Cardiac Complications after Non-cardiac Surgery;

Perioperative Risk Prediction and Reduction Strategies

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ISBN 978-94-6108-482-8

Lay-out and printed by Gildeprint Drukkerijen - Enschede

Cardiac Complications after Non-cardiac Surgery;

Perioperative Risk Prediction and Reduction Strategies.

Cardiale complicaties na niet-cardiale chirurgie;
Perioperatieve risico inschatting en reductie strategieën.

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

2 Oktober 2013 om 11.30 uur

Erik Jan Bakker
geboren te Nieuwegein

PROMOTIECOMMISSIE

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CONTENT

INTRODUCTION

More than 200 million people worldwide undergo non-cardiac surgery annually. It is estimated that 2-5 percent of these patients suffer a cardiac complication (i.e. myocardial infarction, congestive heart failure, arrhythmia), resulting in death in approximately 0.5 percent of all patients.

The frequent occurrence of devastating cardiac complications necessitates a thorough assessment of the risk of cardiac complications in every patient scheduled for non-cardiac surgery. This risk is influenced by the preoperative condition of the patient and the invasiveness of the planned procedure, and is modifiable by various interventions. Chapter 1 provides an overview of cardiac risk assessment and risk reduction strategies.

Surgery induces several changes that predispose to cardiac complications: the induced catecholamine surge, tachycardia, and increased myocardial contractility may, in the presence of a flow-limiting coronary stenosis, lead to a myocardial oxygen supply-to-demand mismatch and subsequent myocardial infarction. The systemic inflammatory response and pro-thrombotic state provoked by surgery increase the risk of rupture of unstable coronary plaque and subsequent thrombotic coronary artery occlusion and myocardial infarction.

Pre-existent atherosclerotic coronary artery disease therefore is the common denominator in the fast majority of cardiac complications. Preoperative cardiac risk assessment focuses mainly on markers (both direct and indirect) of coronary artery disease. Despite extensive efforts to improve cardiac risk stratification over the last decades, discriminating between patients who will suffer a cardiac event and those who will recover uneventfully remains a major challenge.

In order to further improve risk stratification, chapters 2-4 evaluate the prognostic value of non-traditional risk factors for cardiac complications in vascular surgery patients. This population is at the highest risk of cardiac events, due to the presence of severe generalized atherosclerosis in the most patients.

Type 1 diabetes mellitus is a well-established risk factor for cardiac events. Even though on theoretical grounds one would expect type 2 diabetes to have a similar effect, the impact of type 2 diabetes on perioperative cardiac outcome remains unclear. Chapter 2 evaluates the role of type 2 diabetes as risk factor for cardiac complications.

ABO blood type is a major determinant of plasma levels of von Willebrand factor, an important factor in blood coagulation. Non-O blood types are associated with an increased risk of both venous and arterial thrombo-embolic events, including myocardial infarction, in the general population. Chapter 3 assesses the prognostic implications of ABO blood type in vascular surgery patients, both in the perioperative period and on the long term.

Aortic valve calcification is a progressive disease continuum, with a spectrum that ranges from aortic valve sclerosis, characterized by thickening and/or calcification of the aortic valve, to aortic stenosis. The pathophysiologic mechanisms in aortic valve calcification and atherosclerosis have substantial overlap. As a result, aortic valve calcification is considered a surrogate marker for coronary artery disease and is therefore associated with adverse cardiac outcome in the general population, even when haemodynamics are not compromised. Chapter 4 explores the prognostic significance of aortic valve calcification in vascular surgery patients.

An ongoing increase in life expectancy is observed worldwide, resulting in an increasing number of elderly patients requiring surgery. It is generally accepted that this population is at increased risk of cardiac complications due to reduced physiological reserve and increased comorbidity. In chapter 5, the risk and determinants of perioperative cardiac complications are assessed in a population of patients aged 80 and older undergoing elective non-cardiothoracic surgery, stratified by procedure-specific risk.

Advances in anesthetic techniques and the shift towards less invasive surgical techniques have reduced surgery-related morbidity and mortality over the last half century. Several other strategies to reduce the risk of cardiac complications after non-cardiac surgery have been evaluated over the last decade, including both pharmacological (e.g. beta-blockers, statins) and non-pharmacological (e.g. coronary revascularization). Chapters 6 and 7 focus on risk reduction strategies.

An example of the shift towards less invasive procedures is endovascular aortic aneurysm repair (EVAR). EVAR elicits a significantly reduced stress response compared with conventional aneurysm repair, resulting in a reduced risk of cardiac complications. However, due to the presence of severe co-morbitiy, cardiac complications still occur frequently. Locoregional anaesthesia attenuates the surgical stress response to a greater degree than general anaesthesia. Chapter 6 evaluates the risk of cardiac complications with locoregional and general anaesthesia in a cohort of patients undergoing EVAR.

Beta-receptor antagonists (beta-blockers) blockers are well-known for their anti-anginal properties. Beta-blockers reduce heart rate and contractility, restoring myocardial supply-to-demand balance in patients with coronary artery disease. Several studies point out that perioperative beta-blocker therapy can reduce the risk of cardiac complications. Adequate dosing of perioperative beta-blocker therapy remains challenging. Heart rate control is often inadequate with a low dose of beta-blocking medication, but high doses are associated with an increased risk of bradycardia, hypotension, stroke, and mortality. Chapter 7 describes the design of a trial evaluating titration of a short-acting intravenous beta-blocker as an add-on to low-dose oral beta-blocker treatment. The aim of this study is to provide adequate heart rate control throughout the perioperative period, without causing the side effects associated with high-dosed oral beta-blocker therapy.

CHAPTER 1

PERIOPERATIVE CARDIAC EVALUATION, MONITORING, AND RISK REDUCTION STRATEGIES IN NONCARDIAC SURGERY PATIENTS

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Curr Opin Crit Care 2011;17(5):409-15.

ABSTRACT

Purpose of review: Cardiac complications after noncardiac surgery cause significant morbidity and mortality. This review will discuss recent developments in risk stratification, monitoring, and risk reduction strategies.

Recent findings: The addition of biomarkers for ischemia, left ventricular function, and atherosclerosis to classic cardiac risk factors improves the prediction of both short and long term outcome after noncardiac surgery. Intraoperative monitoring, using continuous 12-lead ECG assessment and TEE, may timely identify treatable myocardial ischemia and arrythmias. A prudent perioperative beta-blocker and statin regimen can reduce cardiac complications and mortality without increasing the risk of stroke in intermediate to high risk patients. The use of circulatory assist devices might improve outcomes after major surgery in patients with severely reduced left ventricular function.

Summary: Systematic preoperative assessment can identify patients at high risk of cardiac complications and guide the application of appropriate risk reduction strategies.

Cardiac complications are a major cause of postoperative morbidity and mortality. The occurrence of cardiac complications after noncardiac surgery ranges from less than 0.5 to more than 30 percent, depending on the surgical procedure and the patients comorbid conditions[1-2]. Major cardiac complications include sudden cardiac death, myocardial infarction, acute heart failure, and cardiac arrhythmias.

More than 200 million people worldwide undergo noncardiac surgery annually[3]. An estimated quarter of procedures are performed in patients over 65 year of age. As the presence of comorbidities predisposing to cardiac complications rises with age and the population is aging, an increased number of more advanced surgical procedures in patients with cardiac risk factors is to be expected.

The catecholamine surge, tachycardia, and increased myocardial contractility associated with surgery may, in the presence of a flow-limiting coronary stenosis, lead to a myocardial oxygen supply/demand mismatch and subsequent perioperative myocardial infarction (PMI). This mechanism accounts for half of all PMI. The other half is caused by unstable coronary plaque rupture, due to the systemic inflammatory reaction to surgery.

In this article, we will review pre-, intra-, and postoperative assessment and risk-reduction strategies for cardiac complications in noncardiac surgery patients.

The first step: Active cardiac conditions
Postponement of elective noncardiac surgery, evaluation, and treatment according to the specific guidelines is recommended in patients with unstable coronary artery disease, acute heart failure, significant arrythmias and severe valvular heart disease[4].

The second step: Surgery related risk
The risk of cardiac complications varies between surgical procedures, depending on the provoked stress response, length and invasiveness of the procedure and its effects on hemodynamic stability, fluid shifts, blood loss, and body temperature changes. Also, emergency surgery is associated with an increased risk.

Surgical procedures can be divided into high (open aortic and lower extremity vascular surgery), intermediate (carotid, endovascular aortic, abdominal, thoracic, major ENT, orthopedic and intracranial surgery) and low (breast, ocular, gynaecologic, outpatient surgery) risk, with a predicted risk of >5%, 1-5%, and <1% for cardiac complications, respectively[5]. Recently, Noordzij et al. assessed perioperative mortality in 36 surgical categories in a registry of 3.7 million patients and observed a mortality rate ranging from 0.7% in herniated nucleus pulposis surgery to 18.5% in liver transplant[6].

The third step: Exercise capacity

Exercise capacity provides an overall impression of cardiopulmonary function and is expressed by metabolic equivalents (METs, 1 MET equals the basal metabolic rate, Figure 1). Exercise capacity plays an important role in risk assessment for noncardiac surgery. The inability to climb two flights of stairs or run a short distance indicates poor exercise capacity (<4 METs).

When exercise capacity is unclear, cardiopulmonary exercise testing may be performed, as Wilson et al. did in a cohort 847 patients undergoing intra-abdominal surgery[7]. An anaerobic threshold of <11 mL/kg/min was associated with a relative risk of 6.8 (95% CI: 1.6 – 29.5) of in-hospital mortality.

The risk of cardiac complications is considered to be low in patients with normal exercise capacity, regardless of comorbidities[8]. If exercise capacity is poor, the present risk factors and the surgical procedure determine the risk of cardiac complications.

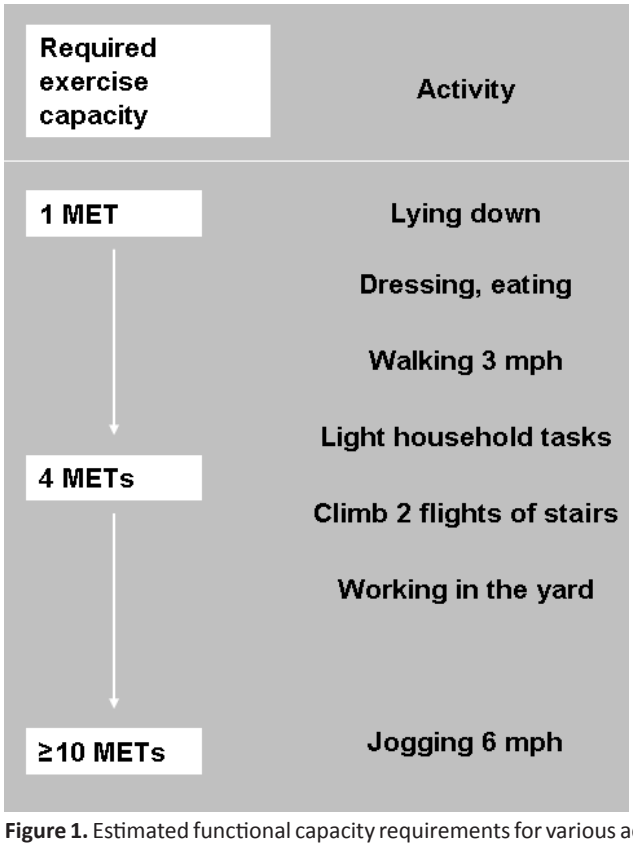

Figure 1. Estimated functional capacity requirements for various activities. MET = metabolic equivalent, mph = miles per hour. Based on Poldermans et al[4]

The fourth step: Clinical risk factors

A useful clinical risk score to assess the risk of cardiac complications is the Lee Revised Cardiac Risk Index (RCRI)[1]. It assigns 1 point to each of the following: high-risk surgery, a history of ischemic heart disease, previous or current congestive heart failure, renal failure with a serum creatinin >2 mg/dL, a history of stroke or transient ischemic attack, and insulin-dependent diabetes mellitus. The risk of a composite of perioperative myocardial infarction, pulmonary edema, ventricular fibrillation or complete heart block is 0.4%, 0.9%, 7% and 11% for 0, 1, 2, and ≥3 risk factors.

Ackland et al. demonstrated that, in patients undergoing major orthopedic surgery, a RCRI ≥3 is associated with a 1.7-fold increase in noncardiac complications (infectious, respiratory and neurological) and prolonged hospital stay[9].

Bertges et al. reported that the RCRI underestimates the risk of cardiac complications in their cohort of vascular surgery patients[10]. Observed event rates were 2.6, 6.7, 11.6, and 18.4 percent in patients with 0, 1, 2, ≥3 risk factors. Bertges et al. derived a the Vascular Study Group- Cardiac Risk Index (VSG-CRI), which adds age, smoking, COPD, and beta-blocker use, and predicts a risk of cardiac complications ranging from 2.6 to 14.3 percent. This model might be more appropriate than the RCRI for risk stratification of vascular surgery patients.

The fifth step: Preoperative testing

Non-invasive cardiac testing is recommended in patients at increased risk of cardiac complications in the 2009 ESC guidelines on perioperative care[4]. Electrocardiography is recommended in patients with clinical risk factors or undergoing intermediate or high-risk surgery. Assessment of left ventricular function should be considered in patients undergoing high-risk surgery.

Cardiac stress testing is recommended in patients with 3 or more RCRI risk factors undergoing high-risk surgery and may be considered in intermediate-risk surgery and patients with 2 or less risk factors undergoing high-risk surgery. Multiple options for cardiac stress testing are available, including exercise electrocardiography, dobutamine stress echocardiography (DSE), MRI, and nuclear imaging.

The additional value of biomarkers for preoperative risk assessment

Biomarkers such as cardiac Troponin (cTn), NT-proBNP and CRP were previously mainly used for diagnostic purposes, but are increasingly showing their ability to predict both postoperative adverse events and long-term prognosis, independently of the classic clinical risk factors. The pathophysiologic processes these biomarkers are thought to represent are shown in Figure 2, their value in risk stratification in Figure 3.

	cTn	Hs-CRP	(NT-pro)BNP
myocardial damage	x		x
myocardial ischemia			x
left ventricular dysfunction			x
atherosclerosis		x	
arrythmias			x
valvular heart disease			x

Figure 2. Biomarkers and the pathofysiologic process they represent. cTn = cardiac troponin, Hs-CRP = high-sensitivity C-reactive protein, (NT-pro)BNP = (N-terminal pro)Brain-type Natriuretic Peptide.

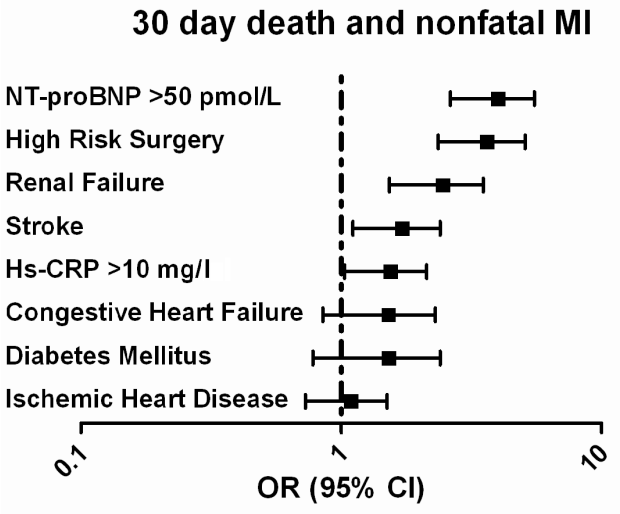

Figure 3. Multivariable analysis of the risk of 30-day mortality and nonfatal MI associated with cardiac risk factors, Hs-CRP, and NT-proBNP in our cohort of 1234 elective vascular surgery patients. MI = myocardial infarction, OR = odds ratio, CI = confidence interval, NT-proBNP = N-terminal pro-Brain-type Natriuretic Peptide, Hs-CRP = high-sensitivity C-reactive protein.

Cardiac Troponin is a marker of cardiomyocyte damage. Therefore, preoperatively increased cTn levels might indicate unstable coronary artery disease which requires additional evaluation (preferably coronary angiography) and possibly treatment prior to elective surgery.

(N-terminal pro)Brain-type Natriuretic Peptide ((NT-pro)BNP) is released from the ventricular myocardium in response to myocardial wall stress and ischemia[11]. Increased baseline levels independently predict perioperative cardiac complications (RR 3.9; 95% CI 3.15 – 4.14) after noncardiac surgery in a study by Choi et al[12]. The added value of NT-proBNP to preoperative risk stratification for patients undergoing vascular surgery is currently investigated prospectively in our centre.

High-sensitivity C-reactive protein (hs-CRP) is a marker of inflammation and is thought to reflect the extent of atherosclerosis[13]. Increased levels of hs-CRP are associated with an increased risk of cardiac complications, independently of clinical risk factors and NT-proBNP[14].

Intra-operative monitoring

As both myocardial ischemia and arrhythmias occur frequently, electrocardiographic monitoring is indicated around major surgery.

Perioperative myocardial ischemia, defined as a prolonged episode of ST-segment depression, is strongly predictive of postoperative cardiac complications and is best detected by continuous 12-lead ECG monitoring[15].

New-onset atrial fibrillation (AF) is common around major noncardiac surgery. Burris et al. report an incidence of 8.5% and identified preoperative hypokalemia, premature atrial contractions, cardiomegaly, and intra-operative surgical adverse events as risk factors for AF[16].

The prevalence of AF increases with age and the prevalence of cardiovascular comorbidities. AF doubles the risk of death, increases the risk of thromboembolic events and decreases quality of life and exercise capacity[17].

Perioperative AF is often asymptomatic, but requires therapy in most patients. Options for monitoring include serial 12-lead ECG recording, telemetry or holter monitoring and the implantable loop recorder (ILR).

An advantage of the ILR, as compared to holter or telemetry monitoring, is the prolonged monitoring window of up to three years. Winkel et al. described the revealing of AF requiring intervention by an ILR in a high risk patient undergoing open aortic surgery[18].

