Medical Ethics Committee of the Erasmus Medical Center was informed about the study protocol, and per institutional practice no official approval was requested.

### Patient characteristics

All patients were screened for cardiac risk factors, including age, hypertension, angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure, diabetes mellitus, and symptoms of other peripheral arterial disease, i.e. intermittent claudication. Smoking status (never, current, or former) and presence of chronic obstructive pulmonary disease (COPD) was noted as well. All prescription and over-the-counter medications were noted at the time of the first outpatient clinic visit and were classified as follows: statins, beta-blockers, aspirin, angiotensin converting enzyme inhibitors, calcium channel blockers; dihydropyridines or non-dihydropyridines, diuretics, nitrates, coumarins, digoxin and non-steroidal anti-inflammatory drugs (NSAIDs). Patients who started statins during the surveillance period were analyzed as non-users up to the date statin therapy was initiated. These patients were excluded from further analysis after initiation of statin therapy.

### Follow-up

The protocol in both hospitals was to screen patients with abdominal aortic aneurysms every 6–12 months by means of ultrasonography. All ultrasound measurements were performed by either a radiologist or a trained and skilled sonographer. Inter- and intra-observer variability has been estimated, based on previous studies from our group, at 96 and 98%, respectively, in our hospital with good reproducibility.[17] The diameter of the aorta was defined as the maximum anterior–posterior diameter. At each follow-up visit changes in medication use were noted. If the diameter of the aortic aneurysm exceeded 5.0 cm, the growth rate was more than 1 cm/year, or the aneurysm became symptomatic CT angiography was performed to evaluate the exact diameter and the possibility of endovascular repair. The results of the CT scan were not considered in this study. Patients who required surgery were censored at the last ultrasonographic measurement prior to surgery.



### Statistical analysis

Continuous data were expressed as mean (±SD) or median (±interquartile range) and compared using the Student's t-test or Mann–Whitney U-test as appropriate, i.e. whether there was a normal distribution or not. Categorical data are presented as percent frequencies and differences between proportions were compared using the chi-square test. The change in maximum AAA diameter was assumed to be linear over time and modeled using linear regression analysis. Growth rate of the AAA for each patient was estimated as the regression coefficient, using time as the independent variable and diameter of AAA as the dependent variable. The time unit was set to 6 months and this growth rate was then doubled to give AAA growth rate in millimeter per year. Multiple regression analysis was performed to test the influence of statins on AAA growth rate. In linear regression analysis annual growth rate was the dependent variable and age, gender, AAA diameter at initial presentation, NSAID use, statin use, and cardiovascular risk factors were used as independent variables. The analysis was weighted with the number of observations (i.e. number of ultrasound measurements) for each patient. The limit of statistical significance was set at p=0.05 (two sided). All analysis was performed using the statistical software SPSS for Windows 12.1 (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

### Baseline characteristics

The study population consisted of 150 patients (88% men). Mean age at first presentation was 69±7.6 years. In total, 59 patients (39%) were chronic statin users. Of these 59 statin users, 24 were on simvastatin, 19 on atorvastatin, 11 on fluvastatin, and five patients received pravastatin therapy. Baseline patient characteristics are shown in TABLE 33.1. There were no significant differences in medical

**TABLE 33.1** Clinical baseline characteristic at first screening visit.

| | Total | Statin users | Non-users | p-value |
|---|---|---|---|---|
| | N=150 | N=59 | N=91 | |
| Males – no. (%) | 126 (88) | 51 (91) | 75 (86) | 0.44 |
| Age – yrs (SD) | 69 (7.6) | 69 (7.8) | 69 (7.5) | 0.94 |
| AAA diameter – mm (SD) | 38 (7.7) | 40 (8.5) | 37 (7.0) | 0.02 |
| Myocardial infarction – no. (%) | 47 (31) | 18 (30) | 29 (32) | 0.86 |
| Angina pectoris – no. (%) | 27 (18) | 12 (20) | 15 (17) | 0.83 |
| Congestive heart failure – no. (%) | 11 (7) | 6 (10) | 5 (5) | 0.36 |
| CVA or TIA – no. (%) | 19 (13) | 8 (13) | 11 (13) | 1.0 |
| Diabetes mellitus – no. (%) | 19 (13) | 9 (16) | 10 (11) | 0.32 |
| Renal failure – no. (%) | 7 (5) | 5 (9) | 2 (2) | 0.11 |
| Hypertension – no. (%) | 64 (43) | 28 (48) | 36 (39) | 0.30 |
| COPD – no. (%) | 41 (27) | 17 (29) | 24 (26) | 0.85 |
| Intermittent claudication – no. (%) | 26 (17) | 17 (29) | 9 (10)* | 0.01 |
| Smoking – no. (%) | 106 (71) | 40 (68) | 66 (72) | 0.72 |

AAA= abdominal aortic aneurysm; CVA = cerebrovascular accident; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

**TABLE 33.2** Medication use.

| | Total | Statin users | Non-users | p-value |
|---|---|---|---|---|
| | N=150 | N=59 | N=91 | |
| NSAID – no. (%) | 60 (40) | 27 (45) | 33 (37) | 0.38 |
| Warfarin derivatives – no. (%) | 23 (15) | 14 (23) | 9 (10)* | 0.03 |
| Beta-blockers – no. (%) | 53 (35) | 24 (41) | 29 (32) | 0.28 |
| ACE inhibitors – no. (%) | 38 (25) | 12 (20) | 26 (29) | 0.24 |
| Diuretics – no. (%) | 35 (23) | 18 (30) | 17 (19) | 0.11 |
| Calcium antagonists – no. (%) | 30 (21) | 12 (21) | 18 (21) | 1.0 |
| Nitrates – no. (%) | 21 (14) | 9 (16) | 12 (13) | 0.63 |
| Angiotensin II antagonists – no. (%) | 9 (6) | 9 (16) | 0* | 0.01 |
| Insulin or oral antidiabetic therapy – no. (%) | 19 (13) | 9 (16) | 10 (11) | 0.32 |
| Pulmonary medication – no. (%) | 21 (14) | 6 (11) | 15 (16) | 0.38 |

NSAID = non-steroidal anti-inflammatory drugs; ACE = angiotensin converting enzyme

history between groups, except for the presence of intermittent claudication (29% in statin users vs. 10% in non-users, p=0.007). Concomitant medication use is presented in TABLE 33.2. Statin users more often were on warfarin derivatives (23 vs. 10%, p=0.03) and angiotensin II antagonists (16 vs. 0%, p<0.001). The mean maximum diameter at first presentation of the AAA was 38±7.7 mm. Statin users had a significantly larger aneurysm at first presentation (40 vs. 37 mm, p=0.02).

## Follow-up

Patients were under surveillance for a median period of 3.1 years (range 1.1–13.1), 2.9 years for statin users and 3.2 years for non-users (p=0.49), with the number of ultrasound examinations varying from 3 to 12 with a mean of 4.7 measurements per patient (4.6 in users and 4.7 in non-users, p=0.89). The overall mean aneurysm growth rate during follow-up was 2.95±2.8 mm/year. Six patients had a negative value of annual aneurysm growth rate (three non-users and three users). All of these patients were included in the analysis. Exclusion of these patients did not result in significant alteration of the results.

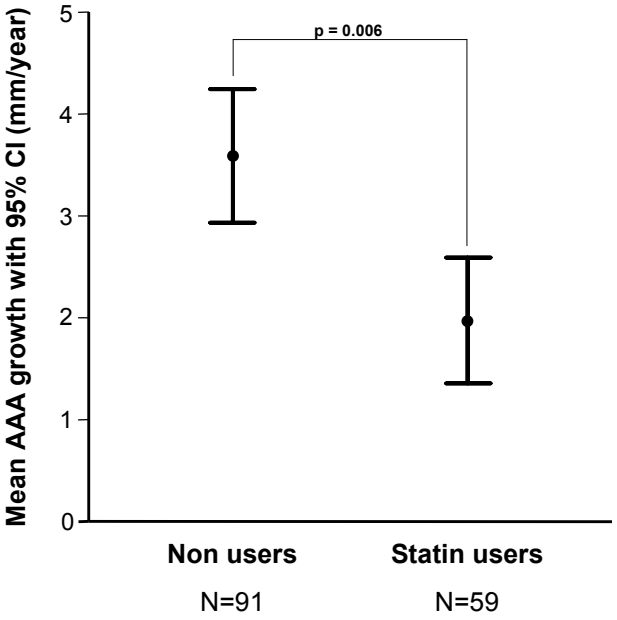


**FIGURE 33.1** Difference in mean annual aneurysm growth rate between statin users (2.0 mm/year) and non-users (3.6 mm/year).



In univariate analysis statin use was associated with a significant attenuation of aneurysm growth (p=0.001, FIGURE 33.1). Increasing age and intermittent claudication (p=0.02) also were associated with an attenuation of AAA growth rate. Other potential factors, such as diabetes mellitus, COPD, AAA diameter at first presentation or other medication use (in particular NSAID use), were not associated with a significant difference in aneurysm growth rate.

The results of multivariate linear regression analysis are shown in TABLE 33.3. In this analysis statin use, age, gender, and aneurysm size at first presentation were associated with a difference in AAA growth rate. Statin users had a significant 1.16 mm lower annual aneurysm growth rate compared

**TABLE 33.3** Adjusted (corrected for other factors in the table) estimated difference in mean annual AAA growth.

| | Adj. estimated difference (mm/year) | 95% Confidence Interval | | p-value |
|---|---|---|---|---|
| | | Lower bound | Upper bound | |
| Age (per year increase) | -0.09 | -0.14 | -0.03 | 0.003 |
| Female | +1.82 | 3.15 | 0.49 | 0.008 |
| AAA diameter at first screening (per mm increase) | +0.06 | 0.01 | 0.11 | 0.049 |
| Claudication intermittens | -0.89 | -1.89 | 0.11 | 0.082 |
| Diabetes mellitus | -0.01 | -1.25 | 1.24 | 0.989 |
| COPD | +0.70 | -0.24 | 1.64 | 0.145 |
| Statin use | -1.16 | -1.99 | -0.33 | 0.006 |
| NSAID use | -0.13 | -0.97 | 0.70 | 0.754 |

AAA = abdominal aortic aneurysm; COPD = chronic obstructive pulmonary disease; NSAID = non steroidal anti-inflammatory drug.

to non-users (95% CI 0.33–1.99 mm/year). For each year increase of age at first presentation the mean aneurysm size growth rate was slowed by 0.09 mm (95% CI 0.03–0.14 mm/year). Females had a significantly higher growth rate than males (mean difference 1.82 mm/year, 95% CI 0.49–3.15 mm/year).

Aneurysm diameter at first presentation also was independently associated with annual aneurysm growth (0.06 mm/year increase per mm difference in AAA size, 95% CI 0.01–0.11). We did not find a significant influence of NSAID use, the presence of COPD, diabetes mellitus, or intermittent claudication on aneurysm growth rate.

## DISCUSSION

This study showed an association between statin use and attenuation of infrarenal abdominal aortic aneurysm growth, irrespective of other known factors influencing aneurysm growth.

Statins frequently are prescribed to lower cholesterol levels as large prospective studies have shown an improved outcome in statin users, mainly by reduction of late cardiac events[18-21]. However, recently other effects independent of serum cholesterol levels, so-called pleiotropic or non-lipid lowering effects, have been described. These recently described pleiotropic effects of statins might be related to the observed attenuation of AAA growth.

The pathophysiology of aortic aneurysm development, growth and eventually rupture is still not fully understood. Inflammation responses aggravated by a genetic susceptibility are probably important determinants. Accumulation and activation of mononuclear inflammatory cells; increased expression of proinflammatory cytokines, chemokines and matrix-degrading proteinases; degradation of elastin and collagen; oxidative and hemodynamic stress; and depletion of smooth muscle cells seem all to play a pivotal role[16]. Some of these inflammatory responses such as interleukin-6 and matrix metalloproteinases (MMPs) could be assessed in animal aortic aneurysm models, by inducing collagen and elastin degradation of the aortic wall. The response of interleukin-6 release is also genetically determined as assessed by the increased levels of interleukin-6 in patients with the 174G/C genotype[22]. The combined effects of inflammatory response and genetic susceptibility in patients with other environmental risk factors as elderly age and smoking might be responsible for the development and growth of AAA.