Transesophageal echocardiographic (TEE) monitoring is a useful tool during noncardiac surgery. Its use is recommended when prolonged severe hemodynamic instability develops[4]. Routine use can be considered in high-risk patients (severely depressed left ventricular function or severe valvular disease) undergoing major surgery. TEE aims to guide hemodynamic management and detect new wall motion abnormalities (NWMA), which have been shown to be strongly predictive of cardiac complications[19].

Early goal-directed fluid and catecholamine therapy (GDT) was previously proven useful in patients with septic shock. The aim of GDT is to optimize tissue oxygen delivery and to prevent ‘oxygen debt’. The role of monitoring devices facilitating GDT, such as Esophageal Doppler and Vigileo, in managing high-risk patients during noncardiac surgery has not been fully established[20].

Biomarkers for postoperative monitoring

The prognostic and diagnostic value of cTn in ischemic heart disease has been thoroughly investigated previously. A recent meta-analysis of 14 studies, enrolling 3318 patients, by Levy et al. demonstrated the independent prognostic value of even mildly increased postoperative cTn levels (OR 3.4; 95% CI 2.2 - 5.2, for mortality)[21]. Assessment of the 'area under the curve' of the cTn release (the product of the cTn level and duration of cTn level elevation) increases its prognostic value[22].

The recently developed high-sensitivity cTn (hs-cTn) essays facilitate quantification of previously undetectable plasma levels of cTn even in the healthy population. Lindahl et al. demonstrated that, in patients admitted with non-ST-elevation acute coronary syndromes, a positive (>99 percentile) hs-cTn value in the presence of a negative traditional cTn, was associated with a three-fold increased 1-year mortality (OR 3.0; 95% CI 1.3 – 6.7)[23]. This risk was comparable to the risk in patients with a positive traditional cTn measurement. To our knowledge, no data exist on the value of hs-cTn in non-cardiac surgery.

The perioperative change in NT-proBNP levels is strongly predictive of mortality (mean follow-up 13 months; HR 3.06; 95% CI 1.2 – 5.7, after adjustment for RCRI factors, age, BMI and left ventricular ejection fraction) in a cohort of 144 vascular surgery patients in a study by Goei et al[24].

Secondary prophylaxis of atherosclerotic complications initiated prior to surgery: medication

Statins are a well-established therapy for primary and secondary prevention of cardiac events in the nonsurgical setting. Statins are potent lipid-lowering, anti-inflammatory, plaque stabilizing agents. Trials have shown a marked reduction in perioperative myocardial ischemia and mortality in noncardiac surgery[25-26]. Initiation of statin therapy is therefore recommended in high-risk surgery patients and continuation is recommended in all patients already using statins[4]. Long acting statins such as extended-release fluvastatin or rosuvastatin are preferable in the perioperative period, as patients are frequently temporarily unable to use oral medication. Voute et al. demonstrate that fluvastatin therapy is generally well tolerated and safe[27].

Beta-blockers are widely prescribed around major surgery. Multiple randomized trials demonstrated a reduction in myocardial ischemia and postoperative cardiac events in intermediate and high risk surgery patients[2,28-29].

Concerns about beta-blocker safety were raised by the POISE trial[29]. This multicenter trial found that the beneficial effect was offset by an increased risk of bradycardia, hypotension, stroke, and all-cause mortality.

In a retrospective analysis of the DECREASE trials, van Lier et al. showed a decreased risk of stroke in beta-blocker users[30]. In a cohort study including 38779 patients by Wallace et al., addition and continuation of beta-blockers were associated with a significant reduction in 30-day and 1-year all-cause mortality (OR ranging from 0.52 to 0.82), as compared to no beta-blockers, while withdrawal of beta-blockers prior to surgery was associated with an increased risk of mortality (OR 3.93 and 1.96 for 30-day and 1-year mortality, respectively) [31].

This discrepancy is thought to arise from different dosing regimens. The POISE trial initiated beta-blocker therapy 2-4 hours prior to surgery, prescribing patients up to 400 mg of metoprololsuccinate on the day of surgery, while the DECREASE trials initiated low-dose bisoprolol (2.5 or 5 mg once daily) on average a month prior to surgery.

Perioperative use of beta-blockers is recommended in patients with ischemic heart disease, in patients undergoing high-risk surgery, and in patients previously treated with beta-blockers, and should be considered in intermediate risk surgery and in patients with risk factors undergoing low risk surgery. The use of high-dose beta-blockers without titration is not recommended[4]. Care should be taken not to treat tachycardia due to causes such as pain or hypovolemia with additional beta-blockers.

Given the rise in heart rate shortly postoperatively due to increased levels of catecholamines, titration of an ultra-short acting beta-blocker, in addition to chronic beta-blocker therapy might further reduce the risk of cardiac complications.

Although useful in primary and secondary prevention of thrombotic cardiovascular events, the evidence for perioperative aspirin therapy is limited. Aspirin continuation is generally supported, as the risk of cardiovascular complications associated with aspirin withdrawal is generally thought to outweigh the risk of bleeding associated with aspirin continuation[4,32]. Oscarsson et al. confirmed this in a randomized study in 220 patients, showing 9% cardiac complications in the placebo group, as compared with 1.8% in the aspirin group (p=0.02) [33]. The trial was terminated early because of slow inclusion and ethical difficulties (aspirin withdrawal in high-risk patients was no longer deemed acceptable by most investigators at the end of the study) and was underpowered for the assessment of bleeding risks.

No compelling evidence exists on preoperative initiation of aspirin in noncardiovascular surgery patients. Therefore, clinical trials addressing this issue are warranted.

The cardioprotective effects in the perioperative setting of phosphodiesterase inhibitors, nitroglycerine, calcium channel blockers, and alpha-2 receptor antagonists are ill-defined.

Myocardial revascularization

Prophylactic myocardial revascularization aiming to reduce perioperative myocardial infarction has been investigated in the CARP (patients with ≥70% stenosis in ≥1 coronary artery) and DECREASE-V (patients with extensive myocardial ischemia, ≥5 of 16 segments on DSE or ≥3 of 6 walls on nuclear imaging) studies[34-35]. No short or long term benefits were observed in either study, with possible exception of left main disease.

Insight into this phenomenon is offered by Galal et al.[19]. In a series of 54 patients undergoing vascular surgery, preoperative DSE predicted the occurrence of, but not the location of NWMAs and infarction.

As myocardial infarction frequently occurs on previously non-stenotic, vulnerable lesions, medical therapy to reduce plaque instability is of greater benefit than revascularization. Preoperative revascularization probably benefits only those patients who have an indication for revascularization, regardless of noncardiac surgery, for example those with significant left main coronary disease.

Circulatory assist devices

Heart failure patients with severe left ventricular dysfunction undergoing major surgery are at extremely high risk. Healy et al. describe a perioperative mortality and cardiac complication rate of 14.3% and 53.6% respectively in patients with a left ventricular ejection fraction of less than 30%[36].

The prophylactic use of circulatory assist devices may have a role in perioperative management of these patients. In the largest cohort of patients receiving prophylactic intraaortic balloon counterpulsation (IABC) for elective abdominal surgery, 18 of 19 patients survived the perioperative phase[37].

Atoui et al described the prophylactic use of the Impella®, a percutaneously implanted left ventricular assist device[38]. The patient, awaiting cardiac transplantation, underwent a laparoscopic cholecystectomy. During pneumoperitoneum, cardiac output was maintained largely due to the mechanical assistance, but the postoperative phase was uneventful, without the need for further hemodynamic support.

Although these results are promising, the evidence for prophylactic use of circulatory assist devices in noncardiac surgery patients with severely reduced cardiac function consists of small cohorts and case reports. Clinical trials addressing this issue are needed.

Conclusion

Patients undergoing noncardiac surgery are at risk of devastating cardiac complications. This risk is defined by the type of surgery and patient characteristics such as age and coronary artery disease. The addition of biomarkers such as hsCRP, NT-proBNP, and cTn can improve risk stratification.

The perioperative use of statins and low-dose beta-blockers titrated to heart rate can reduce the risk of cardiac complications in high risk patients.
The dosing regimen of perioperative beta-blocker therapy needs further investigation, as well as prophylactic use of circulatory assist devices in heart failure patients undergoing noncardiac surgery.

Key points

- Cardiac complications are the cause of significant morbidity and mortality after noncardiac surgery.
- A stepwise evaluation of exercise capacity, clinical risk factors, the planned surgical procedure, and noninvasive testing, can identify the patients at high risk of cardiac complications.
- Medical therapy for secondary prevention of atherosclerotic complications should be initiated prior to surgery in patients at increased risk.

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CHAPTER 2

DIABETES MELLITUS, INDEPENDENT OF INSULIN USE, IS ASSOCIATED WITH AN INCREASED RISK OF CARDIACCOMPLICATIONS AFTER VASCULAR SURGERY

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ABSTRACT

Background: Previous reports on the prognostic value of diabetes mellitus towards cardiac complications after vascular surgery show divergent results. Especially, the role of type 2 diabetes as a cardiac risk factor remains unclear. The aim of the current study was to assess the impact of type 2 diabetes on 30-day cardiac complications after vascular surgery.

Methods: Patients undergoing elective vascular surgery between 2002 and 2011 were included in this retrospective cohort study. Previous diagnosis of type 1 and 2 diabetes and use of oral glucose lowering medications and insulin were recorded. Patients with type 1 diabetes were excluded from the analysis. The main outcome parameter was cardiac complications, a composite of cardiovascular death, nonfatal myocardial infarction, congestive heart failure, severe arrhythmia, and asymptomatic troponin release, within 30 days of surgery. In multivariable analysis, corrections were made for co-morbidities, demographics, medication use, and surgical risk.

Results: Of a total of 1462 patients, 329 (22.5%) patients had type 2 diabetes. Cardiac complications occurred in 155 (13.7%) patients without diabetes and in 68 (20.7%) with type 2 diabetes. In multivariable analysis, type 2 diabetes was associated with a significantly increased risk of 30-day cardiac complications (OR 1.80; 95%-CI 1.25-2.60). Results were similar for type 2 diabetes patients managed with (OR 1.84; 95%-CI 1.01-3.37) and without (OR 1.79; 95%-CI 1.19-2.70) insulin.

Conclusions: Type 2 diabetes is an independent risk factor for cardiac complications after vascular surgery and should be treated as such in preoperative cardiac risk stratification.

INTRODUCTION

Cardiac complications are a major cause of morbidity and mortality after vascular surgery.[1] Diabetes mellitus (DM) is highly prevalent in this population.[2] Both type 1 DM (DM1, characterized by immune-mediated beta-cell destruction leading to absolute insulin deficiency) and type 2 DM (DM2, characterized by insulin resistance) lead to atherosclerotic complications, such as myocardial infarction, stroke and renal failure.[3,4] DM1 is generally considered a risk factor for postoperative cardiac events.[1] However, the effect of DM2 on the incidence of cardiac complications after vascular surgery remains unclear.[1,5,6] The aim of the current study is to assess the impact of DM2 on cardiac complications after vascular surgery.

METHODS

Study population

The study population of this retrospective cohort study consisted of 1484 patients who underwent elective vascular surgery between 2002 and 2011. Patients undergoing open or endovascular aorto-iliac reconstruction, infrainguinal arterial revascularization, and carotid artery desobstruction, were included in the study. The study was performed at a single site at the Department of Vascular surgery of the Erasmus University Medical Center, Rotterdam, the Netherlands. The study complies with the declaration of Helsinki and was approved by the Institutional Review Board of the Erasmus Medical Center. All data were obtained from computerised medical records.

Baseline characteristics

A detailed medical history was obtained from all patients prior to surgery, with the emphasis on cardiovascular history and risk factors, including age, gender, history of congestive heart failure, ischemic heart disease, coronary revascularization, chronic kidney disease (serum creatinin >2mg/dL), hypertension, cerebrovascular disease, body-mass index (BMI), high risk type of surgery (open aorto-iliac repair) and chronic obstructive pulmonary disease. Also, the use of beta-blockers, statins, aspirin, oral anti-coagulants, angotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, and nitrates prior to surgery was recorded. A Revised Cardiac Risk Index[1] score was calculated for all patients.

Diabetes mellitus

Patients were categorized as no DM, DM1 or DM2, based on medication use and previous diagnosis. The use of insulin and oral anti-diabetic medication was recorded in all patients. Patients with DM1 were excluded from the analysis. The last available preoperative glycosylated hemoblobin (A1C) value was obtained for DM2 patients.

Study outcomes

Serial electrocardiograms and troponin T measurements were routinely obtained prior to surgery and postoperatively 3 times a week while admitted to the hospital. Troponin T was measured using the TropT version 2 assay from Roche Diagnostics, Mannheim, Germany. The study endpoint was 30-day cardiovascular complications, a composite of cardiovascular mortality, non-fatal myocardial infarction, new or worsened congestive heart failure, new ventricular arrhythmias (requiring immediate cardioversion, cardiopulmonary resuscitation, or pacing), and asymptomatic troponin T release. Cardiovascular death was defined as any death from cerebro-cardiovascular cause, including death following stroke, myocardial infarction, congestive heart failure, and arrhythmia, or sudden unexpected death. Myocardial infarction was defined as postoperative characteristic rise and fall of troponin T levels above the 99th percentile, with either electrocardiographic or clinical signs of myocardial ischemia. Asymptomatic troponin T release was defined as at least one troponin T value above the 99th percentile in the absence of electrocardiographic and clinical signs of myocardial ischemia and in the absence of other cardiac complications. Patients were routinely scheduled for a follow up visit 30 days after surgery. In patients still admitted or readmitted, follow-up was completed using medical records.

Statistical analysis

Dichotomous data are presented as numbers and percentages. Continuous data are presented as means ± standard deviation. Dichotomous data were compared using Chi-Square tests, continuous data were compared using ANOVA. Univariable and multivariable logistic regression models were used to assess the prognostic value of DM2 towards 30-day cardiovascular complications. Congestive heart failure, ischemic heart disease, chronic kidney disease, cerebrovascular disease, chronic obstructive pulmonary disease, age, gender, BMI, current smoking, high risk surgical procedure, and medication use (beta-blockers, statins, aspirin, oral anti-coagulants, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, calcium channel blockers, nitrates) were considered as possible confounders. A threshold of $p<0.20$ on univariable analysis was used for selection for entry into multivariable analysis. A 2-sided p-value of <0.05 was considered significant for all tests. All analyses were performed using Predictive Analysis SoftWare version 17.0 (SPSS Inc., Chicago, Illinois).

RESULTS

The baseline population consisted of 1484 patients. Of these, 22 had DM1 and were excluded from analysis. The remaining study population of 1462 patients underwent 296 carotid artery desobstructions, 707 aorto-iliac procedures, and 459 infrainguinal revascularizations. Endovascular procedures were performed in 622 patients. The mean age was 68 years, and the majority of patients were male (75%).

Baseline characteristics

Of the 1462 patients, 329 (22.5%) patients had DM2. Of those, 87 (26%) received insulin treatment and 242 (74%) were managed without insulin. Patients with DM2 more frequently underwent infrainguinal revascularization compared with patients without DM, as presented in Table 1. Patients with DM2 had a higher incidence of ischemic heart disease, chronic kidney disease, hypertension, and higher mean BMI, compared with patients without diabetes. In addition, patients with DM2 more frequently received diuretics, oral anticoagulants, and angiotensin converting enzyme inhibitors and angiotensin receptor blockers.

30-day outcome

During 30-day follow-up, 223 (15.3%) patients suffered a cardiovascular complications, including 20 (1.3%) cardiac deaths, 62 (4.2%) non-fatal myocardial infarctions, 20 (1.4%) cases of non-fatal congestive heart failure, 6 (0.4%) cases of non-fatal severe arrhythmia, and 115 (7.9%) had asymptomatic troponin T release. Twenty-three (1.6%) patients died of non-cardiovascular causes.

In total, 155 (13.7%) patients without diabetes had a 30-day cardiac complication, compared with 68 (20.7%) of patients with DM2 ($p < 0.01$), as presented in Table 2. The incidence of cardiac complications was 23.0% in DM2 patients treated with insulin, and 19.8% in DM2 patients managed without insulin ($p=0.54$). Multivariable analysis demonstrated that DM2 is associated with a significant increase in 30-day cardiac complications (OR 1.80; 95%-CI 1.24 – 2.61), with similar adjusted odds ratios DM2 treated with insulin (OR 1.82; 95%-CI 0.99-3.36) and without insulin (OR 1.79; 95%-CI 1.18-2.72). Other factors significantly associated with cardiac complications were high-risk type of surgery, history of congestive heart failure, renal failure, and age, as demonstrated in Table 3. Removal of asymptomatic troponin release did not change the prognostic value of DM2 towards 30-day cardiac complications (OR 1.77; 95-CI 1.09 – 2.88).