Recently, Steinmetz et al.[16] have shown in a mice model that statins suppress the development of experimental AAAs. The positive effect of statins was ascribed to its properties of preserving medial elastin, smooth muscle cells, and beneficially altering aortic wall expression of MMPs[16]. Also other experimental studies have confirmed these positive effects of statins on MMPs[23-25]. In a study by Wilson et al. of 63 infrarenal aortic biopsies obtained during AAA repair the levels of MMP-9 and MMP-3 were significantly lower in patients taking statins[15]. The reduced levels of MMP-9, achieved by inhibition of the activation of neutrophils and macrophages, in statin users was confirmed by Nagashima and co-workers[26].

In our study age, gender, and aneurysm diameter at first presentation were associated with a difference in AAA growth rate. These results are in line with previously reported studies on the influence of these risk factors[27]. In some studies smoking and diabetes were found to have a significant impact on aneurysm growth rate[27], however, we did not come across such an association which may be related

to the small number of patients with diabetes. Therefore, a type II error might have occurred. Since, this analysis is retrospective, for smoking habits we had no information on number of 'pack years' and current exposure, i.e. number of cigarettes per day.

In the past several medical intervention trials for the prevention of abdominal aneurysm expansion have been reported. The propanolol trial investigators did not find a growth benefit of propanolol use in a double-blind randomized study in 358 patients[28]. In a double-blind randomized trial Vammen et al. showed that macrolide antibiotic treatment for 4 weeks was associated with a significant lower expansion rate compared to placebo[29]. Mosorin et al. also found a significant lower expansion rate in patients taking doxicyclin for a period of 3 months compared to patients receiving placebo.[30] These findings have been confirmed by Baxter et al. in a phase II trial in 63 patients[31]. Another therapeutic strategy for the prevention of aneurysm growth is to intervene in the inflammatory response present in aortic aneurysms. In animal models as well as in a very small case control study indometacin indeed seemed to prevent the development and growth of abdominal aortic aneurysms[13,32]. However, in the present study we could not confirm this observation.

A major limitation of this analysis is the use of ultrasonographic examinations for the measurement of aortic diameter. The inter- and intra-observer variability of this screening modality might influence the outcome of any study based on this type of measurement. However, as shown by Singh et al. experienced ultrasonographers and radiologists achieve a high degree of accuracy, which was confirmed in the present study with a low inter- and intra-observer variability[33]. As all non-randomized observational studies this study has some other limitations as well. Though we included several confounding factors in the multiple regression analysis some might have been missed. One of them could be the potentially better blood pressure control in statin users as significantly more statin users were on angiotensin-II-antagonist therapy. Unfortunately, we did not have accurate information on blood pressure control during the study period. Also several other questions could not be answered in this study due to its retrospective nature and should be addressed in future studies including the effect of statin therapy duration on AAA growth and the time between statin therapy initiation and reduction of AAA growth rate.

In conclusion, this study shows a clear association between statin use and a decreased expansion rate of infrarenal aortic aneurysms. This finding is in line with experimental studies in mice and rats, but needs to be confirmed by randomized clinical trials.



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# Chapter 34

## Long-term cardiac outcome in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair

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## ABSTRACT

**Objectives:** To assess long-term outcome of patients at high cardiac risk undergoing endovascular or open AAA repair.

**Methods:** Patients undergoing open or endovascular infrarenal AAA repair with ≥ 3 cardiac risk factors and preoperative cardiac stress testing (DSE) at 2 university hospitals were studied. Main outcome was cardiac event free and overall survival during a median follow-up of 3.3 years. Multivariate Cox regression analysis was used to evaluate the influence of type of AAA repair on long-term outcome.

**Results:** In 124 patients (55 endovascular, 69 open) the number and type of cardiac risk factors, medication use and DSE results were similar in both groups. In multivariable analysis, adjusting for cardiac risk factors, stress test results, medication use, and propensity score endovascular repair was associated with improved cardiac event free survival (HR 0.54; 95% CI 0.30–0.98) but not with an overall survival benefit (HR 0.73; 95% CI 0.37–1.46). Importantly, statin therapy was associated with both improved overall survival (HR 0.42; 95% CI 0.21–0.83) and cardiac event free survival (HR 0.45; 95% CI 0.23–0.86).

**Conclusions:** The perioperative cardiac benefit of endovascular AAA repair in high cardiac risk patients is sustained during long-term follow-up provided patients are on optimal medical therapy but it is not associated with improved overall long-term survival.

## INTRODUCTION

Patients undergoing abdominal aortic aneurysm repair are at significant risk for both perioperative and long-term cardiovascular events. In particular patients at high cardiac risk might benefit from endovascular AAA repair. However, no randomized trials comparing open and endovascular treatment have been reported on patients at high cardiac risk. For example, less than half of the patients in the DREAM trial (44%) and EVAR-1 trial (43%) had a history of cardiac disease[1,2]. A major limitation of non-randomized comparative studies between open and endovascular surgical procedures conducted so far is the lack of objective criteria for baseline cardiac condition[3].

Preoperative cardiac stress testing such as dobutamine stress echocardiography (DSE) provides an objective assessment of the presence and extent of coronary artery disease[4]. In a previous study we used this modality to compare perioperative outcome after open or endovascular AAA repair and found that endovascular repair was superior in terms of cardiovascular outcome[5]. The long-term outcome of these high-risk patients however remained ill-defined.

Therefore we expanded the study population of the previous study and conducted long-term follow-up of these patients. The aim of the present study was to evaluate the long-term effect of endovascular AAA repair compared to open AAA repair in patients at clinical high cardiac risk on cardiac complications and mortality.

## METHODS

### Patients

The study population was composed of patients with 3 or more cardiac risk factors who underwent elective abdominal aneurysm repair between January 2000 and January 2006 at two tertiary referral centers, Erasmus University Medical Center Rotterdam, the Netherlands and University Medical Center Utrecht, the Netherlands and had a preoperative cardiac stress test. The choice for either repair method was at the discretion of the treating vascular surgeon and was mainly based on anatomical considerations. The study was approved by the Erasmus MC medical ethics committee.

### Preoperative cardiac risk assessment

All patients were routinely screened for cardiac risk factors, including age over 70 years, history of or presence of angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure (serum creatinine >170 µmol/l), and diabetes mellitus. The presence of hypertension and chronic obstructive pulmonary disease (COPD) was noted as well. A patient was classified as having COPD at the preoperative screening visit according to symptoms and pulmonary function test (i.e. FEV1 < 70% of maximal age and gender predictive value). According to the ACC/AHA guidelines all patients with 3 or more cardiac risk factors underwent cardiac stress testing prior to surgery.

Perioperative medication use was noted including ACE-inhibitors, platelet aggregation inhibitors, beta-blockers, calcium antagonists, coumarin derivatives, diuretics, nitrates, and statins. Patients unable to take medication orally perioperatively were switched to intravenous formula. If no intravenous formula was available, i.e. statins and ACE-inhibitors, oral medication was restarted as soon as possible after surgery.

### Cardiac stress testing

Resting echocardiography was used to estimate the left ventricular ejection fraction using the Simpson rule. Cardiac stress testing was performed by dobutamine echocardiography as previously described[6]. Myocardial stress induced ischemia was assessed using a semi-quantitative evaluation; a 5-point score in a 17-segement model. Limited ischemia was defined by the presence of 1–4 ischemic segments, while extensive ischemia was defined by ≥ 5 ischemic segments.

### Outcome

All patients were monitored for cardiac events after abdominal aortic aneurysm repair. Twelve-lead ECG and serum troponin-T levels were systematically determined on days 1, 3, and 7 postoperatively or at discharge. The primary outcome of the study was the incidence of all-cause mortality and the combination of myocardial infarction and all-cause death during long-term follow-up. Myocardial infarction was defined as the presence of 2 out of the following 3 criteria: (1) Characteristic ischemic symptoms lasting > 20 min, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 h, or new ST segment depression which persists >24 h, and (3) a positive troponin T, i.e. >0.10 ng/ml, or peak CK-MB >8% of an elevated total creatinine phosphokinase with characteristic rise and fall[7]. Survival status was confirmed by contacting the civil service registry.

### Statistical analysis

Continuous data are presented as median values and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical characteristics between patients undergoing endovascular repair or open repair were evaluated by Wilcoxon's nonparametric tests, Chi-square tests or Fisher's exact tests, as appropriate. The incidence of events over time was further examined by the Kaplan–Meier method, whereas a log-rank test was applied to evaluate differences between the two treatment modalities. We developed a propensity score for the likelihood of undergoing either open or endovascular AAA repair and used applied multivariate logistic regression analysis to calculate the propensity score. The association of type of AAA repair, cardiovascular risk factors and medication use with long-term events was assessed via multivariate Cox regression analysis, including the propensity score, with stepwise backward removal. The limit of statistical significance was set at $p = 0.05$ (two-sided). All analysis was performed using the statistical software SPSS for Windows 12.0.1 (SPSS Inc., Chicago, Illinois, USA).



## RESULTS

### Patient characteristics

A total of 124 patients with 3 or more clinical cardiac risk factors were included in this study. Of these, 69 patients underwent open AAA repair and 55 patients underwent endovascular AAA repair. Clinical baseline characteristics of these patients are shown in TABLE 34.1. Almost all (92%) patients were male, their mean age was 74 ± 6 years, and the median AAA diameter was 60 mm (interquartile range 55–70 mm). There were no statistically significant differences between patients undergoing open or endovascular AAA repair in terms of clinical characteristics or medication use. During non-invasive stress testing approximately half (47%) of all patients had stress inducible myocardial ischemia. A total of 46 (37%) patients had mild myocardial ischemia while another 12 (10%) patients had extensive myocardial ischemia. There was no difference in, mild or extensive myocardial ischemia between the open and endovascular group (respectively 54% vs. 53%, 35% vs. 40% and 12% vs. 7%).

**TABLE 34.1** Baseline clinical characteristics of patients undergoing open and endovascular abdominal aneurysm repair.

| | All patients (N =124) | Open (N = 69) | Endovascular (N = 55) | p-value |
|---|---|---|---|---|
| Men | 114 (92%) | 64 (93%) | 50 (91%) | 0.75 |
| Age (mean, SD) | 74 ± 6 | 74 ± 6 | 74 ± 7 | 0.66 |
| Heart rate prior to surgery | 65 ± 12 | 66 ± 13 | 64 ± 9 | 0.23 |
| **Risk factors** | | | | |
| Previous angina pectoris | 77 (62%) | 41 (59%) | 36 (64%) | 0.71 |
| Previous myocardial infarction | 107 (86%) | 60 (87%) | 47 (84%) | 0.80 |
| Previous heart failure | 25 (20%) | 12 (17%) | 13 (23%) | 0.50 |
| Previous CABG or PTCA | 60 (48%) | 33 (48%) | 27 (48%) | 0.99 |
| CVA or TIA | 46 (37%) | 29 (42%) | 17 (30%) | 0.20 |
| Diabetes Mellitus | 18 (14%) | 10 (15%) | 8 (14%) | 0.95 |
| Renal failure | 28 (22%) | 14 (20%) | 14 (25%) | 0.67 |
| Systemic hypertension | 52 (42%) | 32 (46%) | 20 (36%) | 0.28 |
| COPD | 48 (38%) | 28 (41%) | 20 (36%) | 0.57 |
| **Stress echocardiography** | | | | |
| No ischemia | 66 (53%) | 37 (54%) | 29 (53%) | 0.66 |
| Limited ischemia | 46 (37%) | 24 (35%) | 22 (40%) | |
| Extensive ischemia | 12 (10%) | 8 (12%) | 4 (7%) | |
| **Medication at screening** | | | | |
| Platelet aggregation inhibitors | 90 (72%) | 50 (73%) | 40 (71%) | 0.84 |
| ACE-inhibitors | 51 (41%) | 32 (47%) | 19 (34%) | 0.15 |
| Diuretics | 42 (34%) | 25 (59%) | 17 (41%) | 0.57 |
| Nitrates | 35 (28%) | 19 (27%) | 16 (29%) | 0.95 |
| Beta-blockers | 108 (86%) | 60 (87%) | 48 (86%) | 0.88 |
| Statins | 78 (63%) | 41 (59%) | 37 (67%) | 0.46 |
| Calcium-antagonists | 42 (34%) | 24 (35%) | 18 (32%) | 0.85 |

CABG = coronary artery bypass graft; percutaneous transluminal coronary intervention; CVA = cerebrovascular accident; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; ACE = angiotensin converting enzyme

## Perioperative outcome

Overall 30-day mortality was 4.3% for the open group and 0% for the endovascular group. An additional 3 (4.3%) patients in the open group died during hospitalization but after 30 days of the index procedure. The combined 30-day endpoint of non-fatal myocardial infarction and all-cause death was 12 (17%) in the open and 2 (4%) in the endovascular group ($p = 0.02$). The length of hospital stay was significantly shorter in patients with endovascular AAA repair (median 3 vs. 11 days, $p < 0.001$).

## Long-term outcome

*Type of repair*

During a median follow-up of 3.3 years (interquartile range 1.8–5.6 years) a total of 39 (31%) patients died and a total of 55 (45%) patients reached the combined endpoint of all-cause death and MI. As is shown in FIGURE 34.1A, during long-term follow-up there was no significant difference in overall survival between endovascular and open AAA repair ($p = 0.38$). Also in multivariate analysis patients treated with endovascular had no significant better survival rate (HR 0.73, 95% CI 0.37–1.46, TABLE 34.2). However, patients who underwent endovascular AAA repair did have a statistically significant better cardiac event free survival as compared to patients treated with open repair (FIGURE 34.1B)

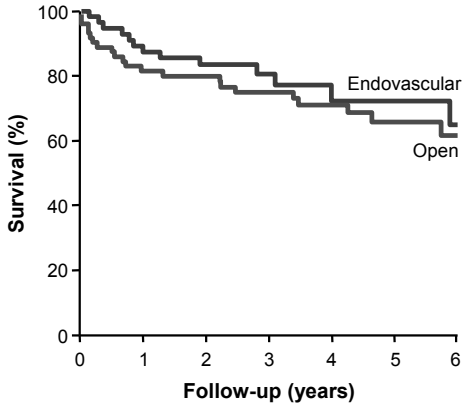


**FIGURE 34.1A** Overall survival of patients undergoing endovascular or open AAA repair.

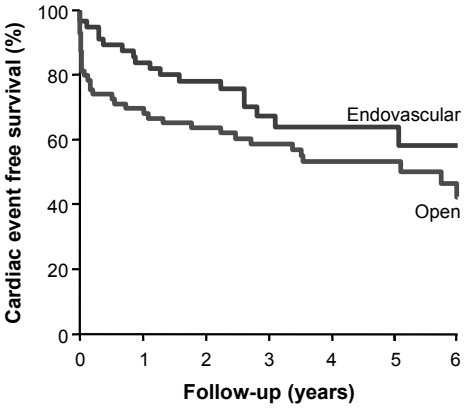


**FIGURE 34.1B** Cardiac event free survival of patients undergoing endovascular or open AAA repair.

**TABLE 34.2** Significant predictors of long-term overall survival status when clinical characteristics, propensity score for type of surgery, medication use and year of surgery were entered as independent variables into a Cox regression model with stepwise backward removal.

| | HR | 95% CI | P-value |
|---|---|---|---|
| Endovascular treatment | 0.73 | 0.37 – 1.46 | 0.37 |
| Age (per year increase) | 1.10 | 1.03 – 1.17 | 0.003 |
| Stress inducible myocardial ischemia | 1.95 | 1.03 – 3.89 | 0.04 |
| Statin use | 0.42 | 0.21 – 0.83 | 0.01 |
| Heart rate < 70 bpm | 0.26 | 0.13 – 0.54 | <0.001 |
| Platelet aggregation inhibitor | 0.47 | 0.23 – 0.97 | 0.04 |

**TABLE 34.3** Significant predictors of long-term cardiac event free survival status when clinical characteristics, propensity score for type of surgery, medication use and year of surgery were entered as independent variables into a Cox regression model with stepwise backward removal.

| | HR | 95% CI | P-value |
|---|---|---|---|
| Endovascular treatment | 0.54 | 0.30 – 0.98 | 0.04 |
| Age (per year increase) | 1.05 | 1.01 – 1.10 | 0.03 |
| Stress inducible myocardial ischemia | 2.60 | 1.45 – 4.67 | 0.001 |
| Statin use | 0.45 | 0.23 – 0.86 | 0.02 |
| Heart rate < 70 bpm | 0.53 | 0.29 – 0.97 | 0.04 |

(HR 0.54, 95% CI 0.30–0.98, TABLE 34.3). It should be noted however that this benefit was mainly driven by the 30-day events. If the first 30 days after surgery were not taken into account there would have been a similar cardiac event free survival among patients treated by endovascular or open repair (HR 0.89, 95% CI 0.44–1.77, p = 0.73).

*Medical therapy*

While type of AAA repair did not have a significant impact on overall long-term survival aggressive medical therapy did seem to be associated with improved overall survival. Patients on statin therapy had a significant survival benefit over patients not on statin therapy; 5-year overall survival 77%

vs. 53% respectively (HR 0.42, 95% CI 0.21–0.83, TABLE 34.2). Also cardiac survival event free was significantly better in patients on statin therapy (HR 0.45, 95% CI 0.23–0.86, TABLE 34.3). As is shown in FIGUREs 34.2A and 34.2B the perioperative benefit of endovascular repair was only sustained in patients on statin therapy in contrast to patients not on statin therapy (FIGURE 34.3). The prescription rate of statins gradually increased over the studied years, from 38% in 2001/2002 to 67% in 2003/2004 and 88% in 2005/2006 ($p < 0.001$). The vast majority of patients were on beta-blocker therapy. Importantly the mean heart rate prior to surgery was 65 beats per minute, indicating adequate beta-

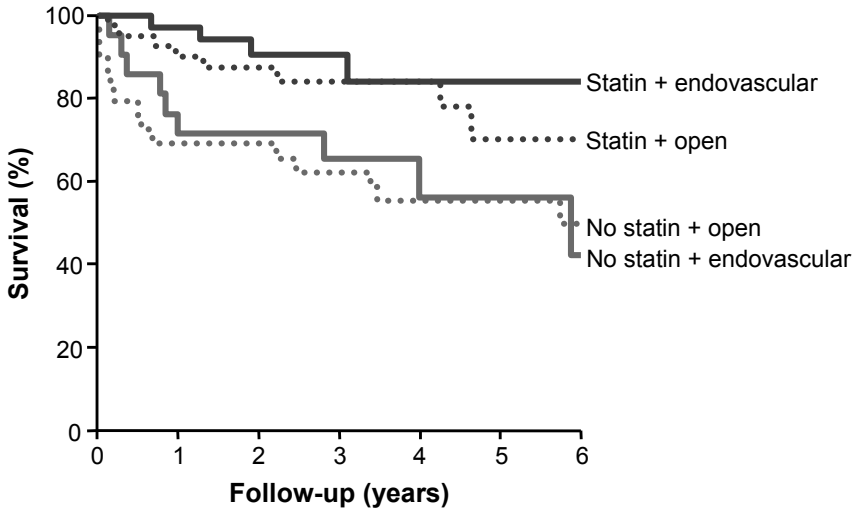


**FIGURE 34.2A** Overall survival of patients undergoing endovascular or open AAA repair, divided into statin users or non-users.

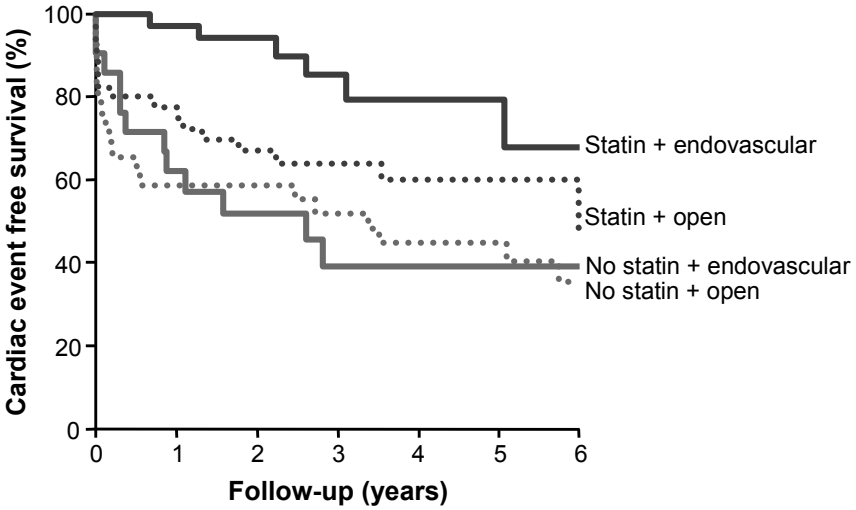


**FIGURE 34.2B** Cardiac event free survival of patients undergoing endovascular or open AAA repair, divided into statin users or non-users.

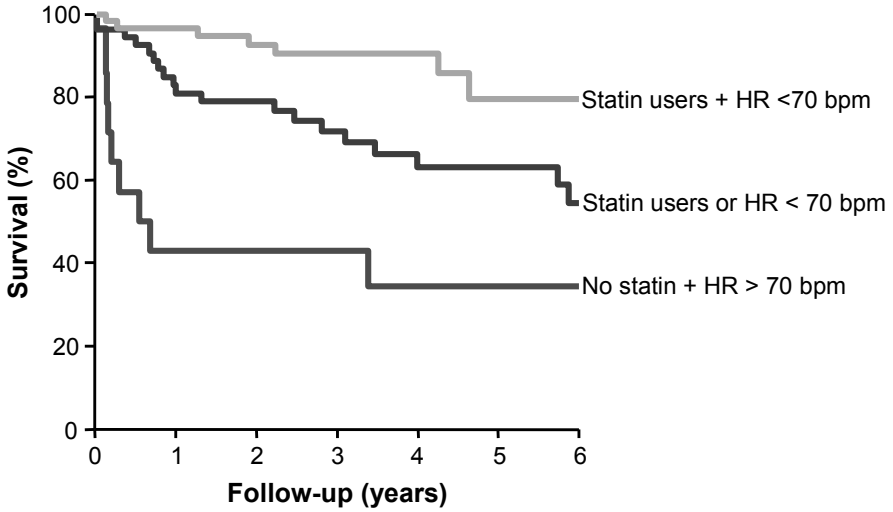


**FIGURE 34.3** Overall survival of patients undergoing endovascular or open AAA repair, divided into patients not on adequate beta-blocker therapy and statin therapy, patients on either adequate beta-blocker therapy or statin therapy, and patients on both adequate beta-blocker therapy and statin therapy.



blocker dosing in most patients. However, 35 (28%) patients had inadequate heart rate control with a rate of >70 beats per minute. Patients on adequate beta-blocker therapy had a significantly better overall survival (HR 0.26, 95% CI 0.13–0.54, TABLE 34.2) and cardiac event free survival (HR 0.53, 95% CI 0.29-0.97, TABLE 34.3). Importantly, there was no significant interaction between statin use and adequate beta-blocker dosing. Furthermore, as shown in TABLE 34.2 patients who were on platelet aggregation inhibitors had a better overall survival than did patients who were not on antiplatelet therapy (HR 0.47; 95% CI 0.23–0.97, p = 0.04).