Table 1. Baseline characteristics according to diabetes mellitus

	No DM (n = 1133)		DM2 (n = 329)		p-value
Demographics					
Mean age (SD)	67.7	(10.6)	68.6	(8.3)	0.12
Male gender (%)	834	(73.6)	263	(79.9)	0.02
BMI (SD)	25.6	(3.9)	27.5	(4.4)	<0.01
Current smoker (%)	488	(43.4)	124	(38.5)	0.13
Surgery type (%)					
Carotid desobstruction	232	(20.5)	64	(19.5)	0.76
Infrainguinal repair	321	(28.3)	138	(41.9)	<0.01
Aorto-iliac repair	580	(51.2)	127	(38.6)	<0.01
Endovascular procedure	490	(43.3)	132	(40.1)	0.31
High risk procedure	273	(24.1)	55	(16.7)	<0.01
Medical history (%)					
Congestive heart failure	107	(9.4)	42	(12.8)	0.10
Cerebrovascular disease	361	(31.9)	120	(36.5)	0.13
Hypertension	710	(62.9)	261	(79.3)	<0.01
Serum creatinin >2mg/dL	136	(12.0)	77	(23.4)	<0.01
Ischemic heart disease	438	(38.7)	163	(49.5)	<0.01
COPD	418	(36.9)	91	(27.7)	<0.01
Revised Cardiac Risk Index not including diabetes					
0-1 risk factor (%)	784	(69.2)	197	(59.9)	<0.01
2 risk fators (%)	246	(21.7)	85	(25.8)	0.12
≥3 risk factors (%)	103	(9.1)	47	(14.3)	0.01
Mean RCRI (SD)	1.2	(1.0)	1.4	(1.0)	<0.01
Medication (%)					
Beta-blocker	916	(80.8)	273	(83.0)	0.42
Statin	865	(76.3)	266	(80.9)	0.10
ACE-I / ARB	452	(39.9)	206	(62.6)	<0.01
Diuretic	265	(23.4)	100	(30.4)	0.01
Nitrate	106	(9.4)	40	(12.2)	0.14
Calcium channel blocker	222	(19.6)	66	(20.1)	0.88
Oral anticoagulant	175	(15.4)	74	(22.5)	<0.01
Aspirin	732	(64.6)	210	(63.8)	0.79

Abbreviatons: DM diabetes mellitus; DM2 type 2 DM; SD standard deviation; COPD chronic obstructive pulmonary disease; ACE-I angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker

Table 2. 30-day cardiac complications

	No DM		Type 2 DM					
			All DM2		No insulin		Insulin	
	(n = 1133)		(n = 329)		(n=242)		(n=87)	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
Cardiovascular events								
Cardiac death	13	(1.1)	7	(2.1)	3	(1.2)	4	(4.6)
Myocardial infarction	41	(3.6)	21	(6.4)	13	(5.4)	8	(9.2)
Congestive heart failure	14	(1.2)	6	(1.8)	5	(2.1)	1	(1.1)
Arrhythmia	6	(0.5)	0	(0)	0	(0)	0	(0)
Troponin release	81	(7.1)	34	(10.3)	27	(11.2)	7	(8.0)
Any cardiac event	155	(13.7)	68	(20.7)	48	(19.8)	20	(23.0)

Table 3. Multivariable analysis of cardiac complications

	OR	(95%-CI)	P-value
Diabetes mellitus type 2	1.80	1.24-2.61	<0.01
Age	1.05	1.03-1.07	<0.01
Male gender	0.91	0.62-1.34	0.63
Congestive heart failure	2.22	1.40-3.53	<0.01
Cerebrovascular disease	1.06	0.75-1.51	0.73
Chronic kidney disease	2.67	1.81-3.92	<0.01
Ischaemic heart disease	1.24	0.88-1.75	0.22
COPD	1.05	0.75-1.47	0.79
High-risk procedure	7.06	4.98-10.00	<0.01
BMI	1.00	0.96-1.05	0.91
Smoker	1.36	0.97-1.91	0.07
Statins	0.99	0.67-1.44	0.94
Diuretics	1.14	0.79-1.64	0.49
Oral anticoagulants	0.71	0.46-1.11	0.14
RAAS inhibitors	1.12	0.80-1.58	0.50
Nitrates	1.12	0.68-1.86	0.65

Glucose control

Preoperative glycosylated hemoblobin measurements were available in 280 DM2 patients (80% of those on insulin and 86% of those not on insulin). Mean A1C was higher in the insulin treated group (7.68% ± 1.75% vs. 6.76% ± 1.00%, p<0.01). Mean A1C was similar in the DM2 patients who did suffer a cardiac complication and those who did not (6.93% ± 1.38% vs. 7.00% ± 1.28%, p=0.73).

DISCUSSION

The results of this study indicate that diabetes mellitus type 2 is an independent predictor of cardiac complications after vascular surgery. The cardiac event rate was similar in DM2 patients treated with and without insulin.

Diabetes is common in the general population with an estimated prevalence of 6.4% of adults worldwide, increasing with age.[7] These patients are at high risk of diabetic complications, both microvascular (nefropathy, retinopathy, neuropathy) and macrovascular (including peripheral arterial disease, myocardial infarction and stroke).[8] Type 2 diabetes is the cause of the majority of diabetes related complications, as this type accounts for approximately 90-95% of all cases.[7]

Hyperglycaemia in itself promotes atherosclerosis through an incompletely understood mechanism in both DM1 and DM2. Hypotheses include increased formation of glycosylation end products, accumulation of cellular sorbitol, and increased activity of vascular protein kinase C.[9-11] Also, in DM2, insulin resistance promotes atherogenic dyslipidemia, hypertension, systemic inflammation, hypercoagulability, and endothelium dysfunction, leading to atherosclerosis.[3,12]

Atherosclerotic complications therefore occur in both type 1 and type 2 diabetes mellitus.[3] It is thus biologically plausible that both DM1 and DM2 are risk factors for cardiac complications after non-cardiac surgery. However, previous reports show divergent results.

In their article on the Revised Cardiac Risk Index, Lee and colleagues only assessed the role of insulin-treated diabetes, and identified it as a major risk factor for cardiac complications after non-cardiac surgery.[1] Insulin use was associated with an increased risk of a composite endpoint including myocardial infarction, pulmonary edema, ventricular fibrillation or primary cardiac arrest, and complete heart block, with an odds ratio of 3.0 (95%-CI 1.3 – 7.1).
Diabetes mellitus was associated with a 2.6-fold increased risk of cardiac events and mortality after vascular surgery in a study by Eagle et al.[13] In a mixed surgical population studied by Boersma et al, DM was strongly associated with perioperative cardiovascular mortality (OR 3.8; 95%-CI 2.7-5.4).[6] A study by Bolsin et al showed a significant association between DM and cardiac complications in a mixed intermediate- and high-risk surgical population (OR 1.95; 95%-CI 1.35-2.[14] These studies, among others, have led to the recognition of all DM as a risk factor for cardiac complications after noncardiac surgery in the 2002 ACC/AHA guidelines on perioperative care.[15] However, as neither of these studies discriminated

between diabetes types and/or insulin use, it is not clear to which extend type 1 and type 2 diabetes contributed to the role of diabetes as a risk factor.

The Vascular Study Group of New England presented their cardiac risk index for vascular surgery in 2010.[2] In this analysis, DM is grouped into DM treated with and without insulin, and a composite endpoint, including myocardial infarction, congestive heart failure, and ventricular and atrial arrhythmias, was used. DM treated with insulin was independently associated with the endpoint (OR 1.4 with 95%-CI 1.1-1.9). In this study, the group of patients with insulin treated diabetes may have consisted of both DM1 and insulin treated DM2 patients. No significant association was observed for DM treated without insulin with an odds ratio of 1.0. However, given the large confidence interval (0.8 – 1.3), no definite conclusions can be drawn regarding the effect of non-insulin-dependent diabetes on cardiac complications after vascular surgery.

In an analysis of 6565 vascular surgical procedures by Hamdan et al., postoperative myocardial infarction occurred in 1.77% of patients with DM, and in 1.30% of those without DM (and 1.13% vs. 1.14% postoperative congestive heart failure)[5]. It is stated that diabetes does not influence the risk of cardiac complications after vascular surgery. Unfortunately, no statistical analysis of these percentages is provided. Of note, the high prevalence of DM in the population of this study (62.3%) might limit generalizability to other vascular surgery populations.

Bolliger et al. studied 360 DM2 patients undergoing major non-cardiac surgical procedures, including vascular, orthopaedic, abdominal, and lung surgery, and found that patients treated with insulin were at higher risk of 30-day major cardiac complications than those managed without insulin (7.4% vs. 1.8%).[16] This might be explained by the higher number of cardiac risk factors in patients treated with insulin. As 30-day cardiac complications were not the primary endpoint of this study, no further exploration with multivariable regression analysis was performed.

In the current study of 1484 vascular surgery patients, type 2 diabetes mellitus is significantly associated with perioperative cardiovascular events, a composite outcome including cardiac death, non-fatal myocardial infarction, congestive heart failure, ventricular arrhythmia, stroke, and asymptomatic troponin release. Multivariable analysis demonstrated an adjusted odds ratio of 1.80 (95%-CI 1.24 – 2.61), with similar odds ratios in DM2 patients managed with and without insulin. A1C levels were similar in DM2 patients with and without a postoperative cardiac event, suggesting that preoperative glycaemic control is not a major determinant of cardiac complications after vascular surgery in type 2 diabetics.

Several limitations apply to this study. First, the study was performed retrospectively. Fasting glucose levels and glucose loading tests were not routinely obtained. Therefore, asymptomatic patients who fulfil the criteria of diabetes might have been misclassified as non-diabetic. This would result in an underestimation of the true effect of diabetes. We depended on previous diagnosis and classification of diabetes. Some misclassification of diabetes type might be present. A1C levels were unavailable in 15% of DM2 patients. Furthermore, the study was performed in a high-risk vascular surgery population at a tertiary referral center, which may limit generalizability to populations at lower risk of cardiac complications. We used a composite outcome measure including cardiac death, myocardial infarction, congestive heart failure, ventricular arrhythmia, and asymptomatic troponin release. We feel that including asymptomatic troponin release in the outcome measure is justifiable given its detrimental effect on long-term prognosis.[17] Removal of asymptomatic troponin release from the composite endpoint did not affect the odds ratios obtained in multivariable analysis.

In conclusion, our data support that type 2 diabetes mellitus is a major independent risk factor for cardiac complications in vascular surgery patients, regardless of the need for exogenous insulin. All diabetes mellitus, regardless of the type of diabetes and need for insulin therapy, should be considered a risk factor for cardiac complications after vascular surgery.

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CHAPTER 3

ABO BLOOD TYPE DOES NOT INFLUENCE THE RISK OF CARDIOVASCULAR COMPLICATIONS AND MORTALITY AFTER VASCULAR SURGERY

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Eur J Vasc Endovasc Surg 2013;45(3):256-60

ABSTRACT

Objectives: Thrombotic complications are common in vascular surgery patients. Non-O blood types are associated with an increased risk of thrombo-embolic diseases . The aim of this study is to assess the prognostic implications of non-O versus O blood type regarding 30-day cardiovascular events and long-term mortality after vascular surgery.

Methods: The population of this retrospective cohort study consisted of 4679 patients undergoing elective major vascular surgery between 1990 and 2011. Baseline characteristics, ABO blood type and follow-up were obtained. Multivariable regression analyses, adjusted for age, gender, medical history, medication, and smoking, were used to evaluate the impact of non-O blood type on 30-day cardiovascular events (cardiovascular death, myocardial infarction, and stroke) and long-term mortality.

Results: Non-O blood type was present in 2627 (56%) patients. Within 30 days after surgery, 129 (4.9%) non-O and 112 (5.5%) O patients suffered a cardiovascular event (P=.42). Non-O blood type was not associated with increased mortality during long-term follow-up (aHR .96; 95% CI .88 – 1.04, with a median follow-up of 4 years). Antiplatelet and anticoagulant drugs did not interact with the relationship between ABO blood type and long-term outcome.

Conclusion: Non-O blood type is not associated with either 30-day cardiovascular complications or long-term mortality in vascular surgery patients.

Key words: ABO Blood-Group System; vascular surgical procedures; cardiovascular complications; mortality.

What this paper adds:
ABO blood type is a major determinant of the risk of atherothrombotic events in the general population. This is the first study to assess the prognostic implications of ABO blood type in vascular surgery patients. ABO blood type did not influence the risk of perioperative cardiovascular complications and long-term mortality in vascular surgery patients.

INTRODUCTION

Atherosclerosis is a systemic disease that affects multiple organ systems.[1] Patients with peripheral arterial disease commonly suffer of concomitant coronary artery disease or cerebrovascular disease. [1-2] These patients are therefore at increased risk for both perioperative and long-term cardiovascular events, including stroke and myocardial infarction.[3-4] Arterial thrombosis is responsible for the majority of these, both in the perioperative and non-surgical setting.[5]

Several studies reported an increased risk of thrombotic events, including myocardial infarction, ischemic stroke, peripheral arterial disease and venous thrombo-embolism, in people with non-O blood types in the general population.[6-10]
It is unclear whether or not ABO blood type influences outcome after vascular surgery. We conducted the current study to evaluate the effect of ABO blood type on both perioperative cardiovascular complications and long-term survival after vascular surgery.

MATERIALS AND METHODS

This retrospective, single-centre study comprised a population of 4679 patients, referred for elective major vascular surgery, including abdominal aortic, carotid artery, and lower limb arterial repair. All patients underwent surgery between 1990 and 2011. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Erasmus Medical Center.

The obtained medical history included risk factors according to the Revised Cardiac Risk Index: ischemic heart disease (history of angina pectoris, myocardial infarction or coronary revascularization), heart failure (clinical signs according to the New York Heart Association, previous hospitalization for decompensated heart failure), cerebrovascular disease (history of transient ischemic attack or ischemic or haemorrhagic stroke), renal dysfunction (serum creatinin >2 mg/dL) and diabetes mellitus (fasting blood glucose ≥ 7.0 mmol/L or insulin or oral anti-diabetic drug use). Also, age, sex, smoking status, hypertension (systolic blood pressure >140 mmHg or diastolic >90 mmHg in non-diabetics, systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg in diabetics or use of antihypertensive medication) and chronic obstructive pulmonary disease were recorded, as well as medication use, with focus on antiplatelet and anticoagulant drugs. Open abdominal aortic repair and open lower limb revascularization were categorized as high-risk procedures, all other procedures as intermediate risk.

Per hospital protocol, chronic aspirin therapy is routinely continued perioperatively. The decision whether or not to interrupt vitamin K antagonist therapy and whether or not to initiate bridging therapy with heparin or low molecular weight heparin (LMWH) was made on a case-to-case basis. Per hospital protocol, thromboprophylaxis is routinely initiated the night prior to surgery using prophylactic doses of low molecular weight heparin (LMWH) in patients not receiving therapeutic doses of LMWH or oral anticoagulants. LMWH is continued until discharge from the hospital.

Study endpoints were 30-day cardiovascular events, including cardiovascular mortality, nonfatal myocardial infarction, and cerebrovascular events, and 30-day and long-term all-cause mortality. Myocardial infarction was defined as the presence of biochemical evidence of myocardial necrosis (the typical rise and fall of either cardiac Troponin T with at least one measurement >0.03 ng/mL or of creatin kinase with an MB fraction of >10%) combined with characteristic symptoms or electrocardiographic signs of ischemia (new-onset ST-T changes or left bundle branch block or development of pathological Q-waves). Cause of death within 30 days after surgery was obtained from hospital records and was classified as either cardiovascular or non-cardiovascular death. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as primary or secondary cause, including death following myocardial infarction, cardiac arrhythmias, congestive heart failure, stroke, and surgery related bleeding complications. Sudden unexpected death was also classified as a cardiovascular death.

All data was tabulated according to O and non-O blood type. Categorical variables are described as numbers and percentages. Continuous variables were described as means ± standard deviation. Duration of follow-up was described as median with interquartile range. Categorical data were compared using a Chi-Square test. Continuous data were compared using ANOVA. Cumulative long-term survival was determined using the Kaplan-Meier method and log-rank test. Logistic regression analysis was performed to evaluate the effect of non-O blood type on 30-day cardiovascular events. Cox regression analysis was performed to assess the effect of non-O blood type on long-term survival. Subgroup analysis was performed for age (>65, <65), gender, statin use, and antiplatelet/anticoagulant medication use. Multivariate regression analyses were adjusted for high-risk type of surgery, gender, age, hypertension, diabetes mellitus, smoking status, renal failure, ischemic heart disease, hypercholesterolemia, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, the use of beta-blockers, statins, antiplatelet and anticoagulant drugs. We reported crude and adjusted odds ratios and hazard ratios and their 95% confidence intervals. For all tests, a $P < .05$ (two-sided) was considered significant. All analyses were performed using PASW version 17.0 statistical software (SPSS inc., Chicago, IL).

RESULTS

The study population consisted of 4679 consecutive patients who underwent elective vascular surgery. Abdominal aortic repair was performed in 1814 (39%) patients, lower extremity revascularization in 1834 (39%) patients and carotid surgery in 1027 (22%) patients, respectively. The median follow-up was 4 (IQR 2 – 8) years. The majority of patients were men (73%) and the mean age was 66 ± 12 years. Non-O blood type was present in 2627 (56%) patients. Of all patients, 52% had no or one risk factor, 31% had two risk factors and 17% had three or more risk factors according to the Revised Cardiac Risk Index. O and non-O groups differed significantly regarding male gender (74% vs. 72%, P=.04), ischemic heart disease (34% vs. 37%, P=.02), aspirin use (48% vs. 45%, P=.04). There were no significant differences between O and non-O groups regarding other comorbidities, medication use, age and surgical characteristics, as demonstrated in Table I.

Table 1. Baseline characteristics according to blood type.