## DISCUSSION

This study showed that, despite a reduced incidence of adverse perioperative events, endovascular repair of elective infrarenal AAA in cardiac high-risk patients has a similar long-term survival, compared to patients undergoing open AAA repair. However, the perioperative cardiac benefit is sustained during a median follow-up of 3.3 years in this high-risk population provided patients are on optimal medical therapy. Furthermore, aggressive medical treatment seems to have more impact on overall and cardiac event free survival than does the choice of AAA treatment modality.

Patients undergoing major non-cardiac surgery are at significant risk of cardiovascular morbidity and mortality. The prognosis after vascular surgery is predominantly determined by the presence and extent of underlying coronary artery disease[8]. In the landmark study performed over 20 years ago Hertzer et al. found that only 8% of a group of 1000 patients undergoing non-cardiac vascular surgery had normal coronary angiography results[9]. This high prevalence of underlying cardiac disease has later also been confirmed by functional tests such as dobutamine stress echocardiography[10]. Considering this high prevalence of coronary artery disease in vascular surgery patients it is hardly surprising that cardiac death after AAA repair accounts for approximately 40% and 65% of all 30-day and long-term mortality, respectively[11]. It might be argued that optimal medical therapy

is warranted to sustain the initial cardiovascular survival benefit in patients who underwent endovascular AAA repair.

In previous studies perioperative and long-term statin therapy have been associated with improved outcome in patients undergoing AAA repair. Several recent retrospective studies have shown a beneficial effect of statins on perioperative cardiac outcome with adjusted hazard ratio's ranging from 0.20 to 0.62[12]. Importantly, Kertai et al. also found the effect of statins to be independent of β-blocker use[13]. So far only one placebo-controlled, randomized trial has investigated the influence of statin use on perioperative cardiovascular complications. In a group of 100 patients treatment with 20 mg of atorvastatin was associated with a significant 3.1-fold ($p = 0.022$) reduction in cardiovascular complications within 6 months after vascular surgery[14]. Kertai et al. described the influence of statin use on long-term outcome after open AAA repair in 570 patients with a median follow-up of 4.7 years[15]. It was shown that, in this group of unselected AAA patients, statin use was associated with a 2.5-fold reduction in the risk of all-cause mortality (HR 0.4; 95% CI 0.3–0.5) and a 3-fold reduction in the risk of cardiovascular mortality (HR 0.3; 95% CI 0.2–0.6). Interestingly, the present study included only high cardiac risk patients but the reduction in the risk for mortality and cardiovascular complications was similar to the reported figures of Kertai et al.

Importantly statin use is advocated in the recent TASC II document[16]. Patients with symptomatic or asymptomatic peripheral arterial disease should have their LDL lowered to less than 2.59 mmol/l. Patients with multiple vascular beds affected should be treated even more aggressively with a target LDL <1.81 mmol/l. It should be noted that the cardioprotective effect of statins might not only be by reducing LDL levels but statins might also exert their protective effects by so-called pleiotropic effects.

Another medical intervention that has been proven successful in high-risk patients undergoing major vascular surgery is beta-blocker therapy. In the DECREASE I trial patients with preoperative stress inducible myocardial ischemia had a mere 10-fold reduction in perioperative cardiac events compared to patients who received placebo treatment[17]. Additionally, during a median follow-up of 22 months only 12% of patients on beta-blocker therapy experienced a cardiac event vs. 32% of the patients who were not on beta-blocker therapy ($p = 0.025$)[18]. This treatment effect was later confirmed in the DECREASE I registry patients in which 1299 survivors of vascular surgery were followed for a median duration of 23 months[19]. In multivariable analysis the 360 patients on beta-blockers had a significant risk reduction for cardiac events (HR 0.3; 95% CI 0.2–0.6; $p < 0.001$). However, recently some trials were published that questioned the potential benefit of beta-blockers in vascular surgery patients. In particular the POISE trial might have a negative impact on the willingness to prescribe beta-blockers to patients undergoing major vascular surgery. In the POISE trial the investigators found an increased risk for all-cause death in patients using beta-blockers, in particular driven by an excess in perioperative strokes[20]. There are several explanations for the findings in POISE related to dosing, duration of therapy, beta-blocker withdrawal and adequate titration[21]. When keeping this in mind, beta-blocker therapy still is safe and effective, in particular in patients at high cardiac risk as in the current study.

It should be noted that the patients in the current study were considered to be at high cardiac risk which does not imply that they were considered to be unfit for surgery in general. The term cardiac high-risk in this study is based on our observations in the DECREASE I and II trials[22]. Patients with 3 or more risk factors as in the present study had a 4-fold and 28-fold increased risk for perioperative cardiac events as compared to patients at intermediate or low risk respectively. In terms of overall

survival, patients in the current study had a worse outcome compared to patients in EVAR-1 and DREAM but a much better outcome compared to patients in EVAR-2[1,23,24]. Furthermore, the current study is not a randomized trial and as such has obvious limitations related to the nature of the study. However, keeping these limitations in mind, and using multivariable regression analysis with propensity scoring, the results of this study are in line with previous published studies. It reemphasizes the need for optimal medical therapy in high-risk patients scheduled for AAA repair irrespective of the choice of treatment modality. Physicians should not be pacified by the thought that endovascular treatment is a less invasive treatment, therefore being less stressful for the heart and hence requiring less aggressive medical therapy. On the contrary, in the end patients undergoing endovascular AAA repair could even benefit more from aggressive medical therapy as the initial benefit of endovascular repair might be sustained in these patients.

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# Chapter 35

## Long-term outcome of prophylactic coronary revascularization in cardiac high-risk patients undergoing major vascular surgery: the randomized DECREASE-V pilot study

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## ABSTRACT

**Background:** Prophylactic coronary revascularization in vascular surgery patients with extensive coronary artery disease is not associated with an improved immediate postoperative outcome. However, the potential long-term benefit remains unknown. We performed a study to assess the long-term benefit of prophylactic coronary revascularization in these patients.

**Methods:** Of 1880 patients scheduled for major vascular surgery, 430 had ≥3 risk factors (> 70 yrs, angina pectoris, myocardial infarction, heart failure, stroke, diabetes mellitus, and renal failure). All underwent cardiac testing using dobutamine echocardiography or nuclear stress imaging. Those with extensive stress-induced ischemia (≥ 5 segments or ≥ 3 walls) were randomly assigned for additional revascularization.

**Results:** In total 101 patients showed extensive ischemia and were assigned to revascularization (N=49) or no-revascularization (n=52). After 2.8 years overall survival was 64% for patients randomized to no preoperative coronary revascularization versus 61% for patients assigned to preoperative coronary revascularization (HR 1.18, 95%CI 0.63-2.19, p=0.61). The survival free of all-cause death, nonfatal myocardial infarction, and coronary revascularization was similar in both groups: 49% and 42% respectively for patients allocated to medical treatment or coronary revascularization (HR 1.51, 95% CI 0.89-2.57, p=0.13). Only 2 patients assigned to medical treatment required coronary revascularization during follow-up. Also in patients who survived the first 30 days after surgery there was no apparent benefit of revascularization on cardiac events (HR 1.35, 95% CI 0.72-2.52, p=0.36).

**Conclusions:** Preoperative coronary revascularization in high-risk patients undergoing major vascular surgery is not associated with an improved postoperative or long-term outcome compared to best medical treatment.

## INTRODUCTION

According to the guidelines of the American College of Cardiology /American Heart Association (ACC/AHA), it is recommended to perform coronary angiography in patients with high-risk noninvasive test results. Subsequently, myocardial revascularization should be performed in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved[1]. However in both the CARP trial and DECREASE V trial prophylactic preoperative coronary revascularization was not associated with improved immediate postoperative outcome[2,3]. As has been shown recently, early surgery after coronary stent placement might actually lead to an increase in adverse cardiac events due to in-stent thrombosis or bleeding complications[4]. This might explain the lack of perioperative benefit. However it was expected that at least long term outcome, i.e. after the potentially hazardous perioperative period, should be improved in these patients. Therefore, we analyzed the long-term outcome of the randomized DECREASE V trial to assess whether there is a long-term benefit of prophylactic coronary revascularization in high-risk patients undergoing major vascular surgery.

## METHODS

The study design and the perioperative results of the original DECREASE V trial have been published previously[2]. In brief, patients were considered eligible for the study if they were scheduled for an elective open abdominal aortic or infrainguinal arterial reconstruction. Patients were screened for the prevalence of cardiac risk factors including age over 70 years, angina pectoris, prior myocardial infarction, compensated congestive heart failure or a history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction (serum creatinine >160 μmol/L), and prior stroke or transient ischemic attack. All patients with at least 3 risk factors underwent cardiac stress testing prior to surgery. Those who experienced extensive stress-induced ischemia were enrolled in the DECREASE V trial. All patients provided informed consent, and the Erasmus MC medical ethics committee and local research ethics committees approved the study. Out of 1880 screened patients 101 (5.3%) were considered eligible, had ≥ 3 risk factors, extensive stress induced myocardial ischemia and were subsequently randomized. A total of 49 patients were allocated to best medical treatment and preoperative coronary revascularization and 52 patients to best medical treatment only.

Cardiac stress testing was performed by dobutamine echocardiography or dobutamine or dipyridamole perfusion scintigraphy, as previously described[5,6]. Test results were scored by the extent of stress-induced ischemia using a 17-segment model in dobutamine echocardiography and a 6-wall model in stress perfusion scintigraphy. Limited ischemia was defined by the presence of 1-4 ischemic segments or 1-2 ischemic walls, while extensive ischemia was defined by ≥ 5 ischemic segments or ≥ 3 ischemic walls.

All patients were monitored for cardiac events after screening. Twelve-lead ECG and serum troponin-T level were systematically assessed one, three, seven, and 30 days after surgery. Outpatient follow-up was performed at 30 days if a patient had been discharged from the hospital. At the outpatient clinic all patients were screened at 3-months intervals for cardiac events by clinical history and 12-lead ECG and additional tests were performed whenever indicated by the treating physicians. For this report the outcomes were long-term all-cause death and a combined end-point of all-cause death, nonfatal myocardial infarction, and coronary revascularization during follow-up.

Myocardial infarction (MI) was defined as the presence of 2 out of the following 3 criteria: (1) Characteristic ischemic symptoms lasting > 20 minutes, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists > 24 hours, and (3) a positive troponin T, i.e. >0.10 ng/ml, or peak creatinine kinase-MB >8% of an elevated total creatinine phosphokinase with characteristic rise and fall.

Continuous data are presented as median values and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical and surgical characteristics between patients allocated to revascularization or no-revascularization were evaluated by Wilcoxon's nonparametric tests, Chi-square tests or Fisher's exact tests, as appropriate. The incidence of outcome events over time was examined by the Kaplan-Meier method. Multivariate (Cox) regression was used to compare differences in overall survival and cardiac event free survival between the allocated treatment strategies, adjusted for baseline clinical risk factors. Patients who had an event prior to surgery but after screening were included in the analyses as the day of screening was considered to be baseline. Analyses were performed according to the intention to treat principle. All statistical tests were 2-sided and a p-value <0.05 was considered significant.

## RESULTS

Baseline variables in patients who underwent preoperative coronary revascularization (n=49) or best medical treatment only (n=52) are shown in TABLE 35.1. In patients allocated for coronary revascularization, 32 underwent a percutaneous coronary intervention, bare metal stent in 2 and drug eluting stents in 30. Patients continued with dual-antiplatelet therapy during surgery. After surgery, patients with bare metal stents stopped dual-antiplatelet therapy after 3 months and continued with aspirin afterwards. Patients with drug eluting stent continued dual-antiplatelet therapy during follow-up. A bypass procedure was performed in 17 patients. The impact of drug eluting stents versus bare metal stents could not be assessed due the number of patients included in the study.