	O (n=2052)	**Non-O** (n=2627)	**p-value**
Demographics			
Mean age (SD)	67 (11)	66 (11)	.23
Mean BMI (SD)	26 (4)	26 (4)	.28
Male gender (%)	1527 (74)	1884 (72)	.04
Surgery type			
Carotid surgery	470 (23)	557 (21)	
Abdominal aortic surgery	810 (40)	1004 (38)	.09
Peripheral arterial surgery	769 (38)	1065 (41)	
Medical history (%)			
Congestive heart failure	122 (6)	178 (7)	.25
Cerebrovascular disease	648 (32)	766 (29)	.08
Hypertension	985 (48)	1188 (45)	.06
Diabetes mellitus	366 (18)	463 (18)	.88
Current smoking	663 (32)	863 (33)	.71
Creatinin >2mg/dL	190 (9)	270 (10)	.26
Ischemic heart disease	690 (34)	973 (37)	.02
COPD	800 (39)	1018 (39)	.88
Revised Cardiac Risk Index			
Cardiac risk factors (SD)	1.6 (1.0)	1.6 (1.0)	.28
Medication use (%)			
Aspirin	979 (48)	1175 (45)	.04
Anticoagulants	686 (33)	904 (34)	.49
Beta-blockers	949 (46)	1173 (45)	.29
Statins	770 (38)	965 (37)	.58

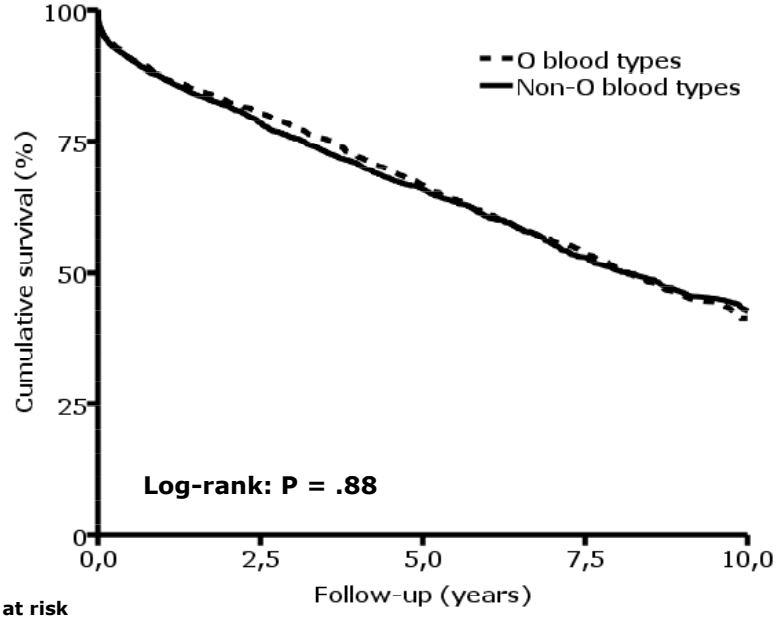
Abbreviations: COPD Chronic Obstructive Pulmonary Disease

During 30-day follow-up 241 (5.2%) patients had a cardiovascular event, including 132 (2.8%) cardiovascular deaths, 66 (1.4%) non-fatal myocardial infarctions, and 36 (0.8%) non-fatal strokes, as presented in Table II. No significant differences between O and non-O blood types were observed regarding stroke (1.0% vs. 0.6%, P=.09), non-fatal myocardial infarction (1.5% vs. 1.4%, P=.51), cardiovascular death (2.8% vs. 2.8%, P=1.00), and cardiovascular events (5.5% vs. 4.9%, P=.42). Within 30 days of surgery, 228 patients died of any cause. No significant difference was observerd between O and non-O blood type (4.9% vs. 4.8%, P=.89). Multivariate analyses demonstrated that non-O blood type was not associated with 30-day cardiovascular events (odds ratio (OR) 0.87, 95% confidence interval (CI) 0.67 – 1.13, P=.32).

Table 2.

30-day outcome			Univariable		Multivariable	
	N	(%)	OR	(95% CI)	OR	(95% CI)
Stroke						
O blood type	24 / 2052	(1.2)	ref		ref	
Non-O blood type	17 / 2627	(0.6)	0.55	(0.29 – 1.03)	0.56	(0.30 – 1.05)
Myocardial infarction						
O blood type	38 / 2052	(1.9)	ref		ref	
Non-O blood type	47 / 2627	(1.8)	0.87	(0.63 – 1.49)	0.96	(0.61 – 1.50)
Cardiovascular death						
O blood type	58 / 2052	(2.8)	ref		ref	
Non-O blood type	74 / 2627	(2.8)	0.99	(0.70 – 1.41)	0.91	(0.64 – 1.30)
Cardiovascular events						
O blood type	112 / 2052	(5.5)	ref		ref	
Non-O blood type	129 / 2627	(4.9)	0.90	(0.69 – 1.16)	0.87	(0.67 – 1.13)
All-cause mortality						
O blood type	101 / 2052	(4.9)	ref		ref	
Non-O blood type	127 / 2627	(4.8)	0.98	(0.75 – 1.28)	0.91	(0.69 – 1.20)

During long-term follow-up 1233 (47%) patients with non-O blood type died, compared with 981 (48%) patients with O blood type (P= .60). Cumulative survival for all patients is shown in Figure 1 (log rank P= 0.88). In a multivariate model, non-O blood type was not associated with long-term mortality (hazard ratio (HR) 0.96; 95% CI 0.88 – 1.04). We performed several subgroup analyses and found no interaction between the association between ABO blood type and long-term mortality by age, gender, surgical procedure, and antithrombotic medication use, as demonstrated in Figure 2.



N at risk					
O	2052	1368	906	562	329
Non-O	2627	1777	1166	715	437

Figure 1: Kaplan Meier estimates for long-term all-cause mortality, stratified according O and non-O blood type.

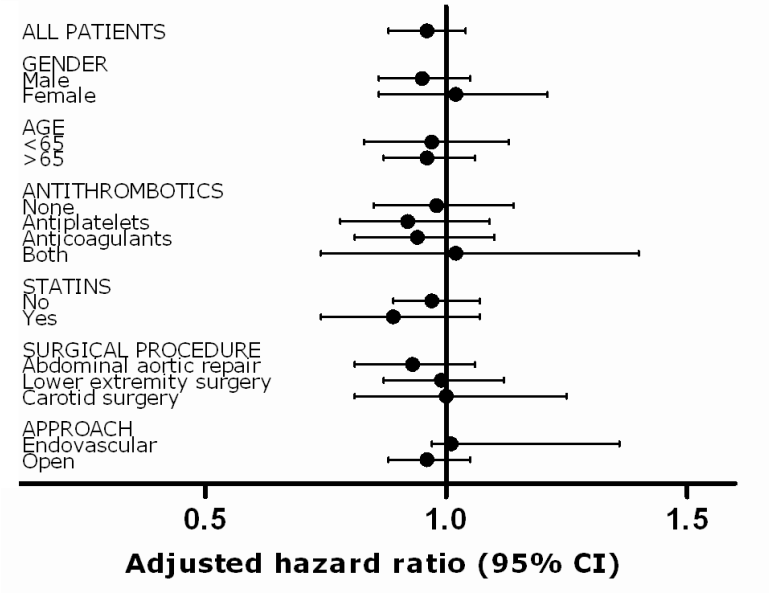


Figure 2: Non-O blood types and long-term mortality hazard in subgroups.

DISCUSSION

The current study demonstrated that non-O blood type was not associated with an increased prevalence of either 30-day cardiovascular events or long-term mortality, as compared with O blood type. After adjusting for cardiovascular risk factors, age, gender, smoking, and medication use, the odds ratio for 30-day cardiaovascular events and hazard ratio for long-term mortality were 0.87 (95% CI 0.67 – 1.13) and 0.96 (95% CI 0.88 – 1.04).

Von Willebrand factor is an important factor in hemostasis. It mediates platelet adherence to the subendothelium in vascular injury and serves as a carrier protein of clotting factor VIII, increasing plasma half-life of clotting factor VIII from 2 to 12 hours.[12-13] Increased levels of Von Willebrand factor are associated with an increased risk of both arterial and venous thrombosis.[14-18]

A major determinant of the circulating Von Willebrand factor level is ABO blood type. In individuals with non-O blood types, the plasma levels of von Willebrand factor are elevated by 25-30%, as compared with individuals with O blood type.[11 19] The mechanism through which ABO blood type influences plasma levels of Von Willebrand factor is not fully understood. It has been suggested that the A and B antigen on the surface of large, highly thrombogenic Von Willebrand particles inhibit proteolysis into smaller, less thrombogenic particles by the enzyme ADAMTS13, effectively decreasing Von Willebrand factor clearance.[20-21] Clotting factor VIII levels are consequently higher in individuals with non-O blood types.

In the general population, non-O blood type has been linked to an increased risk of peripheral arterial disease, myocardial infarction, ischemic stroke and venous thromboembolism, with odds ratios of 1.45, 1.25, 1.14, and 1.79, respectively.[6-10]

Peripheral arterial disease patients are at increased risk of cardiovascular events, both in the perioperative and non-surgical setting, most importantly myocardial infarction.[22] Thrombotic arterial occlusion the site of a ruptured atherosclerotic plaque is responsible for most of these events.[5] Chronic aspirin therapy is recommended for peripheral arterial disease patients to prevent both peripheral, cerebral, and myocardial thrombotic complications.[23]

To our knowledge, no data were available on the effect of ABO blood type on cardiovascular events and prognosis in peripheral arterial disease patients. In the current study, we found no evidence of such relationships. These findings are comparable to the results reported by Ketch et al., who reported no difference in 1-year mortality between non-O and O blood type in a cohort of 1198 patients who underwent a percutaneous coronary intervention for

acute myocardial infarction (HR 0.89; 95% CI 0.63 – 1.25).[24] In contrast, Carpeggiani et al. reported an increased long-term mortality in patients with non-O blood type in a cohort consisting of 4901 patients hospitalized for coronary artery disease, with a hazard ratio of 1.24 (95% CI: 1.01-1.52).[25] Their results were driven mainly by a strong relation found in women under the age of 65 (HR 4.61; 95% CI 1.93-11.00). In a subanalysis of women under 65, we found no significantly increased long-term mortality for non-O blood types (HR 0.95; 95% CI 0.69 – 1.30).

The association between ABO blood type and thrombotic events, as seen in the general population, might be influenced by the use of antiplatelet and anticoagulant medication. In a cohort of 661 patients with unprovoked venous thromboembolism, being treated with vitamin K antagonists, elevated clotting factor VIII levels were not associated with the risk of recurrent venous thromboembolism (0.7% per patientyear, as compared with 1.1% per patientyear in patients without thrombophilia).[26] In the study by Ketch in myocardial infarction patients, routinely treated with antiplatelet therapy, the rate of recurrent thrombotic events (myocardial infarction, stent thrombosis, target vessel revascularization) was similar in patients with non-O and O blood types.[24] In our study, the prognostic implications of ABO blood type after vascular surgery were similar in patients using antiplatelet drugs, anticoagulant drugs, both, or neither. The routine administration of perioperative thromboprophylaxis might have influenced the relationship between ABO blood type and perioperative events.

Another factor potentially influencing the relationship between ABO blood type and thrombotic events is the use of statins. Jaumdally et al. describe a decline in serum Von Willebrand factor levels after intensifying of statin therapy (atorvastatin 80mg daily).[27] Statin use did not influence the prognostic implications of ABO blood type in our study.

In the general population, non-O blood types lead to an increased risk of peripheral arterial disease, myocardial infarction, and stroke. However, non-O blood type seems not to be associated with outcome in patients after vascular surgery (current study) and myocardial infarction[24]. 'Index event bias' may attribute to this paradox, as all patients are selected based on an index atherothrombotic event (the requirement of vascular surgery).[28]

We assessed only the fenotype and not genotype of the ABO blood group. The highest levels of clotting factor VIII and Von Willebrand factor are observed in $A_1A/A_1B/BB$, intermediate levels in A_1O/BO and the lowest levels in OO genotype.[29] Possibly, by comparing O to non-O instead of $A_1A/A_1B/BB$ to OO, the effects of ABO on prognosis were diluted.

Although vascular surgery patients are considered to be at relatively low risk of venous thromboembolism, it would be interesting to assess the effects of ABO blood type on the risk of postoperative venous thromboembolism in our population.[30] Unfortunately, due to the retrospective study design, we were not able to systematically assess the presence of postoperative deep venous thrombosis and pulmonary embolism.

In conclusion, non-O blood type is not associated with increased incidence of 30-day cardiovascular events or long-term mortality after vascular surgery in our population.

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CHAPTER 4

INFLUENCE OF AORTIC VALVE CALCIUM ON OUTCOME IN PATIENTS UNDERGOING PERIPHERAL VASCULAR SURGERY

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Am J Cardiol 2012;110(8):1195-9

ABSTRACT

Vascular surgery patients are at increased risk for adverse cardiovascular events due to silent coronary artery disease and increased propensity for left ventricular dysfunction. The Revised Cardiac Risk Index (RCRI) is commonly used for preoperative risk stratification. Aortic valve calcium is associated with cardiovascular mortality in the general population. The present study evaluates the prognostic implications of aortic valve calcium on 30-day postoperative and long-term outcome in vascular surgery patients. Echocardiographic aortic valve evaluation was completed in 1172 vascular surgery patients. Aortic valve sclerosis was defined by thickening and/or calcium of one or more cusps of a tricuspid aortic valve not inducing stenosis, i.e. with a maximal velocity at continuous Doppler < 2.5 m/sec, and stenosis was defined as a maximal velocity > 2.5 m/sec. Troponin-T measurements and electrocardiograms were performed routinely after surgery. Study endpoints were the composite of postoperative cardiovascular events and long-term mortality. Aortic valve sclerosis was present in 416 (36%) patients and aortic valve stenosis in 30 (3%) patients. After multivariate regression analyses adjusted for age, gender, RCRI, hypertension, hypercholesterolemia and medication, aortic valve sclerosis was associated neither with postoperative nor long-term outcome. In contrast, aortic valve stenosis was associated with a higher postoperative and long-term event rate (OR 3.9; 95% CI 1.7-8.7 and HR 2.1 (95% CI 1.2 – 3.7). In conclusion, this study shows that aortic valve calcium is common in vascular surgery patients. Its presence is associated with postoperative and long-term outcome.

Key words: aortic valve calcium; vascular surgery; prevalence; prognosis

INTRODUCTION

Patients with peripheral arterial disease (PAD) undergoing vascular surgery are known to be at increased risk for perioperative and late cardiovascular events due to silent coronary artery disease (1,2) and greater propensity for left ventricular dysfunction (3). The Revised Cardiac Risk Index (RCRI) is commonly used for preoperative risk stratification in this patient population (4,5). Aortic valve calcium is associated with cardiovascular mortality in the general population (6). It is unknown whether the presence of aortic valve calcium increases the risk of cardiovascular events in patients with PAD.

The aim of the present study is to evaluate the prognostic implications of aortic valve calcium on 30-day postoperative and long-term outcome in patients with PAD requiring vascular surgery.

METHODS

This prospective cohort study included 1484 vascular surgery patients at the Erasmus Medical Centre in Rotterdam, during the period between 2002 and 2011. The study complies with the declaration of Helsinki and was approved by the Institutional Review Board. Patients were screened prior to surgery at the outpatient clinic, by means of physical examination, laboratory measurements, electrocardiograms (ECG) and lung function tests.

Before surgery, a detailed medical history was obtained from every patient. Baseline characteristics included age, gender, blood pressure, coronary heart disease (angina pectoris, prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting), cerebrovascular disease (history of stroke or transient ischemic attack), renal dysfunction (estimated GFR (eGFR) < 60 ml/min/1.73m^2), heart failure (by history), diabetes mellitus (by history or requirement for anti-diabetic medication), hypertension (blood pressure ≥ 140/90 mmHg in non-diabetics and ≥ 130/80 mmHg in diabetics or requirement for anti-hypertensive medication), hypercholesterolemia (low-density lipoprotein cholesterol ≥ 135 mg/dL or requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification) and smoking status. Medication use was recorded for aspirin, oral anticoagulants, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, nitrates and statins.

The cardiac risk score was determined for every patient using the Revised Cardiac Risk Index (RCRI). The RCRI assigns one point to each of the following characteristics: high-risk surgery, coronary heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes mellitus, and renal insufficiency (serum creatinine > 2.0 mg/dL) (7).

Aortic valve evaluation with transthoracic echocardiography was performed preoperatively or within 30-days postoperatively, using a portable Acuson Cypress Ultrasound system (Acuson, A Siemens Company, Mountain View, CA, USA) with a 7V3c transducer or a portable Vivid-I Ultrasound System (Vivid-I, GE Healthcare, Solingen, Germany) with a 3S-RS transducer. Aortic valve evaluation included assessment of cusps anatomy and valvular calcium. Continuous-wave Doppler echocardiography was used to measure aortic jet velocity. *Aortic valve sclerosis* (AVS) was defined by thickening and/or calcium of one or more cusps of a tricuspid valve not inducing stenosis, i.e. with a maximal velocity < 2.5 m/s, *aortic valve stenosis* (AoS) was defined as a jet velocity > 2.5 m/s (6,8). Jet velocity was chosen, since this is the strongest predictor of clinical outcome in patients with aortic valve stenosis (9). Patients with moderate AoS (jet velocity 3.0-4.0 m/s) or severe AoS (jet velocity > 4.0 m/s) were referred to a cardiologist for regular follow-up. Patients with unstable cardiac conditions or severe aortic stenosis requiring preoperative intervention were excluded.

Serial electrocardiograms and troponin-T (TnT) measurements were routinely obtained before surgery and postoperatively on day 1, 3 and 7. Study endpoints were 30-day cardiovascular (CV) events and long-term mortality. Thirty-day CV events are a composite of non-fatal myocardial infarction, new or worsened congestive heart failure, severe cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), stroke (including transient ischemic attack), cardiovascular mortality (any death from a cerebrovascular cause, including death following myocardial infarction, congestive heart failure, arrhythmia, stroke, and surgery related bleeding complications or sudden unexpected death), and asymptomatic TnT release. Myocardial infarction was defined as the characteristic rise and fall of (postoperative) TnT levels above the 99th percentile with either electrocardiographic or clinical signs of myocardial ischemia. TnT level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany). Thirty-day follow-up was completed by patients' visits to the outpatient clinic, and for patients still admitted or re-admitted at the Erasmus MC follow-up was completed using the Erasmus MC medical records. Long-term mortality was ascertained by approaching the municipal civil registries. Follow-up was completed in all patients.

Continuous variables were described as mean ± standard deviation (SD) and dichotomous data as numbers and percentages. Continuous data were compared using ANOVA and categorical data using chi-squared tests. Cumulative long-term survival was determined by the Kaplan-Meier method and compared with the log rank test. The prognostic value of AVS and AoS towards 30-day and long-term follow-up was evaluated with logistic and Cox regression analyses, respectively. Multivariate analyses were primarily adjusted for predefined potential confounders (age, gender, RCRI, hypertension and hypercholesterolemia). A second multivariate analysis was performed to adjust for medication with known beneficial

effects (aspirin, beta-blockers, statins and ACE-inhibitors). For all tests, a P value <.05 (2-sided) was considered significant. All statistical analyses were performed using SPSS 17.0 statistical software (SPSS Inc., Chicago, Ill).