The 30-day outcome of the study population has been described in detail previously[2]. Two patients died prior to vascular surgery because of a ruptured aneurysm after successful bypass surgery and

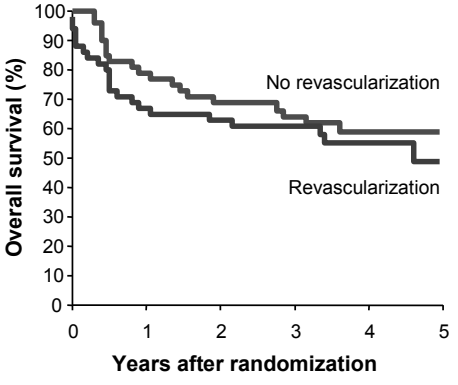


**FIGURE 35.1** Overall survival in 101 randomly assigned patients.

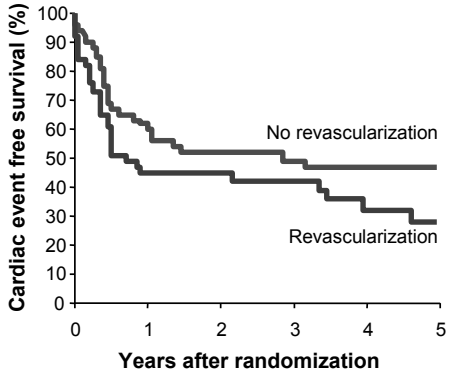


**FIGURE 35.2** Cardiac event-free survival in 101 randomly assigned patients.

**TABLE 35.1** Baseline characteristics.

| | Revascularization | | |
|---|---|---|---|
| | Yes | No | p-value |
| | N=49 | N=52 | |
| Age (years) | 71 (64, 74) | 70 (63, 75) | |
| Men – no. (%) | 42 (86%) | 47 (90%) | 0.55 |
| Diabetes mellitus – no. (%) | 18 (37%) | 15 (29%) | 0.53 |
| Current angina pectoris – no. (%) | 25 (51%) | 22 (42%) | 0.43 |
| Prior myocardial infarction – no. (%) | 49 (100%) | 50 (96%) | 0.50 |
| Prior heart failure – no. (%) | 23 (47%) | 24 (46%) | 1.0 |
| Prior CVA – no. (%) | 20 (41%) | 13 (25%) | 0.14 |
| Prior renal failure – no. (%) | 9 (18%) | 11 (21%) | 0.81 |
| Medications | | | |
| Aspirin – no. (%) | 37 (76%) | 30 (58%) | 0.09 |
| Beta-blocker – no. (%) | 34 (70%) | 36 (69%) | 1.0 |
| ACE-inhibitor – no. (%) | 28 (57%) | 22 (42%) | 0.17 |
| Statin – no. (%) | 34 (69%) | 30 (58%) | 0.30 |
| Coronary artery narrowed > 50% | | | |
| Right coronary – no. (%) | 39 (80%) | - | |
| Left artery descending – no. (%) | 46 (94%) | - | |
| Left circumflex – no. (%) | 37 (76%) | - | |
| Number of narrowed arteries – no. (%) | | | |
| 1 | 0 | - | |
| 2 | 12 (24%) | - | |
| 3 | 33 (67%) | - | |
| Left main – no. (%) | 4 (8%) | - | |

CVA = cerebrovascular accident; ACE = angiotensin converting enzyme

one patient suffered from a myocardial infarction after an unsuccessful coronary revascularization. Revascularization did not improve 30-day outcome after vascular surgery. The incidence of all-cause death or nonfatal MI for patients with preoperative revascularization or medical treatment only was 43 vs. 33% respectively (HR 1.4, 95% CI 0.7- 2.8 p = 0.30).

During a median follow-up of 2.8 years (interquartile range 0.9–4.2 years) 42/101 patients died. After 2.8 years overall survival was 64% for patients randomized to no preoperative coronary revascularization versus 61% for patients assigned to preoperative coronary revascularization (HR 1.18, 95%CI 0.63-2.19, p=0.61; FIGURE 35.1). As is shown in FIGURE 35.2 the incidence of all-cause death, nonfatal myocardial infarction, and coronary revascularization was similar in both groups: event free survival after 2.8 years was 49% and 42% respectively for patients allocated to medical treatment or coronary revascularization (HR 1.51, 95% CI 0.89-2.57, p=0.14). In the no-revascularization group 2 (4%) patients underwent coronary revascularization during follow-up; one patient underwent coronary artery bypass surgery 12 months after vascular surgery because of unstable angina pectoris and one patient underwent PCI using drug eluting stents 27 months after vascular surgery because of progressive angina pectoris complaints.

It might be argued that preoperative coronary revascularization, in particular stent placement, might lead to an increased 30-day risk for in-stent thrombosis or bleeding after discontinuation or continuation of antiplatelet therapy[4]. Therefore we performed a separate analysis including only patients

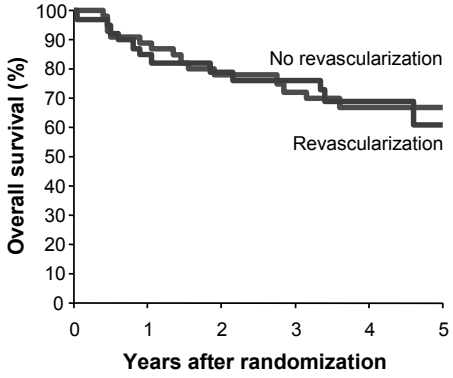


**FIGURE 35.3** Overall survival of patients who survived the first 30 days after surgery.

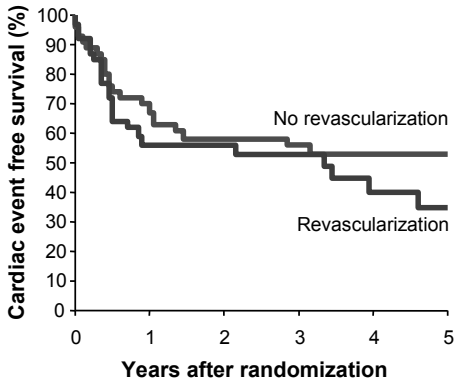


**FIGURE 35.4** Cardiac event-free survival of patients who survived the first 30 days after surgery.

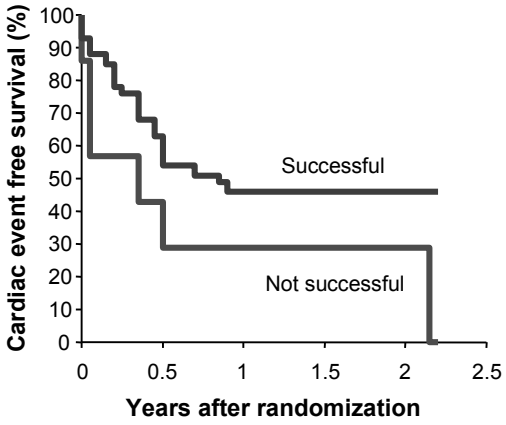


**FIGURE 35.5** Cardiac event-free survival after successful or not successful preoperative revascularization.



who survived at least 30 days after surgery (n=36 and n=46 respectively for revascularization and medical treatment only). As is shown in FIGURES 35.3 and 35.4 also in these survivors no apparent benefit of revascularization was observed. Of the revascularized patients 47% had an event within a median of 2.8 years of follow-up versus 44% in those who did not undergo preoperative coronary revascularization (HR 1.35, 95% CI 0.72–2.52, p=0.36). Also all-cause mortality did not differ between both groups (HR 0.79, 95% CI 0.35–1.78, p=0.57).

There was no difference in long-term event free survival between patients who underwent preoperative PCI or CABG (HR 0.91, 95% CI 0.44-1.88, p=0.80). After a median of 2.8 years event free survival was 41% vs. 44% respectively for PCI and CABG. In addition for the endpoint all-cause death no significant difference was observed (HR 0.81, 95% CI 0.33-1.96, p=0.64). However, patients with an incomplete revascularization procedure had the worst outcome; 6/7 (86%) patients died within 2 years after the attempted revascularization compared to 13/42 (31%) with complete revascularization (HR 4.07, 95% CI 1.53–10.82, p=0.005, FIGURE 35.5).

## DISCUSSION

The DECREASE-V study did not show a long-term benefit of prophylactic preoperative coronary revascularization in stable patients with multiple cardiac risk factors and extensive stress induced myocardial ischemia scheduled for major vascular surgery.

The current findings are in line with results of large randomized trials in the non-surgical population. Patients with stable multivessel coronary artery disease do not have a better survival after coronary stenting or bypass grafting as compared to medical treatment only. The recently published MASS II was the first randomized controlled clinical trial to report on 5-year outcomes of non-surgical patients with stable multivessel coronary artery disease treated with either bare metal stenting, CABG, or best medical treatment only[7]. It was shown in this study that optimal medical therapy in patients with stable multivessel coronary artery disease results in similar long-term outcome in terms of cardiac related death or all-cause mortality. The authors concluded, "patients with mild to moderate angina can be safely managed medically, whereas PCI or CABG is appropriate if symptoms are not adequately controlled by medication or if other high-risk features are apparent." The COURAGE trial also found no additional benefit of coronary revascularization additionally to optimal medical therapy in 2287 patients with objective evidence of myocardial ischemia and significant coronary artery disease[8]. During a median follow-up of 4.6 years cumulative event rate of all-cause death and myocardial infarction were 19.0% in the PCI group and 18.5% in the medical-therapy group. As discussed by the COURAGE trialists, these findings may be explained by differences in atherosclerotic plaque morphology and vascular remodeling associated with acute coronary syndromes, as compared with stable coronary artery disease. Medical treatment in both MASS II and COURAGE included rigorous statin and aspirin therapy. This might have prevented vulnerable plaques, which are usually difficult to detect and impossible to treat with coronary angioplasty or bypass, to rupture and cause acute coronary syndromes. It is important to realize that vulnerable coronary lesions are not necessarily severely stenotic, and severely stenotic lesions are not necessarily unstable. Focal management of severely stenotic coronary lesions with PCI in both MASS II and COURAGE did not reduce the rate of death and myocardial infarction, presumably because the treated, severely stenotic lesions were not likely to trigger an acute coronary event[8].

Remarkably, in MASS II and COURAGE annual mortality rates were approximately 1-2% whereas in CARP and DECREASE V the annual mortality rates in patients who survived surgery were 6.8% and 8.2% respectively. Baseline angiographic cardiac status in MASS II and COURAGE was not significantly better or worse than CARP and DECREASE V: 3-vessel disease was present in 58% and 31% versus 33% and 75% respectively. In line with these findings, it has been recently shown that patients with so-called "polyvascular" disease, i.e. multiple vascular beds affected, have a significant worse outcome compared to patients with coronary artery disease only[9]. In REACH event rates (cardiovascular death, MI, stroke, or hospitalization for a cardiovascular event) increased with the number of symptomatic vascular beds: 5.3% of patients with risk factors only to 12.6% with 1, 21.1% with 2, and 26.3% with 3 disease locations[9]. As all patients in DECREASE V and CARP had proven coronary artery disease and were planned for non-cardiac vascular surgery, these patients can be considered to have polyvascular disease. This indicates that patients scheduled for vascular surgery with extensive coronary artery disease should be considered to be a different population than patients without peripheral arterial disease but with coronary artery disease only. However, also in this patient population with stable severe coronary artery disease optimal medical therapy seems to be equal to coronary revascularization in addition to best medical treatment.

The findings of both CARP and DECREASE V support the current guidelines of the ACC/AHA on perioperative management in high-risk patients to reserve revascularization only for cardiac unstable patients. Considering the high long-term mortality and cardiac event rates, these patients should be regularly screened for the presence of ischemic complaints and aggressive anti-ischemic medical therapy must be installed.

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# Summary and conclusions

Cardiac complications are a major cause of perioperative morbidity and mortality in patients undergoing non-cardiac surgery. It is estimated that the incidence of such complications is between 0.5% and 1.0%. Worldwide, about 100 million adults undergo some form of non-cardiac surgery each year, and so between 500,000 and 1,000,000 people will suffer from perioperative cardiac complications; one of four of them will die from this cause. In particular patients undergoing vascular surgery are prone to develop perioperative cardiovascular complications as they have a high generalized atherosclerotic burden. In order to prevent the devastating effects of perioperative cardiovascular complications, it is of critical importance to identify those at increased risk and treat them accordingly. In this thesis preoperative cardiovascular risk stratification and strategies to reduce perioperative cardiovascular risk are evaluated. Furthermore, as discussed in this thesis, preoperative risk evaluation should also be considered as an excellent opportunity to take measures to reduce the risk for long-term adverse cardiovascular events.

### Part I. Preoperative cardiovascular risk assessment

In part one of this thesis current and new cardiovascular risk stratification strategies are evaluated.

**Chapter 1** provides an overview of the magnitude of the problem of perioperative cardiac complications in patients undergoing vascular surgery. It should be appreciated that nearly all vascular surgery patients (i.e. 92%) have some form of coronary artery disease. Therefore, rigorous perioperative screening for cardiac complications is warranted. This is of special concern as an estimated 75% of patients who have objective evidence of MI are not diagnosed as such because symptoms are masked by residual anesthetic effects, administration of analgesic agents, competing somatic stimuli such as incisional pain, and other factors. If patients are screened adequately, the true incidence of perioperative cardiac complications in this patient population appears to be as high as 20%. This high incidence of perioperative cardiac events highlights the importance of preoperative cardiac screening. This chapter also provides an overview of current screening methods, including clinical cardiac risk factor indices, laboratory measurements, cardiac (stress) imaging modalities, and invasive coronary testing. Subsequently, risk reduction strategies are discussed including medical therapy and prophylactic coronary revascularization. Possible protective medical therapy includes perioperative statin use and adequately dosed perioperative beta-blocker therapy. In contrast, prophylactic coronary revascularization in high risk patients does not seem to be associated with a reduced perioperative cardiac event rate. This chapter also highlights the importance of long-term cardiac risk reduction in this patient population as patients undergoing vascular surgery are at high

risk for long-term cardiac events, even those without perioperative cardiac complications. In fact, patients who undergo vascular surgery have a worse prognosis than patients who experienced an acute coronary event. This difference is partially caused by a marked undertreatment of patients undergoing vascular surgery compared to patients with established, symptomatic coronary artery disease. Optimal medical treatment of these patients is of critical importance and recent guidelines such as the ACC/AHA guidelines and the TASC2 guidelines should be adhered to, so that the patient lives long enough to enjoy the benefits of vascular surgery.

**Chapter 2** provides an overview of cardiac complications in the general non-cardiac surgery population. Although the pathophysiology of perioperative myocardial infarction is not entirely clear, plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is implicated in a similar manner to that causing myocardial infarctions in the non-operative setting. The incidence of plaque rupture may be increased by the stress response to major surgery. This response includes sympathetic activation promoting sheer stress on arterial plaques, enhanced vascular reactivity conducive to the development of vasospasm, reduced fibrinolytic activity, platelet activation and hypercoagulability. Heightened sympathetic tone also increases myocardial oxygen requirements (for example through tachycardia and increased contractility), leading to a mismatch between oxygen supply and demand that, when sustained, can lead to infarction. Therefore, to improve postoperative cardiac outcome after non-cardiac surgery a dual approach is required. First, one must focus on correcting the mismatch of myocardial oxygen supply and demand. Second, one must stabilize the coronary artery atheromatous plaque. At present, these needs seem to be best met with a combined medical therapy of cardioselective beta-blockers, statins and, if possible, aspirin.



**Chapters 3 and 4** describe current evidence on preoperative cardiac risk evaluation strategies. In chapter 4 a simple normogram of nine steps is presented to optimize patients scheduled for non-cardiac general surgery. The combination of clinical cardiac risk factors, type of surgery and ECG results allows to make an initial crude assessment of a patient's perioperative cardiac risk. This risk estimation can be used to identify those patients at increased risk who should undergo further cardiac testing. If a patient is at increased risk, further cardiac (stress) testing might be warranted and appropriate medical therapy should be initiated.

Based on over 100,000 non-cardiac surgical procedures, **chapter 5** describes a refinement of the widely used Revised Cardiac Risk Index. When more detailed information, including age, the type of surgery (defined as low, low-intermediate, intermediate-high, and high), whether it was laparoscopic or open, and whether it was emergent, was added to the Revised Cardiac Risk index, the predictive value increased significantly. This refinement of the Revised Cardiac Risk Index might be most applicable to situations in which administrative data are to be used to assess outcomes and to compare outcomes in different hospitals or regions.

The Revised Cardiac Risk Index is also widely used for risk stratification of patients scheduled for vascular surgery. However, age is not taken into account in this index. As shown in **chapter 6**, the value of the Revised Cardiac Risk Index varies significantly among different age categories in vascular surgery patients. In chapter 6 it is shown that including age, risk of surgery and hypertension as factors in the Revised Cardiac Risk Index improves the predictive value considerably. It clearly stratifies vascular surgery patients into low, intermediate and high risk. In addition, this model provides long-term prognostic value.

In surgical patients at increased cardiac risk based on clinical risk factors, further cardiac stress testing might be warranted. **Chapter 7** describes different cardiac stress testing modalities and their possible use for preoperative cardiac risk stratification. While there is no direct comparison, several meta-analyses compared different techniques with respect to sensitivity and specificity. A positive trend in favor of dobutamine stress echocardiography was found. Nevertheless, because the tests have comparable accuracy, there is no definite answer to the question of which test to choose. The choice of test should be based on the center's experience and short-term availability.

Another important question is which patients should undergo additional cardiac stress testing. In other words, in which patients do stress test outcomes change perioperative management. In **chapter 8** the value of preoperative cardiac testing in intermediate-risk vascular surgery patients receiving beta-blocker therapy was assessed. In 770 randomized intermediate risk patients, those assigned to no cardiac stress testing had a similar incidence of cardiac death or myocardial infarction at 30-days after surgery as those assigned to testing. The strategy of no testing brought surgery almost 3 weeks forward. Therefore, cardiac testing can safely be omitted in intermediate-risk patients, provided that beta-blockers aiming at tight heart rate control are prescribed.

In **chapter 9** the impact of abdominal aortic aneurysm size on perioperative cardiac events is studied. Abdominal aortic aneurysm size and growth has been found to be associated with local generation of inflammation markers. As inflammation also plays a pivotal role in perioperative adverse cardiac events, it was hypothesized that patients with a large abdominal aortic aneurysm are at increased risk for cardiac events. As shown, indeed abdominal aortic aneurysm size is independently associated with perioperative nonfatal myocardial infarction and cardiovascular death in 500 patients undergoing open abdominal aortic aneurysm repair. Patients with a larger aneurysm have a higher risk of perioperative cardiac complications.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted by the heart in response to ventricular wall stress and has prognostic value in patients with heart failure, coronary artery disease and heart valve abnormalities. It was hypothesized that NT-proBNP might have additional prognostic value as a simple objective risk marker for postoperative cardiac events among vascular surgery patients. As shown in **chapter 10**, NT-proBNP is an excellent tool for further risk stratification with an optimal cut-off value of 350 pg/ml. In multivariate analysis, NT-proBNP > 350 pg/ml was significantly associated with a 4.7-fold increased risk for perioperative cardiac events. NT-proBNP > 350 pg/ml was also associated with an independent 1.9-fold increased risk for long-term mortality during a median follow-up of 2.4 years.

## Part II. Perioperative risk reduction

In part two of this thesis perioperative cardiovascular risk reduction strategies are described, i.e. beta-blocker therapy, statin therapy, prophylactic coronary revascularization and endovascular treatment modalities.

In chapters **11 and 12** the design and results of the DECREASE IV study are described. Beta-blockers and statins reduce perioperative cardiac events in high-risk patients undergoing vascular surgery by restoring the myocardial oxygen supply/demand balance and/or stabilizing coronary plaques. However, their effects in intermediate risk patients remained ill-defined. The DECREASE IV study evaluated the effectiveness and safety of beta-blockers and statins for the prevention of perioperative cardiovascular events in intermediate-risk patients undergoing non-cardiovascular surgery. In this randomized trial, including 1066 patients at intermediate cardiac risk, bisoprolol was associated

with a significant decrease in the incidence of cardiac death and nonfatal myocardial infarction while statin therapy was associated with a trend towards improved postoperative cardiac outcome. Importantly, there was no increased risk for postoperative stroke in patients on beta-blocker therapy.

The positive findings of DECREASE IV for perioperative beta-blocker therapy were confirmed in a meta-analysis described in **chapter 13**. In 15 randomized trials including 1077 patients perioperative beta-blocker therapy was associated with a 65% reduction in perioperative myocardial ischemia, a 56% reduction in myocardial infarction, and a 67% reduction in the composite endpoint of cardiac death and non-fatal myocardial infarction.

Major concerns of perioperative beta-blocker use are ischemic complications, such as stroke. In **chapters 14, 15, and 16** the impact of beta-blocker therapy on this type of complications is evaluated. As shown, beta-blocker therapy is not associated with an increase in ischemic complications of the esophagogastric anastomosis in patients undergoing esophagectomy for cancer. Furthermore, it is highlighted that perioperative beta-blockers are not a "fire-and-forget" type of medication. It should be started well ahead of surgery to allow a safe and adequate titration of beta-blockers. It is shown that if prophylactic beta-blocker therapy is initiated at a low dose and up titrated in the preoperative period, the risk of stroke seems to be similar to that of patients not on beta-blockers while the cardioprotective effect is maintained.





In **chapters 17, 18, 19, 20, 21, and 22** the benefits and possible pitfalls of perioperative statin use in vascular surgery patients are investigated. Several retrospective studies have demonstrated an association between perioperative statin therapy and a reduction in perioperative cardiac events. However, there were also concerns regarding the safety of perioperative statin therapy. In **chapter 18** a cohort of 981 vascular surgery patients is studied. In this study we found that perioperative statin use in a large group of patients was not associated with an increased risk of myopathy, i.e. CK elevation with or without muscle complaints, after major vascular surgery.

As shown in chapters **19 and 20**, statin use is associated with improved recovery from acute kidney injury after major surgery and a beneficial effect on long-term survival. Also in patients requiring suprarenal clamping during abdominal aortic aneurysm repair perioperative statin therapy is associated with a preserved renal function. On the other hand, it must be realized that perioperative statin therapy discontinuation, which is inevitable in approximately 25% of patients undergoing major vascular surgery, might be associated with an increase in cardiac events as is shown in **chapter 21**. Statin discontinuation was associated with an increased risk for postoperative troponin release, and the combination of myocardial infarction and cardiovascular death. Interestingly, fluvastatin extended release was associated with less perioperative cardiac events compared to atorvastatin, simvastatin, and pravastatin.

In **chapter 22** the results of the DECREASE III trial are described. In this double-blind, placebo-controlled trial, statin naïve patients were randomly assigned to receive, in addition to beta-blocker, either 80 mg fluvastatin extended release once daily or placebo, starting 37 days prior to surgery. Two hundred fifty patients were assigned to fluvastatin and 247 to placebo. The incidence of myocardial ischemia in the fluvastatin group was significantly lower compared to the placebo group, respectively 10.8% vs. 19.0%. The incidence of cardiac death or myocardial infarction was also significantly reduced in the fluvastatin group. Importantly, fluvastatin use was not associated with an increased risk for myopathy, liver dysfunction or all-cause death. Therefore, it is concluded that in patients undergoing vascular surgery, fluvastatin therapy is associated with an improved postoperative cardiac outcome.

In **chapters 23, 24, 25, and 26** perioperative treatment of patients with coronary stents as well as the impact of prophylactic coronary revascularization in high cardiac risk patients are described.

Recent coronary stent placement might be potentially harmful for patients undergoing non-cardiac surgery. Surgery increases the thrombosis risk due to a perioperative stress response, including sympathetic activation promoting sheer stress on arterial plaques, enhanced vascular reactivity conducive to vasospasm, reduced fibrinolytic activity, platelet activation, and hypercoagulability. In addition, while the surgical patient is in a hypercoagulable state dual antiplatelet therapy is often interrupted because of the fear for excessive bleeding complications during surgery. As shown in these chapters, there is an association between early non-cardiac surgery after coronary artery stenting and perioperative adverse cardiovascular events. Importantly, in patients undergoing early surgery, discontinuation of antiplatelet therapy during the perioperative period may be a major cause of the increase in major adverse cardiac events. The type of stent (i.e. bare-metal or drug-eluting) does not seem to influence cardiovascular outcome.