RESULTS

The study population consisted of 1484 vascular surgery patients, of which 1172 patients had complete echocardiographic aortic valve evaluation. Open vascular surgery was performed in 660 (56%) patients, and 511 (44%) patients underwent endovascular surgery; 338 (29%) underwent lower extremity artery repair, 569 (49%) underwent abdominal aortic repair, and 251 (21%) underwent carotid artery repair. General anesthesia was applied in 97% of open vascular surgery and in 45% of endovascular surgery. Spinal and local (infiltration) anesthesia was used in 11% and 44% of patients in endovascular surgery, respectively.

Mean age of the study population was 68 (± 10) years and most (74%) were men. Aortic valve sclerosis was diagnosed in 416 (36%) patients and AoS in 30 (3%) patients. Of this, 14 (1.2%) had mild aortic stenosis (peak velocity 2.5 – < 3.0 m/sec), 9 (0.8%) had moderate aortic stenosis (peak velocity 3.0 – < 4.0 m/sec) and 7 (0.6%) had severe aortic stenosis (peak velocity > 4.0 m/sec).

Baseline characteristics of the study population according to aortic valve calcium are listed in *Table 1*. Patients with aortic valve calcium were older (p<0.001) and had higher incidence of coronary heart disease (p 0.005), renal dysfunction (p<0.001), diabetes mellitus (p 0.036) and hypertension (p<0.001). Patients with aortic valve calcium had a higher RCRI compared to patients with normal aortic valves (p<0.001). Regarding medication, there were no differences in the use of aspirin, calcium antagonists, ACE-inhibitors, angiotensin II antagonists, diuretics, nitrates and statins, but patients with aortic valve calcium more often received oral anticoagulants (p 0.012) and beta-blockers (p 0.015).

Table 1. Baseline characteristics according to aortic valve calcium

	normal AoV [N=726]	**AVS** [N=416]	**AoS** [N=30]	**P**
Demographics				
Age (mean ± SD)	67 (11)	71 (9)	75 (7)	<0.001
Men	536 (74%)	313 (75%)	21 (70%)	0.754
Coronary heart disease	270 (37%)	185 (45%)	18 (60%)	0.005
Cerebrovascular disease	234 (32%)	149 (36%)	10 (33%)	0.466
Renal dysfunction	147 (20%)	139 (33%)	12 (40%)	<0.001
Heart failure	58 (8%)	50 (12%)	2 (7%)	0.070
Diabetes Mellitus	156 (22%)	117 (28%)	6 (20%)	0.036
Hypertension	449 (62%)	321 (77%)	21 (70%)	<0.001
Hypercholesterolemia	660 (91%)	374 (90%)	24 (80%)	0.135
COPD	220 (45%)	153 (45%)	9 (43%)	0.980
Smoker, current	323 (45%)	165 (40%)	15 (50%)	0.210
Surgery type				
Open	400 (55%)	242 (58%)	18 (60%)	0.734
Endovascular	326 (45%)	173 (42%)	12 (40%)	0.251
Medication				
Aspirin	488 (68%)	270 (65%)	17 (57%)	0.342
Oral anticoagulants	105 (15%)	89 (21%)	6 (20%)	0.012
β-blockers	575 (80%)	360 (87%)	25 (83%)	0.015
Calcium antagonists	125 (17%)	93 (22%)	6 (20%)	0.114
ACE-inhibitors	196 (27%)	132 (32%)	10 (33%)	0.230
Angiotensin II antagonists	117 (16%)	89 (21%)	6 (20%)	0.090
Diuretics	163 (23%)	119 (29%)	8 (27%)	0.074
Nitrates	62 (9%)	52 (13%)	3 (10%)	0.106
Statins	574 (80%)	336 (81%)	19 (63%)	0.073
Revised Cardiac Risk Score				<0.001
0-1 risk factor	462 (64%)	198 (48%)	12 (40%)	
2 risk factors	176 (24%)	131 (32%)	9 (30%)	
≥ 3 risk factors	86 (12%)	86 (21%)	9 (30%)	

abbreviations: AoV aortic valve; AVS aortic valve sclerosis; AoS aortic valve stenosis; ACE angiotensin converting enzyme; COPD chronic obstructive pulmonary disease

During the 30-day follow-up, 203 (17%) patients had a CV event; of which 115 (16%) patients with a normal aortic valve compared to 72 (17%) patients with AVS and 16 (53%) patients with AoS ($p < 0.001$, *Table 2*). After adjustment for potential confounders, AoS but not AVS, was associated with an increased risk of CV events at 30-days (AoS: OR 3.9; 95% CI 1.7 – 8.7 and AVS: OR 0.8; 95% CI 0.6 – 1.1) (*Table 2*). These results were not influenced by correction for medication use in a second multivariate analysis. RCRI greater than or equal to 2 points and age were other risk factors associated with postoperative CV events (RCRI 2 points: OR 3.2; 95% CI 2.2 – 4.7, RCRI ≥ 3 points: OR 5.0; 95% CI 3.2 – 7.6 and age: OR 1.0; 95% CI 1.0 - 1.1).

During the long-term follow-up 253 (22%) patients died; of which 140 (19%) patients with a normal aortic valve compared to 98 (24%) patients with AVS and 15 (50%) patients with AoS ($p < 0.001$, *Table 2*). Cumulative survival for all patients, stratified according to aortic valve calcium, was studied using Kaplan-Meier survival analyses and is demonstrated in *Figure 1* (log rank $p < 0.001$) (*Table 2*). Multivariate analyses demonstrated that AoS was associated with long-term mortality with a hazard ratio of 2.1 (95% CI 1.2 – 3.7); no association was observed for AVS and long-term outcome with a hazard ratio of 1.0 (95% CI 0.7 – 1.3). RCRI greater than or equal to 2 points and age were also associated with long-term mortality (RCRI 2 points: HR 1.9; 95% CI 1.4 – 2.6, RCRI ≥ 3 points: HR 3.1; 95% CI 2.3 – 4.2, age: HR 1.0; 95% CI 1.0 – 1.1). Similar hazard ratios were obtained after additional adjustment for medication use (aspirin, beta-blockers, ACE-inhibitors and statins).

The incremental value of aortic valve calcium in the prediction of long-term mortality is presented in *Figure 2*.

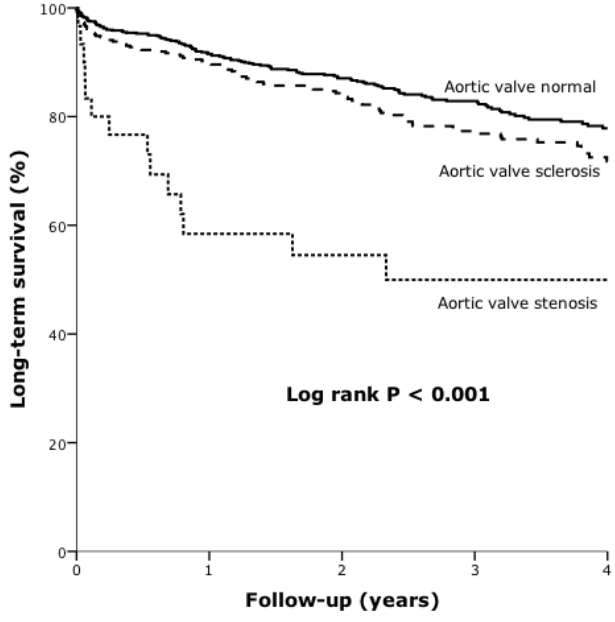

Figure 1. Kaplan-Meier curves of long-term survival in patients with aortic valve calcium after vascular surgery

Table 2. Association between aortic valve calcium and outcome

		Univariate		Multivariate (1)		Multivariate (2)	
30-day CV events		OR	[95% CI]	OR	[95% CI]	OR	[95% CI]
normal aortic valve	115/726 (16%)	reference		reference		reference	
aortic valve sclerosis	72/416 (17%)	1.1	0.8-1.6	0.8	0.6-1.1	0.8	0.5-1.1
aortic valve stenosis	16/30 (30%)	6.1	2.9-12.9	3.9	1.7-8.7	3.8	1.7-8.6
Long-term mortality		HR	[95% CI]	HR	[95% CI]	HR	[95% CI]
normal aortic valve	140/726 (19%)	reference		Reference		reference	
aortic valve sclerosis	98/416 (24%)	1.4	1.1-1.8	1.0	0.7-1.3	0.9	0.7-1.2
aortic valve stenosis	15/30 (50%)	3.6	2.1-6.2	2.1	1.2-3.7	2.0	1.2-3.4

analysis 1: adjusted for age, gender, RCRI, hypertension, hypercholesterolemia
analysis 2: adjusted for variables in analysis 1 plus aspirin, beta-blockers, ACE-inhibitors, statins

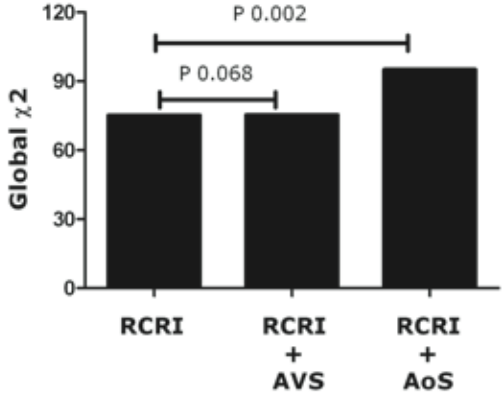

Figure 2. Incremental value of aortic valve calcium in the prediction of long-term mortality

DISCUSSION

This study shows that aortic valve calcium is common in vascular surgery patients, with a prevalence of 36% for AVS and 3% for AoS. Its presence is associated with postoperative cardiovascular events and long-term mortality.

Aortic valve calcium is a disease continuum, which comprises aortic valve sclerosis and aortic valve stenosis (10). Aortic valve sclerosis does not cause hemodynamic perturbations, and its impact on cardiovascular mortality in the general population (6) has been attributed to underlying coronary artery disease (11). In PAD patients polyvascular atherosclerotic disease is common, and its presence is an independent CV risk factor (12). In the present study patients with aortic valve calcium had more coronary heart disease. They had higher cardiac risk scores, represented by the RCRI. The RCRI is a risk stratification tool in non-cardiac surgery, which is well validated in different studies (4,13,14). Not only postoperative,

but also long-term outcome is associated with RCRI (14). In unadjusted analyses the presence of AVS was not associated with 30-day postoperative cardiovascular events but it was with long-term mortality, however after correction for comorbidities and cardiovascular risk factors in multivariate analyses this association was no longer present. The presence of AVS is probably attenuated in this cohort of vascular surgery patients with extensive polyvascular disease.

In this study, the presence of AoS in vascular surgery patients increased the risk for postoperative CV events almost fourfold, even after correction for common cardiovascular risk factors. In line with these findings, Rohde et al. reported an OR of 2.1 (95% CI 1.0-4.5) for the association of postoperative cardiac events with the presence of AoS defined by a peak instantaneous gradient ≥ 20 mmHg, in patients undergoing non-cardiac surgery (15). Kertai et al. found a fivefold increase in perioperative complications in patients with AoS, defined by a mean gradient ≥ 25 mmHg (16). In both studies nearly 40% of patients underwent a high-risk surgical procedure, defined as expected length of stay of ≥ 2 days (15) and as major vascular surgery (16). In the present study, more than 40% of patients underwent high-risk surgery and almost 60% underwent intermediate-risk surgery, as defined by ESC guidelines (4).

In addition to increased postoperative cardiac events, the presence of AoS in vascular surgery patients was also associated with long-term outcome in the present study. Previous cohort studies in patients with AoS reported similar outcomes. Patients with mild to moderate AoS (jet velocity 2.5 to 3.9 m/s) had a 1.8 times higher mortality than expected with event free survival 95±2%, 75±3% and 60±5% at 1, 3 and 5 years, respectively (17). In asymptomatic patients with severe AoS (jet velocity ≥ 4 m/s) event free survival was even worse: 80%, 63% and 25% at 1, 2 and 5 years respectively (18). Comparable event free survival was reported by Rosenhek (19).

Standard of care for severe, symptomatic AoS is aortic valve replacement (20). No medical therapy is able to delay the inevitability of surgery. Although atherosclerosis and aortic valve calcium share pathological features, such as lipid deposition, and the presence of ACE has been demonstrated in sclerotic aortic valves (10), statins and ACE-inhibitors have not proven to be successful in reducing AoS progression. Retrospective studies showed promising results (17,21-24), but these were not confirmed by prospective, randomized trials (25-27). In the present study, there was no difference in use of ACE-inhibitors or statins in patients with aortic valve calcium. Reported hazard ratios did not change after correction for medication use. It would be interesting to see if AoS progression is different in this population of vascular surgery patients in comparison with patient populations in aforementioned randomized trials, since in these trials patients with peripheral arterial disease (26,27) or patients on statin therapy (25), were excluded.

Several limitations of the current study should be considered. First, the presence, but not the extent of valvular calcium, which is a strong negative predictor of poor outcome (19), was recorded. Second, in a number of patients echocardiography was performed postoperatively. Since aortic valve calcium is slowly progressive (10), its presence at the time of surgery was expected. Third, no follow-up echocardiography was performed to evaluate progression of aortic valve calcium and last, this is an observational study, the causal relationship between aortic valvular disease and clinical outcomes cannot be established.

In conclusion, the prevalence of aortic valve calcium in vascular surgery patients is high. Its presence is associated with 30-day postoperative and long-term outcome, particularly in patients with aortic valve stenosis.

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CHAPTER 5

CARDIAC RISK ASSESSMENT IN ELDERLY SURGICAL PATIENTS

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Submitted

ABSTRACT

This study assesses the risk and determinants of cardiac complications after noncardiothoracic surgery in elderly patients, stratified by procedure-specific risk. We retrospectively analysed data of 1764 patients aged over 80. The outcome measure was in-hospital Major Adverse Cardiac Events (MACE). MACE occurred in 1.3% of 916 low-risk surgical procedures and the presence of signs of exercise-induced myocardial ischaemia was the only predictor of MACE. Intermediate-risk procedures resulted in MACE in 5.5% of 806 patients, with ischemic heart disease, heart failure, peripheral vascular disease and atrial fibrillation as independent risk factors. In this population, both the Revised Cardiac Risk Index and ASA classification were moderately predictive of MACE (c-statistic of 0.65 for both). 35% of 40 patients suffered MACE after high-risk surgery. In conclusion, low risk procedures can be performed savely in octogenerians. MACE is however frequent in intermediate risk procedures and commonly applied risk models are inadequate in this population.

Cardiac complications are common after noncardiac surgery. These serious events cause significant morbidity and mortality. A major determinant of the risk of cardiac complications is the magnitude of the planned surgical procedure, with event rates ranging from less than 1 percent in low-risk procedures such as eye and breast surgery to over 5 percent in major vascular procedures. Therefore, the 2009 European Society of Cardiology (ESC)/ European Society of Anaesthesiology (ESA) guidelines on perioperative cardiac care recommend to proceed directly to surgery in low-risk procedures, but to perform additional risk stratification in intermediate and high-risk procedures. [1] The Revised Cardiac Risk Index (RCRI) is recommended as a useful tool to assess the individual patients cardiac risk. [2]

An ongoing increase in life expectancy is observed worldwide. [3] This results in an increasing number of elderly patients requiring surgery. It is generally accepted that this population is at increased risk of cardiac complications due to reduced physiological reserve and increased comorbidity. [4] In the high-risk population of patients aged 80 years and older, limited data are available to support the aforementioned guideline recommendations.

The aim of the current study is to assess the risk and determinants of cardiac complications after elective noncardiothoracic surgery in patients aged 80 years and older, stratified by procedure-specific risk.

METHODS

Study design and population

We retrospectively analysed the data on all patients aged 80 years and older who underwent surgery in the Erasmus Medical Centre, a large tertiary referral centre in the Netherlands, between 2004 and 2011, and required at least one night of postoperative hospitalisation. Exclusion criteria were emergency surgery, cardiothoracic procedures, unavailability of the necessary computerised medical charts, and procedures conducted within 30 days after an index procedure. In case of multiple eligible procedures per patient, only the most recent procedure was included. All data were obtained from computerised medical charts. The study was approved by the Erasmus MC ethical committee. Given the retrospective design, no informed consent was required under Dutch law.

Surgical risk

In accordance to the ESC guidelines on perioperative cardiac care [1], open aortic and lower limb vascular surgery were considered high cardiac risk procedures. All other vascular procedures, abdominal, head and neck, neurological, major orthopedic (spine and hip), transplant, and major urological surgery were considered intermediate risk procedures. All

other procedures, including eye, reconstructive, dental, breast, endocrine, gynaecological, minor orthopedic, and minor urological procedures were considered low risk.

Patient characteristics

The collected patient data include age, gender, history of ischaemic heart disease (a history of myocardial infarction, history of positive exercise test, current angina pectoris complaints, nitrate therapy, or ECG with pathological Q waves), history of myocardial revascularisation, current inducible ischemia (typical anginal chest pain at exertion reported at the preoperative visit to the anaesthesiology outpatient clinic, or signs of ischemia on a preoperative cardiac stress test), history of congestive heart failure, cerebrovascular disease (stroke or transient ischaemic attack), diabetes mellitus (previous diagnosis or glucose-lowering medication), insulin therapy for diabetes mellitus, hypertension (previous diagnosis or antihypertensive medication), chronic obstructive pulmonary disease, atrial fibrillation, peripheral vascular disease, body-mass index ($kg.m^{2\ -1}$), anaemia (preoperative haemoglobin <13.8 $mg.dl^{-1}$ in men and <12.1 $mg.dl^{-1}$ in women), aortic valve stenosis (Maximum flow velocity over the aortic valve >2,5 $m.s^{-1}$ on echocardiography), estimated glomerular filtration rate <60 ml/min (eGFR, by MDRD formula). A RCRI score was calculated for all patients by assigning one point to each of the following: history of ischaemic heart disease, congestive heart failure, cerebrovascular disease, insulin therapy for diabetes mellitus, serum creatinin >2 $mg.dl^{-1}$, and 'high-risk procedure' (defined by the RCRI as intraperitoneal or open supra-inguinal vascular surgery) and assigning patients with 0, 1, 2, and more risk factors to RCRI class I, II, III, and IV, respectively. For comparison with the RCRI, an ASA physical classification was obtained from anaesthesia charts in the vast majority of cases, or based on patient history if not available from anaesthesia charts.