It was also hypothesized that some very high cardiac risk patients might benefit from preoperative prophylactic coronary revascularization. Therefore, the randomized DECREASE V pilot study was conducted. As shown in **chapter 25**, 1888 patients scheduled for vascular surgery were screened. Those at high cardiac risk based on clinical risk factors, i.e. ≥ 3 risk factors, and with extensive stress-induced ischemia were randomly assigned for additional revascularization or best medical treatment only. Of 430 high-risk patients, 101 (23%) showed extensive ischemia and were randomly assigned to revascularization or no revascularization. Revascularization did not improve 30-day outcome. Also, no benefit during 1-year follow-up was observed after coronary revascularization.

Endovascular treatment of abdominal aortic aneurysms is possibly associated with a reduced incidence of perioperative cardiovascular complications. This might be due to the reduced myocardial stress during an endovascular procedure. In patients undergoing an endovascular procedure no aortic clamping and declamping are performed, the procedure is done under loco-regional anesthesia, and in combination with a reduced blood loss a more hemodynamic stable condition is achieved. As is shown in **chapters 27, 28, and 29**, indeed endovascular treatment is associated with an improved perioperative cardiac outcome. In **chapter 28** patients at high cardiac risk, i.e. 3 or more cardiac risk factors, undergoing endovascular abdominal aortic aneurysm repair had a significantly reduced incidence of perioperative myocardial damage compared to patients undergoing open repair. As shown in chapter **27 and 28**, the perioperative cardiac benefits of endovascular therapy are irrespective of the presence and extent of underlying coronary artery disease. However, as indicated in these chapters the long-term durability of this perioperative cardiac advantage remains to be awaited.

### Part III. Long-term risk reduction

The preoperative evaluation offers a unique opportunity to identify patients at increased perioperative risk and initiate appropriate lifestyle changes and risk reduction therapy, as these will also improve long-term outcome. In **chapters 30, 31, 32, 33, 34, and 35** the long-term prognosis and factors influencing the long-term outcome of vascular surgery patients are described.

**Chapter 31** describes a study involving a total of 2,730 patients undergoing vascular surgery and a matched cohort, using propensity scores, of 2,730 patients with coronary artery disease who underwent coronary angioplasty. Vascular surgery patients had a worse long-term prognosis and received less medication (beta-blockers, statins, angiotensin-converting enzyme inhibitors, aspirin, nitrates, and calcium antagonists) than patients with coronary artery disease did. Based on these

results, it is concluded that long-term prognosis of vascular surgery patients is significantly worse than for patients with coronary artery disease, which might be attributable to the undertreament of patients with peripheral arterial disease.

As shown in **chapter 32**, patients with temporary worsening of renal function after open abdominal aortic aneurysm repair are at high risk for poor long-term outcome. During 6.0 ± 3.4 years follow-up, the risk of late mortality was 1.7-fold increased in the persistent renal function worsening group, followed by those with temporary renal function worsening.

Screening for abdominal aortic aneurysms in populations at increased risk, i.e. elderly males, to detect those who will benefit from elective repair seems to be safe and cost-effective. However, perioperative complications of elective abdominal aortic aneurysm repair remain a significant problem. Therefore, an attractive option would be the slowing of abdominal aortic aneurysm growth, thereby preventing the abdominal aortic aneurysm to reach a size requiring surgical intervention. In **chapter 33** the effect of statin therapy was studied. In 150 patients under surveillance for infrarenal aortic aneurysms, statin users had a 1.16 mm/year lower abdominal aortic aneurysm growth rate compared to non-users, irrespective of other known factors influencing aneurysm growth.





As indicated in chapters 27 and 28, patients undergoing endovascular abdominal aortic aneurysm repair experience significantly less perioperative cardiac events compared to patients undergoing open repair. In **chapter 34** the long-term outcome of endovascular abdominal aortic aneurysm repair is described for patients at high cardiac risk, i.e. those with ≥ 3 clinical cardiac risk factors. In 124 patients, endovascular repair was associated with improved cardiac event free survival during a median follow-up of 3.3 years but not with an overall survival benefit. Importantly, statin therapy was associated with both improved overall survival and cardiac event free survival. Therefore, it was concluded that the perioperative cardiac benefit of endovascular abdominal aortic aneurysm repair in high cardiac risk patients is sustained during long-term follow-up provided patients are on optimal medical therapy but it is not associated with improved overall long-term survival.

Finally, the long-term outcome of the randomized DECREASE V pilot study is described in **chapter 35**. As was shown in chapter 25, prophylactic coronary revascularization in vascular surgery patients was not associated with an improved perioperative cardiac outcome. As shown in this chapter also long-term outcome is not improved after prophylactic coronary revascularization. After 2.8 years overall survival was 64% for patients randomized to no preoperative coronary revascularization versus 61% for patients assigned to preoperative coronary revascularization. Therefore, it is concluded that preoperative coronary revascularization in high-risk patients undergoing major vascular surgery is not associated with an improved postoperative or long-term outcome compared to best medical treatment only.

# Samenvatting en conclusies

Cardiale complicaties zijn een belangrijke oorzaak van mortaliteit en morbiditeit rond niet-cardiale operaties. Bij ongeveer 0,5% tot 1,0% van alle operaties treedt een cardiale complicatie op. Wereldwijd worden jaarlijks circa 100 miljoen operaties uitgevoerd. De incidentie van perioperatieve cardiale complicaties wordt geschat op 500.000 tot 1.000.000 per jaar. Ongeveer een kwart van deze complicaties leidt tot het overlijden van de patiënt. In het bijzonder patiënten die een operatie aan de slagaders ondergaan hebben een verhoogde kans op het ontwikkelen van perioperatieve cardiale complicaties. Dit is vooral het gevolg van de uitgebreide atherosclerose bij deze patiëntengroep. Om perioperatieve cardiale complicaties bij deze patiënten te voorkomen, is het uitermate belangrijk om een goede inschatting van het perioperatieve risico te maken. Op basis van deze risico-inschatting kan de juiste perioperatieve therapie worden ingesteld. Het onderzoek beschreven in dit proefschrift was gericht op het optimaliseren van de preoperatieve inschatting van het cardiale risico en het verminderen van het perioperatieve cardiale risico. De preoperatieve risico-inschatting moet eveneens gezien worden als een uitgelezen mogelijkheid om de juiste therapie te starten om ook complicaties op lange termijn te voorkomen.

## Deel I. Preoperatieve cardiovasculaire risico-inschatting

In deel één van dit proefschrift worden bestaande en nieuwe modellen voor het inschatten van het perioperatieve cardiovasculaire risico besproken.

**Hoofdstuk 1** geeft een overzicht van de omvang van het probleem van perioperatieve cardiale complicaties bij patiënten die een operatie aan een slagader (vaatchirurgie) ondergaan. Bijna alle patiënten (92%) die een vaatchirurgische ingreep ondergaan, hebben ook een vorm van coronairlijden. Daarom is het bij deze patiënten uitermate belangrijk om rond de operatie te screenen op het ontstaan van cardiale complicaties, zodat tijdig adequate therapie kan worden gestart. Wanneer patiënten die een grote operatie van de vaten ondergaan systematisch worden gescreend, blijkt de incidentie van cardiale complicaties rond 20% te liggen. Men moet zich hierbij realiseren dat 75% van alle cardiale complicaties bij deze patiënten niet als zodanig wordt gediagnosticeerd doordat de symptomen vaak, door bijvoorbeeld pijnstilling en pijnklachten van andere organen, gemaskeerd worden.

**Hoofdstuk 2** geeft een overzicht van perioperatieve cardiale complicaties bij patiënten die een niet-vaatchirurgische, niet-cardiale operatie ondergaan. De pathofysiologie van het perioperatieve hartinfarct is niet volledig duidelijk. Coronaire plaque ruptuur, leidend tot formatie van trombus en

afsluiting van de kransslagader, lijkt een belangrijke rol te spelen bij het ontstaan van het perioperatieve hartinfarct. Het optreden van deze plaque rupturen wordt versterkt door de lichamelijke stress respons die ontstaat tijdens grote chirurgische ingrepen. Ook leidt deze stress respons tot een verhoogde zuurstofbehoefte van het hart zelf. Echter, wanneer in de kransslagaders een vernauwing aanwezig is als gevolg van atherosclerose kan er door het hart niet voldaan worden aan deze verhoogde zuurstofbehoefte. Als deze situatie te lang voortduurt, zal dit uiteindelijk leiden tot een hartinfarct. Daarom is het van belang om een tweesporen beleid te volgen bij de preventie van perioperatieve cardiale complicaties. Ten eerste dient de behoefte en aanbod van zuurstof te worden gebalanceerd. Ten tweede moet de zogenaamde instabiele coronaire plaque, die op het punt staat te ruptureren, worden gestabiliseerd. Het lijkt dat dit het beste te bereiken is door een combinatie van statines, bètablokkers en, indien mogelijk, aspirine.

In **hoofdstukken 3 en 4** worden modellen voor het inschatten van het perioperatieve cardiale risico besproken. In **hoofdstuk 4** wordt een normogram van negen stappen beschreven om de patiënt preoperatief te optimaliseren. De combinatie van klinische risicofactoren, type operatie en ECG resultaten maakt het mogelijk een eerste, ruwe, schatting van het operatierisico te maken. Deze schatting kan worden gebruikt om te beslissen of een patiënt nadere cardiale evaluatie nodig heeft en welke medicamenteuze therapie gestart moet worden.

Gebaseerd op gegevens van meer dan 100.000 operaties, wordt in **hoofdstuk 5** een verbetering van de veel gebruikte Revised Cardiac Risk Index voorgesteld. Wanneer meer gedetailleerde informatie, zoals type operatie en leeftijd, wordt toegevoegd, neemt de voorspellende waarde aanzienlijk toe.

De Revised Cardiac Risk Index wordt ook veel gebruikt voor het schatten van het perioperatieve cardiale risico van patiënten die een vaatchirurgische operatie ondergaan. In hoofdstuk 6 is de invloed van leeftijd op de voorspellende waarde van de Revised Cardiac Risk Index onderzocht. Deze bleek verschillend te zijn voor verschillende leeftijdsgroepen. Het onderzoek toont aan dat de voorspellende waarde van de Revised Cardiac Risk Index aanzienlijk is te verbeteren indien leeftijd als factor wordt meegenomen in deze index.

Bij patiënten die op basis van klinische risicofactoren een verhoogd perioperatief cardiaal risico hebben, kan verdere cardiale analyse middels een zogenaamde cardiale stress test nodig zijn. **Hoofdstuk 7** geeft een overzicht van verschillende stress test modaliteiten. Hoewel er nauwelijks directe vergelijkingen zijn gemaakt tussen de verschillende modaliteiten, is wel een aantal meta-analyses verschenen. Deze laten een trend ten faveure van de dobutamine stress echocardiografie zien. Echter, de verschillen met de andere modaliteiten zijn klein. Daarom is het niet mogelijk te zeggen welke test het meest geschikt is voor perioperatieve risico-inschatting. Het verdient aanbeveling de keuze voor een bepaalde test af te laten hangen van de ervaring van een medisch centrum met een bepaalde test.

Een ander belangrijk vraagstuk is welke patiënt baat heeft bij een aanvullende cardiale stress test. In **hoofdstuk 8** wordt de waarde van preoperatieve cardiale stress tests onderzocht in patiënten met een gemiddeld risico die een vaatchirurgische ingreep ondergaan. In 770 gerandomiseerde patiënten was de incidentie van perioperatieve cardiale complicaties gelijk in de groep die had geloot voor aanvullende stress test en de groep die had geloot voor geen aanvullende stress test. Patiënten die geen cardiale stress test ondergingen konden gemiddeld drie weken eerder geopereerd worden. Daarom is geconcludeerd dat een aanvullende cardiale stress test, bij patiënten met een gemiddeld

hoog risico op perioperatieve cardiale complicaties, achterwege gelaten kan worden mits de patiënt op adequate medicamenteuze therapie is ingesteld.

**Hoofdstuk 9** laat, op basis van een studie met 500 patiënten, zien dat de grootte van een aneurysma van de abdominale aorta geassocieerd is met de cardiale uitkomst na operatieve correctie van dit aneurysma. Patiënten met een groter aneurysma hebben een significant grotere kans op perioperatieve complicaties.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) wordt afgescheiden door het hart als reactie op stress op de wand van het hart. NT-proBNP heeft prognostische waarde voor patiënten met hartfalen en voor patiënten met coronairlijden. In **hoofdstuk 10** is onderzocht of NT-proBNP ook prognostische waarde heeft voor patiënten die een vaatchirurgische ingreep ondergaan. Inderdaad, NT-proBNP bleek een zeer goede marker voor perioperatief cardiaal risico te zijn. Een verhoogd NT-proBNP was geassocieerd met een bijna vijf maal zo grote kans op perioperatieve complicaties. Ook was een verhoogd NT-proBNP geassocieerd met een bijna twee maal zo grote kans op sterfte gedurende een follow-up van 2,4 jaar.

## Deel II. Perioperatieve risicoreductie

In deel twee van dit proefschrift worden verschillende strategieën besproken gericht op risicoreductie: bètablokker therapie, statine therapie, profylactische revascularisatie van de kransslagaders en endovasculaire behandelingsopties.

In **hoofdstuk 11 en 12** worden de opzet en de resultaten van de DECREASE IV studie beschreven. In de DECREASE IV studie is de effectiviteit en veiligheid van het perioperatief gebruik van statines en bètablokkers onderzocht in 1066 patiënten met een gemiddeld hoog cardiaal risico. Bètablokkers bleken geassocieerd te zijn met een significante reductie in het aantal perioperatieve cardiale complicaties. Voor statines werd een niet-significante trend gevonden voor een betere perioperatieve cardiale uitkomst.

Deze positieve bevindingen voor bètablokkers werden bevestigd in een meta-analyse (**hoofdstuk 13**). Bij 1077 patiënten uit 15 gerandomiseerde studies werd een significant voordeel voor bètablokkers gevonden wat betreft perioperatieve myocardischemie, perioperatief hartinfarct en de combinatie van cardiale sterfte en hartinfarct.

Recentelijk is er twijfel ontstaan over de veiligheid van perioperatief bètablokker gebruik. Het zou mogelijk geassocieerd zijn met een grotere kans op een beroerte en andere complicaties ten gevolge van een verminderde doorbloeding. **Hoofdstukken 14, 15 en 16** behandelen de invloed van bètablokker therapie op dit soort complicaties. Bètablokker therapie is niet geassocieerd met een grotere kans op doorbloedingsproblemen van een buismaagreconstructie bij patiënten bij wie de slokdarm is verwijderd in verband met kanker. Ook wordt in deze hoofdstukken benadrukt dat bètablokkers met verstand gedoseerd moeten worden. Men moet tijdig beginnen met bètablokker therapie en de dosis op geleide van bloeddruk en hartslagfrequentie aanpassen. Wanneer bètablokkers tijdig in een lage dosering worden gestart en de dosis, indien nodig, adequaat wordt aangepast, is het risico op beroerte niet verhoogd terwijl de kans op cardiale complicaties wel verlaagd is.

In **hoofdstukken 17, 18, 19, 20, 21 en 22** zijn de voordelen en mogelijke nadelen van perioperatief gebruik van statines onderzocht. Meerdere retrospectieve studies suggereren een verband tussen statine gebruik en een kleinere kans op perioperatieve cardiale complicaties. Echter, er zijn ook

bedenkingen ten aanzien van de veiligheid van perioperatief statine gebruik. In **hoofdstuk 18** zijn 981 vaatchirurgische patiënten onderzocht. Perioperatieve behandeling met statines bleek niet geassocieerd met een verhoogd risico op aan statine gerelateerde bijwerkingen zoals myopathie. Uit de **hoofdstukken 19 en 20** blijkt, dat statine gebruik is geassocieerd met een beter herstel van nierfunctie na acute nierschade die op kan treden tijdens een operatie. Ook lijkt statine gebruik geassocieerd te zijn met een betere uitkomst op de lange termijn. Men moet zich echter wel realiseren dat het stoppen van statines rond een operatie geassocieerd is met een grotere kans op cardiale complicaties, vergeleken met patiënten die niet stoppen met statine gebruik, zoals blijkt uit **hoofdstuk 21**. Het zo snel mogelijk hervatten van statine gebruik na een operatie lijkt daarom uitermate belangrijk.

In **hoofdstuk 22** worden de resultaten van de DECREASE III studie beschreven. In deze dubbelgeblindeerde, placebo-gecontroleerde studie werden patiënten die nog niet met statines werden behandeld voor een vaatchirurgische operatie gerandomiseerd. In totaal lootten 250 patiënten voor behandeling met fluvastatine en 247 voor placebo. De incidentie van myocardischemie was twee maal lager in de groep patiënten die fluvastatine gebruikte. Ook de incidentie van cardiale sterfte en hartinfarct was significant verlaagd in de groep van fluvastatine gebruikers. Dit leidde tot de conclusie dat perioperatieve behandeling met fluvastatine geassocieerd is met een betere cardiale uitkomst in patiënten die een vaatchirurgische operatie ondergaan.

In **hoofdstukken 23, 24, 25 en 26** wordt de perioperatieve behandeling van patiënten met stents in de kransslagaders besproken. Ook werd de invloed van profylactische revascularisatie van de kransslagaders in hoog risico patiënten onderzocht. Uit dit onderzoek komt naar voren dat patiënten die een operatie ondergaan, vlak nadat ze een stent in één of meer kransslagaders hebben gekregen, een verhoogde kans hebben op perioperatieve complicaties. Ook blijkt het stoppen van aspirine en clopidogrel bij deze patiënten de kans op cardiale complicaties te vergroten.
Zeer hoog risico patiënten zouden mogelijk baat kunnen hebben bij het profylactisch revasculariseren van afwijkingen in de kransslagaders. Zoals blijkt uit de DECREASE V pilot studie, beschreven in **hoofdstuk 25**, is dit echter niet het geval. In 101 gerandomiseerde patiënten hadden patiënten, die geloot hadden voor profylactische revascularisatie geen betere uitkomst rond de operatie, dan patiënten die alleen met medicijnen behandeld werden.

Endovasculaire behandeling van het aneurysma van de abdominale aorta is mogelijk geassocieerd met een kleinere kans op perioperatieve cardiale complicaties. Zoals in **hoofdstukken 27, 28 en 29** wordt beschreven lijkt endovasculaire behandeling inderdaad te resulteren in minder perioperatieve complicaties. In **hoofdstuk 28** werden patiënten met een zeer hoog cardiaal risico die een endovasculaire of open behandeling van het aneurysma van de abdominale aorta ondergingen met elkaar vergeleken. Patiënten die endovasculair werden behandeld hadden een significant kleinere kans op perioperatieve cardiale schade. De kleinere kans op complicaties was onafhankelijk van de aanwezigheid en ernst van het onderliggend cardiaal lijden. Echter, het is de vraag of endovasculaire behandeling ook op de lange termijn een voordeel biedt ten opzichte van de open behandeling van het aneurysma van de abdominale aorta.

### Deel III. Langetermijns risico reductie

De preoperatieve evaluatie biedt een unieke kans om patiënten te identificeren die ook op de langere termijn een grotere kans op cardiale complicaties hebben. De preoperatieve evaluatie is daarom ook een uitgelezen mogelijkheid om door middel van veranderingen in levensstijl en medicatie de prognose van patiënten te verbeteren. In **hoofdstukken 30, 31, 32, 33, 34 en 35** wordt de prognose op langere termijn van patiënten die een vaatchirurgische ingreep moeten ondergaan uiteen gezet.

In **hoofdstuk 31** is in een groep van 2730 vaatchirurgische patiënten aangetoond dat de kans op overlijden gedurende een follow-up van gemiddeld 6,4 jaar ruim 2 maal zo groot is als bij hartpatiënten die een dotterbehandeling van de kransslagaders hebben ondergaan. Dit heeft mogelijk te maken met de onderbehandeling van vaatchirurgische patiënten. Hartpatiënten kregen significant vaker de juiste medicatie. Op basis hiervan is geconcludeerd dat de prognose van vaatchirurgische patiënten slechter is dan van hartpatiënten en dat dit mogelijk te maken heeft met medicamenteuze onderbehandeling.

Zoals in **hoofdstuk 32** wordt beschreven, hebben vaatchirurgische patiënten die kort na de operatie tijdelijk of permanente nierfunctiestoornissen hebben gehad een slechtere prognose op de langere termijn. Gedurende een follow-up van 6 jaar hadden patiënten met tijdelijke nierfunctiestoornissen een 1,5 maal grotere kans en patiënten met permanente nierfunctiestoornissen een 1,7 maal grotere kans op mortaliteit. Behandeling met statines is in deze patiëntengroepen geassocieerd met verbeterde uitkomsten.

Screenen op het aneurysma van de abdominale aorta in groepen met een grotere kans hierop is veilig en kosteneffectief. Echter, ook het electieve herstel van het aneurysma van de abdominale aorta gaat gepaard met een aanzienlijke kans op morbiditeit en mortaliteit. Het vertragen van de groei van een aneurysma, waardoor er niet geopereerd hoeft te worden, is daarom een aantrekkelijke optie. In **hoofdstuk 33** wordt de associatie tussen statine gebruik en een tragere groei van het aneurysma van de abdominale aorta beschreven. Deze lijkt onafhankelijk te zijn van andere bekende factoren die invloed hebben op aneurysmagroei.

In **hoofdstuk 34** wordt de langetermijns uitkomst van patiënten met een zeer hoog cardiaal risico die een endovasculair herstel van het aneurysma van de abdominale aorta hebben gehad vergeleken met de uitkomst van patiënten die een open herstel hebben ondergaan. Na een gemiddelde follow-up van ruim 3 jaar was endovasculaire behandeling geassocieerd met minder cardiale complicaties. Echter, de totale overleving verschilde niet tussen beide groepen. Verder kwam naar voren dat met name het gebruik van statines een gunstig effect heeft op de langetermijns uitkomsten.

In **hoofdstuk 35** worden de langetermijns resultaten van de DECREASE V pilot studie beschreven. Ook op de langere termijn bleek preoperatieve profylactische coronair revascularisatie van zeer hoog risico patiënten niet geassocieerd te zijn met een betere uitkomst. Daarom is geconcludeerd dat preoperatieve coronair revascularisatie in zeer hoog risico, maar stabiele, patiënten niet zinvol is.

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# Curriculum Vitae

Olaf Schouten werd geboren op 14 juni 1977 te Gouda. Na het eindexamen Gymnasium, aan het Coornhert Gymnasium in Gouda, studeerde hij Geneeskunde aan de Erasmus Universiteit Rotterdam. In 2002 werd het artsexamen behaald. Aansluitend werkte hij als arts-onderzoeker op de afdeling heelkunde, sector vaatchirurgie, onder leiding van prof.dr. H. van Urk. Hierna volgde in december 2003 een aanstelling als arts-onderzoeker onder leiding van prof.dr. D. Poldermans. Het onderzoek wat gedurende deze aanstelling heeft plaatsgevonden vormt de basis van dit proefschrift. In 2005 ontving hij een AGIKO-stipendium van ZonMw. In het kader hiervan begon hij in 2007 in het Erasmus MC te Rotterdam (opleider: prof.dr. J.N.M. IJzermans) aan de opleiding tot chirurg. Tussen mei 2008 en mei 2009 heeft hij wederom een jaar wetenschappelijk onderzoek verricht onder leiding van prof.dr. D. Poldermans. De opleiding tot chirurg zal in mei 2009 in het Reinier de Graaf Gasthuis te Delft (opleider: dr. L.P.S. Stassen) worden voortgezet.