Outcome measures

The main outcome measure of the study is the in-hospital occurrence of major adverse cardiac events (MACE), a composite of cardiac death, myocardial infarction, heart failure, and arrhythmia. Cardiac death was defined as any death with a cardiac complication as the primary or secondary cause, including death following myocardial infarction, congestive heart failure, cardiac arrhythmia, and resuscitation. Unexpected sudden death was also considered as cardiac death. All other deaths were considered of non-cardiac cause. Myocardial infarction was defined as at least one measurement of troponin T above the 99^{th} percentile combined with electrocardiographic and/or clinical signs of cardiac ischemia. Postoperative serial troponin measurements were not routinely performed. Congestive heart failure was defined as postoperative new, worsened, or acute heart failure diagnosed by a treating physician, combined with either pulmonary edema or pulmonary vascular redistribution on a chest X-ray or requirement of intravenous diuretics. Arrhythmia included

ventricular arrhythmias (requiring immediate cardioversion, cardiopulmonary resuscitation, or pacing). MACE was assessed by two investigators (EB and TV) by consensus.

Statistical analysis

Dichotomous data are presented as numbers and percentages. Continuous data are presented as means ± standard deviation. Statistical significance of between-group differences was assessed with Chi-square tests, t-tests, and Mann-Whitney U tests as appropriate and a p-value <0.05 was considered significant. To identify independent predictors of MACE, a logistic regression model was constructed using stepwise deletion, in which MACE was the dependent variable. Independent variables were selected based on an association with MACE in univariate analysis with a p-value <0.2. A simple risk prediction model was constructed by adding the beta values of the independent predictors as obtained in multivariable analysis. The cut-off for variable deletion was 0.2. Discriminatory power (the ability to discriminate between patients with different outcomes) of risk prediction models was assessed using the area under the curve of Receiver Operator Characteristic curves (c-statistic). A c-statistic of 1.0 indicates perfect specificity and sensitivity, while a c-statistic of 0.5 indicates that the models predictions are no better than chance. Calibration was tested using the Hosmer-Lemeshow goodness-of-fit test, with a Hosmer-Lemeshow p-value >0.05 indicating good calibration of the model. All statistical tests were performed with PASW 17.0 (SPSS inc., Chicago, IL).

RESULTS

The study population consisted of 1762 patients, undergoing 319 (18%) ocular surgeries, 296 (17%) ear-nose-throat surgeries, 207 (12%) orthopaedic surgeries, 185 (11%) vascular procedures, 168 (10%) abdominal surgeries, 152 (9%) urologic procedures, 110 (6%) gynaecologic surgeries, 110 (6%) reconstructive surgeries, 88 (5%) neurosurgical procedures, and 127 (7%) other procedures. The mean age was 84 ± 3 years and 937 (53%) patients were female.

A total of 70 (4.0%) patients suffered MACE, including 14 (0.7%) cardiac deaths, 28 (1.6%) non-fatal myocardial infarctions, 19 (1.1%) cases of congestive heart failure, and 9 (0.5%) arrhythmias.

Of the 916 (52%) patients undergoing a low risk procedure, 12 (1.3%) suffered MACE. The only baseline characteristic significantly associated with MACE in univariate analysis in these patients was the presence of current exercise-induced myocardial ischaemia (6.6 vs 0.9%, p<0.01).

Table 1. Univariate associations between clinical characteristics and MACE

Surgical risk		**Low**			**Intermediate**			**High**		
		MACE / Procedures	%	p-value	MACE / Procedures	%	p-value	MACE / Procdures	%	p-value
Ischemic heart disease	yes	6 / 252	(2.4)	0.10	23 / 212	(10.8)	<0.01	8 / 23	(34.8)	1.00
	no	6 / 664	(0.9)		21 / 594	(3.5)		6 / 19	(35.3)	
Inducible myocardial ischaemia	yes	4 / 61	(6.6)	<0.01	9 / 38	(23.7)	<0.01	2 / 9	(22.2)	0.45
	no	8 / 855	(0.9)		35 / 768	(4.6)		12 / 31	(38.7	
Prior coronary revascularization	yes	2 / 93	(2.2)	0.35	7 / 91	(7.7)	0.33	4 / 11	(36.4)	1.00
	no	10 / 823	(1.2)		37 / 715	(5.2)		10 / 29	(34.5)	
Cerebrovascular disease	yes	4 / 160	(2.5)	0.24	14 / 183	(7.7)	0.14	3 / 8	(37.5)	0.87
	no	8 / 756	(1.1)		30 /623	(4.8)		11 / 32	(34.4)	
Congestive heart failure	yes	0 / 60	(0.0)	0.36	12 / 62	(19.4)	<0.01	5 / 8	(62.5)	0.10
	no	12 / 856	(1.4)		32 / 744	(4.3)		9 / 32	(28.1)	
Peripheral vascular disease	yes	1 / 60	(1.7)	0.56	15 / 159	(9.4)	0.02	14 / 40	(35.0)	
	no	11 / 856	(1.3)		29 / 647	(4.5)		0 / 0		
Hypertension	yes	7 / 554	(1.3)	1.00	34 / 527	(3.6)	0.10	13 / 32	(40.6)	0.22
	no	5 / 362	(1.4)		10 / 279	(6.5)		1 / 8	(12.5)	
Diabetes mellitus	yes	2 / 157	(1.3)	1.00	11 / 138	(8.0)	0.15	4 / 10	(40.0)	0.72
	no	10 / 759	(1.3)		33 / 668	(4.9)		10 / 30	(33.3)	
Insulin use for diabetes mellitus	yes	1 / 49	(2.0)	0.49	1 / 29	(5.5)	1.00	2 / 4	(50.0)	0.60
	no	11 / 867	(1.3)		43 / 777	(3.4)		12 / 36	(33.3)	
Creatinin clearance <60 ml/min	yes	4 / 271	(1.5)	0.76	20 / 244	(8.2)	0.03	7 / 14	(50.0)	0.18
	no	8 / 645	(1.2)		24 / 562	(4.3)		7 / 26	(26.9)	
Creatinine >2 mg/dL	yes	0 / 32	(0.0)	0.51	2 / 25	(8.0)	0.64	1 / 2	(50.0)	0.65
	no	12 / 884	(1.4)		42 / 781	(5.4)		13 / 38	(34.2)	
Atrial fibrillation	yes	5 / 199	(2.5)	0.15	17 / 140	(12.1)	<0.01	5 / 13	(38.5)	1.00
	no	7 / 717	(1.0)		27 / 666	(4.1)		9 / 27	(33.3)	

Age	80-84	8 / 582	(1.4)	0.97	32 / 605	(5.3)	0.43	11 / 30	(36.7)	0.75
	85-89	3 / 253	(1.2)		8 / 161	(5.0)		3 / 9	(33.3)	
	>90	1 / 81	(1.2)		4 / 40	(10.0)		0 / 1	(0.0)	
High-risk surgery according to RCRI	yes	0 / 0	(0.0)		9 / 192	(5.7)	0.72	14 / 40	(35.0)	
	no	12 / 916	(1.3)		35 / 614	(4.7)		0 / 0	(0.0)	
Anaemia	yes	5 / 281	(1.8)	0.53	22 / 337	(6.5)	0.28	8 / 16	(50.0)	0.18
	no	6 / 511	(1.2)		22 / 463	(4.8)		6 / 24	(25.0)	
COPD	yes	2 / 167	(1.2)	1.00	6 / 140	(4.3)	0.68	0 / 7	(0.0)	0.08
	no	10 / 749	(1.3)		38 / 666	(5.7)		14 / 33	(42.4)	
Aortic valve stenosis	yes	1 / 31	(3.2)	0.34	2 / 34	(5.9)	0.71	2 / 4	(50.0)	0.19
	no	11 / 885	(1.2)		42 / 772	(5.4)		12 / 36	(33.3)	

An intermediate risk procedure was performed in 806 (46%) patients. Of these, 44 (5.5%) suffered MACE. This risk is significantly higher compared with low risk procedures (p<0.01). Univariate associations are demonstrated in Table 1. In this population, multivariable analysis (Table 2) identified ischaemic heart disease (OR 1.98; 95%-CI 0.97 – 4.07 without signs of inducible ischaemia and OR 5.58; 95%-CI 2.31 – 14.74 in the presence of inducible ischaemia), congestive heart failure (OR 2.93; 95%-CI 1.28 – 6.68), peripheral vascular disease (OR 1.65; 95%-CI 0.82 – 3.32), and atrial fibrillation (OR 2.01; 95%-CI 0.98 – 4.12). The observed rates of MACE were 3.2% in RCRI class I, 4.3% in class II, 10.3% in class III, and 17.6% in class IV (Table 3). This results in an area under the Receiver-Operater curve of 0.651 (Figure 1). This is comparable to the predictive value of the ASA physical classicication (area under ROC 0.649). Both models were well-calibrated (Hosmer-Lemeshow goodness-of-fit p=1.00 for both). A simple risk score created by adding the beta values of the independent predictors as shown in Table 2 resulted in an area under the ROC of 0.74.

Table 2. Multivariate predictors of MACE in patients undergoing intermediate risk surgery.

	OR	(95%-CI)	B-coefficient	P-value
Coronary artery disease				
No	1		0	ref
Without presence of inducible ischemia	1.98	(0.97 – 4.07)	0.685	0.06
With presence of inducible ischemia	5.58	(2.31 – 14.74)	1.764	<0.01
Congestive heart failure	2.93	(1.28 – 6.68)	1.074	0.01
Peripheral arterial disease	1.65	(0.82 – 3.32)	0.500	0.16
Atrial fibrillation	2.01	(0.98 – 4.12)	0.695	0.06

Table 3. Univariate associations between risk prediction models and MACE in intermediate risk surgery

	Events / patients	(%)	OR	(95%-CI)
ASA physical class				
Class I	0 / 28	(0)		
Class II	12 / 408	(2.9)	1	
Class III	31 / 363	(8.5)	3.1	(1.6-6.1)
Class IV	1 / 7	(14.3)	5.5	(0.6-49.3)
C-statistic (standard error)	**0.649** (0.04)			
Revised Cardiac Risk Index				
Class I	10 / 313	(3.2)	1	
Class II	14 / 323	(4.3)	1.4	(0.6-3.1)
Class III	14 / 136	(10.3)	3.5	(1.5-8.0)
Class IV	6 / 34	(17.6)	6.5	(2.2-19.2)
C-statistic (standard error)	**0.651** (0.05)			

Only 40 patients underwent a high risk surgical procedure. Of these, 14 (35%) suffered MACE (95%-CI 21% - 50%). None of the patient characteristics available was significantly associated with MACE on univariate analysis.

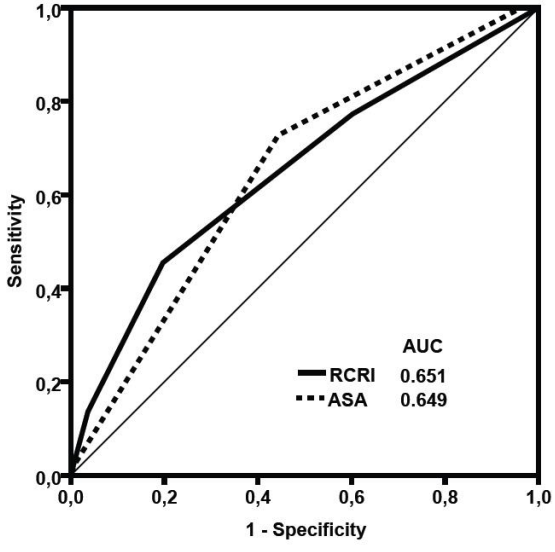

Figure 1. Receiver-Operator curves of the Revised Cardiac Risk Index (——, area under the curve 0.651) and ASA classification (----, area under the curve 0.649) in intermediate risk surgery.

DISCUSSION

Our data show that the risk of cardiac complications after low cardiac risk surgery in a large cohort of patients aged 80 or older is 1.3 percent. Of note, this includes only patients requiring at least overnight hospital stay, not outpatients. These data suggest that, even in the very elderly, it is generally save to proceed to a low risk surgical procedure without further assessment of the patient if no unstable cardiac condition is present (as advocated in guidelines on perioperative cardiac care). Extra attention should be paid to elderly patients with angina pectoris on exertion, as 6.6 percent of these suffered MACE after low cardiac risk procedures in the current study, whereas a <1% event rate is to be expected in the general low-risk surgical population [1-2].

The rate of MACE after intermediate cardiac risk procedures was 5.5 percent in our population, while a 1-5 percent event rate is to be expected in an unselected intermediate risk surgical population of mixed age. [1] Given this high event rate, risk stratification is of vital importance to guide clinical decision making for both the anaesthesiologist and surgeon.

Our data suggest that the use of the Revised Cardiac Risk Index [2] (as advocated in the ESC guidelines) is of limited help in the octogenarian surgical population. With a c-statistic of 0.651, the RCRI performs only moderately better than chance, and no better than the ASA classification. This is striking as the RCRI has been specifically developed for the prediction of MACE, while the ASA physical score is merely a very simple (and subjective) classification of general health, intended to facilitate comparison of patient populations undergoing anaesthesia. [6] A meta-analysis demonstrated better discriminatory power of the RCRI in populations of mixed age and surgical risk (pooled c-statistic 0.75; 95%-CI 0.72-0.79). [7]
This discrepancy between the predictive value of the RCRI in the general and elderly population may arise from the following: in intermediate risk surgery, we identified ischaemic heart disease, congestive heart failure, peripheral vascular disease, and atrial fibrillation as independent predictors of MACE in our population. Cerebrovascular disease, insulin use for diabetes and renal dysfunction, as incorporated in the RCRI were not independently associated with MACE. Of note, the latter two factors were not significantly associated with cardiac events in the population used by Lee et al. to validate the RCRI either. [2]

We identified only 40 patients undergoing high cardiac risk procedures (open aortic and peripheral arterial surgery). The event rate in this population was 35 percent, compared with approximately 10-15 percent after high-risk surgery in a population of mixed age. [8] Even though this is a very small sample, we feel it is save to state that high cardiac risk procedures in patients aged 80 and older are associated with an extreme risk of cardiac complications by any standard. Unfortunately, no further analyses could be performed given the small number of cases. A bias may be present in this particular group, as high-risk surgery in elderly patients is only likely to be performed in very selected patients.

Several studies identify ageing as a major risk factor for cardiac complications after noncardiac surgery. [9,10] Two main mechanisms are thought to be responsible for this observation. First, as atherosclerosis increases with age, coronary artery disease is common in elderly patients, although it may be asymptomatic. Furthermore, normal ageing of the cardiovascular system leads to stiffening of the arterial system, systolic hypertension, increased afterload and left ventricular wall thickness, and impaired left ventricular relaxation. [4] Combined with an age-dependent increased duration of systole and decreased duration of diastole, these changes lead to impaired diastolic left ventricular function and decreased coronary filling time. This diastolic dysfunction is usually asymptomatic under normal conditions, but is (together with blunted beta-adrenoreceptor responsiveness) a cause of the reduced tolerance of elderly patients for both exercise and for the physical stress provoked by surgery. This is not adequately represented in the RCRI, which may explain the limited value of the RCRI in the octogenerian intermediate-risk surgical population. We constructed a simple risk model

including the independent predictors of MACE after intermediate risk surgery. The c-statistic of this model was significantly improved compared to the RCRI but still a moderate 0.74, suggesting that preoperative cardiac risk stratification based on medical history alone may be of limited use in the very elderly surgical patient. We think that functional tests such as exercise testing may be of additional value in the very elderly requiring noncardiac intermediate to high risk surgery, as these probably provide an insight in the severity of both the cardiopulmonary comorbidity and the 'normal' ageing of the cardiovascular system. The additional value of exercise testing has been confirmed in younger patients, but future studies addressing this hypothesis are needed in the octogenerian surgical population. [11]

In conclusion, low cardiac risk surgery is safe even in the very elderly, and cardiac risk stratification may not be necessary for the majority of patients. Intermediate and high-risk procedures are associated with >5 percent risk of major cardiac events and present tools for cardiac risk stratification of limited value in this population.

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CHAPTER 6

GENERAL ANAESTHESIA IS ASSOCIATED WITH ADVERSE CARDIAC OUTCOME AFTER ENDOVASCULAR ANEURYSM REPAIR

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Eur J Vasc Endovasc Surg 2012;44(2):121-5

ABSTRACT

Objectives: Endovascular aneurysm repair (EVAR) is associated with reduced cardiac stress compared with open repair and is an attractive therapeutic option, especially in cardiac fragile patients. General and locoregional anaesthesia differ regarding the stress response evoked by surgery. The aim of the study is to compare the incidence of cardiac events after EVAR under general or locoregional anaesthesia.

Methods: A total of 302 consecutive patients undergoing infrarenal EVAR between 2002 and 2011 were analyzed in this retrospective cohort study. Selection of anaesthesia type was at the discretion of the treating physicians. Medical history, medication use, anaesthesia technique, and follow-up were obtained. The study endpoint was 30-day cardiac complications, including cardiac death, non-fatal myocardial infarction, heart failure, ventricular arrhythmia and troponin T release. Multivariable analysis, adjusted for the propensity of receiving a locoregional technique and cardiac risk factors according to the Revised Cardiac Risk Index was used to assess the association between cardiac events and anaesthesia type.

Results: A total of 173 patients underwent general anaesthesia and 129 locoregional anaesthesia. Obesity, aspirin use, and therapeutic anticoagulation were more common in patients receiving general anaesthesia. Cardiac events were observed in 13.3% of patients receiving general anaesthesia and in 4.7% of patients receiving locoregional anaesthesia (P=.02), or 6.4% vs 0.8% (P=.02) when asymptomatic troponin release is excluded from the endpoint. In the general anaesthesia group, 2 cardiac deaths, 6 non-fatal myocardial infarctions, 2 cases of non-fatal heart failure, 1 non-fatal cardiac arrest, and 12 cases of troponin T release were observed, compared with 1 myocardial infarction and 5 cases of troponin T release in the locoregional anaesthesia group. In multivariable analysis, general anaesthesia was associated with adverse cardiac events (OR 3.8; 95%-CI 1.1 – 12.9). Non-cardiac complications occurred in 11.6% of patients in both groups (P=1.00).

Conclusion: General anaesthesia was associated with an increased risk of cardiac events in EVAR, compared with locoregional anaesthesia.

INTRODUCTION

Endovascular therapy represents an opportunity to reduce the stress response associated with abdominal aortic aneurysm repair, compared with the conventional open approach.[1] EndoVascular Aneurysm Repair (EVAR), given its inherently minimally invasive nature, is associated with less haemodynamic fluctuations, endocrinologic stress reaction, blood loss, and postoperative pain. Subsequently EVAR is associated with a reduced risk of cardiac complications (3.1% vs. 21.8%), pulmonary complications and periprocedural mortality (1.7% vs. 4.7%), as compared with conventional open aneurysm repair.[2-6] EVAR is therefore an attractive treatment strategy, especially in the more frail patients requiring aneurysm repair.

Cardiac complications are a major cause of morbidity and mortality following noncardiac surgery, most importantly myocardial infarction. The increased risk of myocardial infarction, through either prolonged myocardial oxygen supply-to-demand mismatch or coronary plaque rupture, is thought to arise from the stress response evoked by the surgical procedure.[7] The various types of anaesthesia attenuate the surgical stress response to a different extent. Differences in postoperative cardiac event rates between anaesthesia types have been demonstrated previously.[8]

The performance of EVAR procedures was demonstrated to be feasible under multiple types of anaesthesia, including general, epidural, spinal, and local anaesthesia.[9] However, no conclusive data exist on anaesthesia type and cardiac outcome in EVAR. The aim of the current study is to assess the association between anaesthesia type and cardiac events after EVAR procedure. *Materials and Methods*

A total of 302 consecutive patients undergoing infrarenal EVAR between 2002 and 2011 were analyzed in this retrospective cohort study. Emergency procedures were excluded, as were hybrid procedures. The study was performed at a single site at the Department of Vascular Surgery of the Erasmus Medical Center, Rotterdam, the Netherlands. The study complies with the declaration of Helsinki and was approved by the Institutional Review Board.

Baseline characteristics

A detailed medical history was obtained from all patients prior to surgery, with the emphasis on cardiovascular history and risk factors. Congestive heart failure was defined as a history of congestive heart failure or the presence of S3 gallop or rales at both bases during physical examination. Ischemic heart disease was defined as a history of myocardial infarction,

evidence of prior myocardial infarction on an electrocardiogram or echocardiogram. Additional clinical data included age, gender, diabetes mellitus, renal dysfunction (creatinin >2 mg/dl), hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥90 mmHg in non-diabetics, systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg in diabetics, or the use of anti-hypertensive drugs), cerebrovascular disease (history of stroke or transient ischemic attack), smoking status, body-mass index (BMI) and chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases), and the presence of aortic valve stenosis (flow velocity over the aortic valve >2.5 m/s) are reported. Also, the use of beta-blockers, statins, aspirin, clopidogrel, oral anti-coagulants, angotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, and nitrates was recorded.

Antiplatelet, anticoagulant, and thromboprophylaxis policy

Chronic aspirin therapy is routinely continued perioperatively. The decision whether or not to interrupt vitamin K antagonist therapy and to initiate bridging therapy with heparin or low molecular weight heparin (LMWH) was made on a case-to-case basis. Per hospital protocol, thromboprophylaxis is routinely initiated the night prior to surgery using prophylactic doses of low molecular weight heparin (LMWH) in patients not receiving therapeutic doses of LMWH or oral anticoagulants. The preoperative dose is administered >12 hours prior to surgery.

Anaesthesia type

Selection of anaesthesia type was made on a case-to-case basis, reflecting the anaesthesiologists, surgeons, and patients considerations. Of all patients, anaesthesia charts were examined for the type of anaesthesia used, including general, epidural, and local anaesthesia. Anaesthesia type was categorized as either general or locoregional. Adjuvant sedation in patients undergoing epidural or local techniques without need of mechanical ventilation was not scored as general anaesthesia.

Cardiac outcome

Serial electrocardiograms and troponin T measurements were routinely obtained prior to surgery and on postoperative days 1, 3, and 7, unless discharged earlier, and whenever clinically indicated. Troponin T was measured using the TropT version 2 assay from Roche Diagnostics, Mannheim, Germany. The study endpoint is 30-day adverse cardiac events, a composite of cardiovascular mortality, non-fatal myocardial infarction, new or worsened congestive heart failure, new arrhythmias (requiring immediate cardioversion, cardiopulmonary resuscitation, or pacing) and troponin T release. Also, 30-day 'major' cardiac events are reported, a composite of cardiac death, non-fatal myocardial infarction,

new or worsened congestive heart failure, and new arrhythmias, but not including troponin T release. Cardiovascular death was defined as any death from cardiovascular cause, including death following myocardial infarction, congestive heart failure, arrhythmia, and surgery related bleeding complications, or sudden unexpected death. Myocardial infarction was defined as postoperative classic rise and fall of troponin T levels above the 99th percentile, with either electrocardiographic or clinical signs of myocardial ischaemia. Troponin T release was defined as at least one troponin T value above the 99th percentile in the absence of electrocardiographic and clinical signs of myocardial ischaemia and in the absence of other cardiac complications. Patients were routinely scheduled for a follow up visit 30 days after surgery. In patients still admitted or readmitted, follow-up was completed using medical records. Cause of death was ascertained by reviewing medical records or death certificates.

Non-cardiac outcome

We report major pulmonary, renal, cerebrovascular, urological, and infectious complications requiring intervention, as well as all surgical procedures for bleeding and device failure complications required within 30 days of the initial EVAR procedure. Length of hospital stay (in days) after EVAR procedure is reported.

Statistical analysis

Dichotomous data are presented as numbers and percentages. Continuous data are presented as means ± standard deviation. Dichotomous data were compared using Chi-Square tests, continuous data were compared using ANOVA or Mann-Whitney U tests as appropriate. Univariable and multivariable logistic regression models were used to assess the association between anaesthesia type (general vs. locoregional) and 30-day cardiac events. The following factors were considered as possible confounding factors: age, gender, congestive heart failure, ischemic heart disease, preoperative creatinin, preoperative hemoglobin, chronic obstructive pulmonary disease, diabetes mellitus, prior stroke, aortic valve stenosis, obesity (BMI >30), the use of beta-blockers, statins, aspirin, clopidogrel, oral anti-coagulants, therapeutic anticoagulation at the time of surgery, angotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, and nitrates. All possible confounders were included in a multivariable logistic regression model to compute a propensity score for the likelihood of receiving locoregional versus general anaesthesia. To assess the association between anaesthesia type and cardiac outcome, a multivariable logistic regression model was applied. The Revised Cardiac Risk score and propensity score were entered as covariables. A 2-sided p-value of <.05 was considered significant for all tests. All analyses were performed using PASW version 17.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Of the 302 patients enrolled, general anaesthesia was applied in 173 (57%) patients, and locoregional anaesthesia in 129 (43%) patients, including 78 (26%) cases of epidural and 51 (17%) cases of local anaesthesia.

Baseline characteristics

General anaesthesia and locoregional anaesthesia groups differed significantly regarding the presence of hypertension (71% vs 58%, P=.03) and hypercholesterolemia (94% vs 87%, P=.05). Obesity was more common in patients receiving general anaesthesia (24% vs 9%, P<.01). Other comorbid conditions, age, and gender were well-balanced between both groups. General anaesthesia patients were more frequently treated with aspirin (73% vs 49%, P<.01). Surgery was performed under therapeutic anticoagulation (continuation of oral anticoagulants with an International Normalized Ratio > 1.8 or bridging therapy with heparin or LMWH in therapeutic doses) in 7% of general anaesthesia patients and 2% of locoregional anaesthesia patients (P=.11). No differences regarding clopidogrel use were observed (6% vs 5%, P=.62). Baseline characteristics are presented in Table 1.

Length of stay

The median (IQR) length of hospital stay after EVAR procedure was 3 (2 - 4) days in the general anaesthesia group and 2 (2 – 4) days in the locoregional anaesthesia group (P<.01).

30-day mortality

In the perioperative period, 4 (1.3%) deaths were observed, all of which occurred in the general anaesthesia group (P=.14).

30-day cardiac events

A total of 29 (9.6%) patients suffered a cardiac event within 30 days of surgery, including 2 cases of cardiac death, 7 myocardial infarctions, 2 cases of new congestive heart failure, 1 cardiac arrest and 17 cases of asymptomatic Troponin T release. All cases of myocardial infarction and heart failure were managed medically.

All cases of cardiac death, heart failure, and cardiac arrest occurred in the general anaesthesia group, as well as 6 of the 7 myocardial infarctions. In total, 6.4% of patients in the general anaesthesia group suffered one of these events, compared with 0.8% in the locoregional anaesthesia group (P=.02). Asymptomatic troponin release was observed in 6.9% of general anaesthesia patients and 3.9 % of locoregional anaesthesia patients (P=.32). Significantly more patients in the general anaesthesia group suffered any cardiac event, compared with the locoregional anaesthesia group (13.3% vs 4.7%, P=.02). An overview of all cardiac events is presented in Table 2.

Table 1. Baseline characteristics according to anaesthesia type

	General (n = 173)		**Locoregional** (n = 129)		**P-value**
Demographics					
Mean age (SD)	72	(8)	72	(8)	.75
Male gender (%)	155	(90)	120	(93)	.42
Medical hystory (%)					
Congestive heart failure	16	(9)	21	(16)	.08
Cerebrovascular disease	28	(16)	15	(12)	.32
Hypertension	122	(71)	75	(58)	.03
Hypercholesterolaemia	162	(94)	112	(87)	.05
Diabetes Mellitus	44	(25)	22	(17)	.09
Current smoking	77	(45)	52	(40)	.48
Serum creatinin >2mg/dL	25	(15)	26	(20)	.22
Ischemic heart disease	74	(43)	64	(50)	.25
Aortic valve stenosis	6	(4)	3	(3)	.74
COPD	81	(47)	51	(41)	.29
BMI > 30	41	(24)	12	(9)	<.01
Risk indices (SD)					
Revised Cardiac Risk Index	1.9	(1.0)	2.0	(1.0)	.25
ASA class	2.5	(0.6)	2.5	(0.5)	.59
Medication use (%)					
Anticoagulants	29	(17)	17	(13)	.42
Continuated perioperatively	12	(7)	3	(2)	.11
Aspirin	125	(73)	63	(49)	<.01
Clopidogrel	11	(6)	6	(5)	.62

Abbreviatons: SD standard deviation; LVEF left ventricular ejection fraction; COPD chronic obstructive pulmonary disease; BMI body mass index

Table 2. 30-day cardiac complications

	General (n = 173)		Locoregional (n = 129)		P-value
	n	(%)	n	(%)	
Cardiac events					
Cardiac death	2	(1.2)	0	(0)	.51
Myocardial infarction	6	(3.4)	1	(0.8)	.25
Congestive heart failure	2	(1.2)	0	(0)	.51
Arrhythmia	1	(0.6)	0	(0)	1.00
Troponin release	12	(6.9)	5	(3.9)	.32
Composite cardiac endpoints					
All cardiac events	23	(13.3)	6	(4.7)	.02
All but troponin release	11	(6.4)	1	(0.8)	.02

Multivariable propensity-adjusted regression analysis demonstrated that general anaesthesia, compared with locoregional anaesthesia, was associated with a significantly increased risk of any 30-day cardiac event (OR 3.8; 95%-CI 1.1 – 12.9; P=.03), as well as with an increased risk of 'major' cardiac events, not including asymptomatic troponin release (OR 13.3; 95%-CI 1.2 – 141.8, P=.03).

30-day non-cardiac events

In the study population, 39 major non-cardiac complications occurred in 35 patient, of which 20 (11.6%) were in the general anaesthesia group and 15 (11.6%) in the locoregional anaesthesia group (P=1.00). Data are presented in Table 3.

Of the 2 non-cardiac deaths, one was caused by aspiration, and one by pneumonia. Non-fatal pulmonary complications occurred in 3 patients, including 2 cases of pneumonia, managed with antibiotics, and 1 case of pneumothorax, treated with a chest-tube. All pulmonary complications occurred in the general anaesthesia group (2.9% vs 0%, P=.07).

Additional procedures for endoleak within 30 days of the baseline procedure were required in 4 patients, all of whom received locoregional anaesthesia for the index procedure. Additional surgery for access site bleeding was required by 2 patients in the general anaesthesia group and 4 in the locoregional anaesthesia group. Peripheral macroembolization required embolectomy or thrombolysis in 3 patients in the general anaesthesia group and 1 in the locoregional anaesthesia groups. In total, 5 additional procedures were required in the general anaesthesia group and 9 in the locoregional anaesthesia group (2.9% s 7.0%, P=.11).

Major renal complications occurred in 4 patients, all of whom were in the general anaesthesia group (2.3% vs 0%, P=.14). Of these, 2 required permanent dialysis, 1 required a kidney transplant, and 1 required a PTA procedure of a renal artery due to trash nefropathy.

Table 3. 30-day major non-cardiac complications

	General (n = 173)		Locoregional (n = 129)		p-value
Non-cardiac complication	**n**	**(%)**	**n**	**(%)**	
Non-cardiac complications	22		17		
Patients with ≥1 complication	20	(11.6)	15	(11.6)	1.00
Mortality					
All-cause	4	(2.3)	0	(0)	.14
Non-cardiac	2	(1.2)	0	(0)	
Pulmonary					
Any pulmonary complication	5	(2.9)	0	(0)	.07
Pneumonia	3	(1.7)	0	(0)	
Aspiration	1	(0.6)	0	(0)	
Pneumothorax	1	(0.6)	0	(0)	
Renal					
Renal failure requiring intervention	4	(2.3)	0	(0)	.14
Surgical					
Additional surgical procedure required	5	(2.9)	9	(7.0)	.11
Intervention for endoleak	0	(0)	4	(3.1)	
Acces site bleeding	2	(1.2)	4	(3.1)	
Arterial embolism	3	(1.7)	1	(0.8)	
Other					
Urinary tract infection	2	(1.2)	2	(1.6)	
Access site infection	1	(0.6)	2	(1.6)	
Urine retention	4	(2.3)	2	(1.6)	
Sepsis	1	(0.6)	1	(0.8)	
GI bleeding	0	(0)	1	(0.8)	
Stroke / TIA	0	(0)	0	(0)	
Venous thrombo-embolism	0	(0)	0	(0)	

DISCUSSION

Our data show a high risk of adverse cardiac events after EVAR procedure, probably related to the presence of extensive comorbidity in the study population. This study demonstrates an increased risk of cardiac complications after EVAR with general anaesthesia, compared with locoregional anaesthesia, after adjusting for cardiovascular comorbidity, obesity, and medication use.

The severity of the physiological stress response to surgery depends on the invasiveness and length of the surgical procedure, and its effects on haemodynamic stability, fluid shifts, blood loss, and body temperature changes.[10] The surgical stress response causes tachycardia, increased myocardial contractility, systemic inflammation, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability.[11] In the presence of coronary artery

disease, these changes may result in perioperative myocardial infarction through either rupture of unstable coronary plaque and subsequent coronary thrombosis, or prolonged myocardial oxygen supply to demand mismatch.[7]

A coronary tree unaffected by atherosclerosis is present in only 8 percent of vascular surgery patients. These patients are at high risk of perioperative cardiac events, with a peak incidence on the first postoperative days. [12-13]

The surgical stress response is more effectively attenuated by locoregional anaesthesia, compared with general anaesthesia.[14] It was hypothesized that locoregional anaesthesia might improve cardiac outcomes in major surgery patients. In a case-control study of 88188 patients, Wijeysundra demonstrates that epidural anaesthesia is associated with a small but significant reduction of all-cause mortality after major surgery.[15] In a meta-analysis of 30 trials which randomized for locoregional anaesthesia, Rodgers also found a reduced risk of perioperative myocardial infarction (OR 0.67; 95%-CI 0.45 – 1.00).[8]

Previous studies indicate that the performance of EVAR is feasible under multiple types of anaesthesia including general, neuraxial, and local anaesthesia.[16-17] Analysis of the EUROSTAR cohort of EVAR procedures indicates that surgical outcomes (incidence of endoleaks) are similar for all types of anaesthesia.[18]

No conclusive data exist regarding the relation between anaesthesia type and cardiac outcome in EVAR. In the current study, we observed a significantly increased incidence of cardiac events in the general anaesthesia group (OR 3.8). The confidence interval is compatible with both a very minor increase and a more than 10-fold increase (95%-CI 1.1 – 12.9).

In a cohort study of 424 EVAR procedures by Parra (279 general, 95 regional, and 50 local anaesthetics), cardiac event rates were 7%, 14%, and 0% in the general, regional, and local anaesthetic group, respectively, with a statistically significant difference between the epidural and local anaesthetic group.[9] No multivariable analysis, adjusting for differences in baseline characteristics, was performed. De Virgilio found no difference in cardiac events after EVAR between general and local anaesthesia in a cohort of 229 patients.[19] Analysis of data from EUROSTAR suggests a reduced risk of cardiac events in local (1%) and regional (2.9%), as compared with general anaesthesia (3.7%). However, neither the definition of cardiac complications, nor the method used to score these complications were provided.[18]

Possible explanations of our results include differences in surgical stress response attenuation, and in arterial perfusion due to vasodilation induced by locoregional anaesthesia, although the latter is unlikely due to the limited area of effect of both local anaesthesia and lumbar epidural anaesthesia. Also, differences in fluid requirements between general and locoregional anaesthesia might have influenced tissue perfusion due to hemodilution. Another factor of possible influence is the occurrence of per- and postoperative hypoxemia. Due to the retrospective study design, we are unfortunately not able to provide adequate data on this parameter.

We observed no difference in the non-cardiac complication rate between general (11.6%) and locoregional (11.6%) anaesthesia groups (P=1.00). However, general anaesthesia was associated with a trend towards an increased risk of pulmonary complications (2.9% vs 0%, P=.07) and increased length of stay. This is in accordance with previous reports.[20] A trend towards an increased risk of the requirement for additional surgical procedures for endoleak, access site bleeding, or macro-embolization was observed in the locoregional anaesthesia group (7.0% vs 2.9%, P=.11).

Study limitations include the retrospective cohort design, because of which no causal relationship between anaesthesia type and outcome can be established. This type of study is likely to be subject to selection bias. To reduce selection bias, we excluded patients undergoing hybrid procedures, as well as patients undergoing emergency procedures, as both are likely to influence both the choice of anaesthesia type and the risk of cardiac complications. Additionally, we used propensity-adjusted multivariable regression analysis to adjust for comorbidity, obesity, and antiplatelet and anticoagulant drug use, as these are also known to influence the choice of anaesthesia technique. Possible factors influencing our results are differences in surgical and anaesthetic management over time, and a relatively small sample size. We decided to pool local and regional anaesthesia, as both have been demonstrated to effectively attenuate the surgical stress response, compared with general anaesthesia. The study endpoint is a composite endpoint including asymptomatic troponin release, as postoperative asymptomatic troponin release is known to be highly predictive of both short and long-term mortality.[21] As many patients who suffer postoperative troponin release do not experience any symptoms, the cardiac event rate in this study is higher than in previous studies of EVAR that did not include asymptomatic troponin release in the study endpoints.

In conclusion, general anaesthesia, compared with locoregional anaesthesia, is associated with an increased risk of cardiac events after EVAR. Patient preferences, expected patient compliance, procedure length, and anatomical factors should be considered in selection of anaesthesia type. However, when no contra-indications are present, a locoregional anaesthesia technique might be favorable for EVAR. To our opinion, despite possible difficulties involved, including the need for a very large sample size, as well as reluctance from both surgeons and patients, a randomized trial of general and locoregional anaesthesia techniques in elective EVAR is warranted.

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CHAPTER 7

PERIOPERATIVE ESMOLOL INFUSION FOR HAEMODYNAMIC STABILITY DURING MAJOR VASCULAR SURGERY; RATIONALE AND DESIGN OF DECREASE-XIII

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Eur J Vasc Endovasc Surg 2011;42(3):317-23

ABSTRACT

Objectives: This article describes the rationale and design of the DECREASE-XIII trial, which aims to evaluate the potential of esmolol infusion, an ultra-short acting beta-blocker, during surgery as an add-on to chronic low-dose beta-blocker therapy to maintain perioperative hemodynamic stability during major vascular surgery.

Design: double-blind, placebo-controlled, randomised trial.

Materials & methods: 260 vascular surgery patients will be randomized to esmolol or placebo as an add-on to standard medical care including chronic low-dose beta-blockers. Esmolol is titrated to maintain a heart rate within a target window of 60-80 beats per minute for 24 hours from the induction of anesthesia. Heart rate and ischemia are assessed by continuous 12-lead electrocardiographic monitoring for 72 hours, starting 1 day prior to surgery. The primary outcome measure is duration of heart rate outside the target window during infusion of the study drug. Secondary outcome measures will be the efficacy parameters of occurrence of cardiac ischemia, troponin T release, myocardial infarction and cardiac death within 30 days after surgery and safety parameters such as the occurrence of stroke and hypotension.

Conclusions: This study will provide data on the efficacy of esmolol titration in chronic beta-blocker users for tight heart rate control and reduction of ischemia in patients undergoing vascular surgery as well as data on safety parameters.

INTRODUCTION

Only 8% of patients undergoing major vascular surgery have a normal coronary angiogram.[1] Albeit coronary artery disease (CAD) is asymptomatic in the vast majority of these patients, the risk of perioperative cardiac mortality and morbidity is increased.[2-7] Major cardiac complications occur in 2-3.5% of major surgery patients. The predominant risk factor is CAD, and complications are usually preceded by a prolonged hemodynamic instability leading to myocardial ischemia and infarction. The pathophysiology of perioperative cardiac events is complex. Hemodynamic instability may lead to coronary plaque rupture, initiating coronary artery thrombosis, occlusion and myocardial infarction (type 1 MI).[8-10] In the presence of stable CAD, myocardial oxygen supply/demand mismatch due to tachycardia and increased contractility, induced by perioperative catecholamine surge, may lead to myocardial ischemia, ST segment depression and type 2 MI.[8,11-13] Perioperative myocardial infarction (PMI) is one of the most important predictors of short- and long term morbidity and mortality associated with non-cardiac surgery.[14] Therefore, it is of vital importance to prevent myocardial ischemia by providing hemodynamic stability and adequate heart rate control throughout the perioperative period.

Beta-blockers are widely prescribed perioperatively for perioperative heart rate control. The proposed mechanism of the beneficial effect of beta-blockers consists of a decreased myocardial oxygen demand by reducing heart rate and contractility, also resulting in a lengthening of the diastolic filling period and reduced shear stress.[15] Additional cardioprotective factors are redistribution of coronary blood flow to the subendocardium, and an increase in the threshold for ventricular fibrillation. Beta-blockers are thought to have an anti-inflammatory and plaque-stabilizing effect which might only be achieved after prolonged treatment.[16-18]

Beta-blocker therapy is recommended in patients with known ischemic heart disease (IHD) and patients scheduled for high-risk surgery, based on a reduction in perioperative cardiac mortality and PMI in several trials.[6,19-20] However, this beneficial effect might be offset by the induction of serious side effects.

In the randomized POISE trial metoprolol succinate was initiated shortly prior to surgery.[7] Patients could receive up to 400 mg of metoprolol succinate on the day of surgery. This regimen was associated with a decreased risk of PMI and an increase in overall mortality and stroke.

A factor to be considered when initiating beta-blockers prior to vascular surgery is the frequent presence of asymptomatic left ventricular dysfunction.[21] Patients with LV dysfunction might respond unfavourable to a fixed dose of beta-blocker. Therefore, beta-blockers are commonly titrated over a prolonged period of time in conditions such as hypertension, angina pectoris and heart failure.[22] In the DECREASE I and IV trials, using a regimen of bisoprolol, titrated for heart rate, initiated 30 days before surgery, no increased rate of stroke was observed.[6,23]

A simple approach of chronic low dose long-acting cardioselective beta-blocker therapy titrated for heart rate combined with the perioperative use of a short-acting, easily titratable beta-blocker can provide superior hemodynamic stability. Heart rate control might be improved compared to low dose long-acting beta-blocker mono-therapy, without the adverse effects such as hypotension, bradycardia, progression of asymptomatic left ventricle dysfunction, stroke and mortality associated with high dose long-acting beta-blockers without titration for heart rate. Low-dose long-acting beta-blockers can be started one week prior to surgery, as titration of long acting beta-blocker for tight heart rate control is not mandatory. If low-dose long acting beta-blockers can not be initiated prior to surgery, esmolol can provide hemodynamic control, though the additional effect of chronic beta-blocker therapy is lacking.

We propose a randomized, placebo controlled trial of esmolol, titrated for heart rate, as an add-on to standard medical care, including chronic beta-blockade with metoprolol succinate. Esmolol is an ultrashort-acting beta-blocker with a distribution and elimination half-life of 2 and 9 minutes and therefore easily titratable.[24] Esmolol is highly beta-1 selective and has no intrinsic sympathomimetic activity.[25]

MATERIALS AND METHODS

Study design and objective

This single centre, randomized, placebo controlled study compares a group receiving esmolol (Brevibloc®) as an add-on to metoprolol succinate versus a group receiving metoprolol succinate and placebo. The primary objective is to assess the efficacy of esmolol versus placebo as an add-on to standard medical care for target heart rate control. Secondary objectives are to assess the efficacy of esmolol for reducing the occurrence and duration of myocardial ischemia and to assess safety parameters. Approval from the Medical Ethical Committee was obtained. This trial was registered as NTR2615 on www.trialregister.nl.

Study population

Patients scheduled for major vascular surgery will be enrolled after providing informed consent, if none of the exclusion criteria presented in Table 1 are met.

Table 1 Inclusion and exclusion criteria

INCLUSION CRITERIA	
Major vascular surgery	Abdominal Aortic Aneurysm repair, Aortic stenosis repair, lower limb arterial reconstruction, carotid artery repair
Age ≥ 18 years	
EXCLUSION CRITERIA	
Active bleeding	
Untreated left main disease	
Active cardiac conditions	Unstable angina pectoris, active heart failure, serious cardiac arrhythmias, symptomatic valvular disease, myocardial infarction < 6 months
Preoperative positive Troponin T	
Contraindication for esmolol use	
Previous allergy or intolerance for esmolol	
Cancer	With an expected life expectancy <6 months
Failure to monitor heart rate	With continuous 12-lead electrocardiography because of surgery or baseline electrocardiographic abnormalities
Excessive alcohol abuse	
Pregnancy or planning to become pregnant	
Failure to provide informed consent	

Randomization, blinding and treatment allocation

The randomization for active drug or placebo will be performed by the hospitals pharmacist in a 1:1 ratio, using a computer-generated randomization list. Patient, research fellow, nursing and medical staff are blinded, with exception of the attending anesthesiologist and intensivist, for safety reasons.

Preoperative risk evaluation and initiation of medical therapy

Patients are screened before vascular surgery using the recently published ESC guidelines on perioperative care.[19] In short, patients with unstable cardiac symptoms and patients with >2 points on the Revised Cardiac Risk Index[3] will be sent for additional cardiac evaluation and treatment if indicated. In all patients proceding to surgery, standard medical therapy will be initiated.

Beta-blockers: All patients will be receiving metoprolol succinate according to the ESC guidelines on perioperative care.[19] Patients on beta-blocker therapy other than metoprolol succinate switch to metoprolol succinate 50mg once daily at the screening visit. Beta-blocker naïve patients start with metoprolol succinate 50 mg once daily at the screening visit at least one week prior to surgery. The beta-blocker dose is adjusted after 7 days of treatment and prior to surgery to achieve a resting heart rate of 60 to 70 beats per minute if tolerated. The same dose is continued the day after surgery.

Statins: Patients on chronic statin therapy will continue medication, while statin naïve patients will be treated with fluvastatin extended release at a dose of 80 mg once daily.

Aspirin: All patients are on perioperative aspirin therapy, 80 mg daily, according to recommendations in the AHA/ACC guidelines on peripheral arterial disease.[26]

Angiotensin-converting enzyme inhibitors: Patients on chronic therapy will continue their medication. When LV dysfunction (LVEF <40%) is assessed during preoperative evaluation in untreated patients in stable condition, ACE-inhibitors are initiated as recommended by the ESC Guidelines on heart failure.[22]

Anesthesia Technique

During surgery patients will receive standard of care (hypnotics, opiates and muscle relaxant) in both groups to provide optimal anesthetic and surgical conditions. Balanced anesthesia should adequately control depth of anesthesia with minor intraoperative hemodynamic changes.

Anesthesia technique (intubation, mechanical ventilation parameters, SaO2, end tidal carbon dioxide partial pressure) and all medication used during surgery will be noted, including local or regional technique combined to general anesthesia and with special focus anesthesia depth (MAC), opiates consumptions and duration of anesthesia. Patients will have standard postoperative pain management. BIS monitoring will be applied in all patients.

Hemodynamic Monitoring

Perioperative hemodynamic monitoring will include continuous measurement of HR and ischemia detection using 12-lead Holter monitoring. Holter monitoring will start 12 hours prior to surgery and continue during esmolol infusion and after discontinuation of esmolol infusion for a total of 72 hours. Blood pressure will be measured continuously during surgery and at least every 15 minutes for 48 hours postoperatively, depending on the hemodynamic condition of the patient. After surgery, patients will be admitted to the Intensive Care Unit,

the Post Anesthesia (High) Care Unit, or the post vascular surgery medium care unit for at least 24 hours, at the discretion of the attending anesthesiologist and vascular surgeon. All of these units can provide the level of monitoring and care needed for the current study. Admission to one of these units is customary in our centre after vascular surgery. In patients with a LVEF <35%, additional hemodynamic monitoring using a pulmonary artery catheter is performed during surgery for goal directed fluid and vasoactive drug therapy, as per hospital protocol.

Hemodynamic Management
Tachycardia will be managed with additional beta-blockers only after excluding and treating underlying causes such as pain, bleeding, hypovolemia and infection. If tachycardia is likely to be induced by hypovolemia, a fluid challenge will be administered. If tachycardia does not resolve, it is deemed not to be induced by hypovolemia. Perioperative bradycardia (HR <40 beats/m) will be managed with i.v. injection of atropine. Hypertension (>20% increase from baseline systolic blood pressure) will be managed with i.v. administration of standard care of vasodilating agent. Hypotension (mean arterial pressure <60 mmHg) is managed with fluids or vasopressor medication at the discretion of the attending physician.

If heart rate is >80 BPM intraoperatively, a bolus of 0.25 mg/kg of esmolol or placebo will be administered and a 25 mcg/kg/min continuous infusion will be initiated. If heart rate control is not regained in 5 minutes, an additional 0.25mg/kg bolus will be administered. Continuous infusion will be titrated in steps of 25% of the current dose at 15 minute intervals to maintain a heart rate of 60-80 BPM with a maximum of 300mcg/kg/min. If heart rate does not exceed 80 BPM during surgery, the 25mcg/kg/min continuous infusion of esmolol or placebo is initiated before extubation without bolus infusion and titrated as described earlier. The study drug will be withheld if systolic blood pressure is below 100 mmHg.

If heart rate is outside the target window with no signs of cardiac ischemia detected by continuous electrocardiographic monitoring, after providing the maximum dose of study drug, no additional action will be taken. However, if signs of cardiac ischemia do not resolve rapidly with up titration of esmolol or placebo, rescue treatment with i.v. injection of beta-blocker is provided according to good clinical practice.

Outcome
Primary endpoint: The primary endpoint is total duration of heart rate outside the target window presented in minutes. The target window is defined as a heart rate between 60 and 80 beats per minute.

Secondary endpoints: The secondary study outcome for the efficacy of esmolol is the occurrence of cardiac death and myocardial ischemia, defined as either transient electrocardiographic signs of ischemia or troponin T release or both, within 30 days of surgery. In patients with tachycardia and ischemia, the prescription of rescue medication will be considered to be a secondary study endpoint. Serial Troponin T levels and ECG recordings will be obtained prior to surgery and on day 1, 3, 7 and 30.
Secondary outcome will also include other safety parameters such as the occurrence of bradycardia (i.e. HR< 50 BPM) hypotension (SBP<100) and transient ischemic attack (TIA) confirmed by neurologic exam or stroke as confirmed by neurologic exam and CT-scan.

Sample size calculation
Based on the results of the DECREASE III trial[27] the estimated total length of heart rate outside the target window (60 – 80 bpm) in the control group will be 8.1 ± 5.8 hours. It is anticipated that using esmolol, the total duration of heart rate outside the target window will be reduced by 33%. This estimation is based on the placebo-controlled study in 26 patients published by Raby et al.[28] This means that a group of 260 patients, 130 in each arm is necessary to have a power of 80% and an alfa of 0.05 to detect this difference. We expect that 10% of the population will be excluded from the study based on the exclusion criteria.

Data analysis
Categorical data will be described as numbers and percentages and analyzed using the chi-square test. Continuous data are expressed as medians with interquartile ranges (IQR) and compared using Kruskal-Wallis test. Logistic and Cox regression analysis will used to evaluate the short- and long-term prognosis of hemodynamic instability. In multivariate analysis, adjustments will be made for cardiac risk factors, type of surgery and open or endovascular procedure. Odds and hazard ratios are given with 95% confidence intervals. For all tests, a p-value <0.05 (two-sided) is considered significant. All analysis will be performed using SPSS 17.0 statistical software (SPSS Inc., Chicago, Illinois).

DISCUSSION

This trial is primarily designed to assess the efficacy and safety of perioperative esmolol infusion versus placebo as an add-on to chronic low-dose beta-blocker use for heart rate control. Prevention of perioperative tachycardia reduces perioperative cardiac ischemia.[28] Perioperative ischemia is related to cardiac adverse events and remains an important cause of morbidity and mortality in patients undergoing vascular surgery.[3-4,7,11-12,29] For risk reduction, a perioperative regimen consisting of beta-blockers and a statin, both initiated at least a week prior to surgery, is recommended in this population.[19] Of note, the perioperative

period is characterized by hemodynamic fluctuations. This warrants the use of a placebo and creates a situation where it is difficult for the treating physician to assess treatment allocation of an individual patient.

Randomized controlled trials that assessed the effect of beta-blockers in the perioperative period reported divergent results, as shown in figure 1. The DECREASE-I trial observed a 10-fold reduction in the incidence of perioperative death and MI in vascular surgery patients with evidence of myocardial ischemia on preoperative dobutamine stress-echocardiography, treated with bisoprolol compared to placebo.[6] In a trial by Mangano, perioperative atenolol therapy was not associated with an improved in-hospital outcome; however, it was associated with a 50% reduction in electrocardiogram evidence of myocardial ischemia and significantly lower mortality rates at 6 and 24 months after discharge.[20]

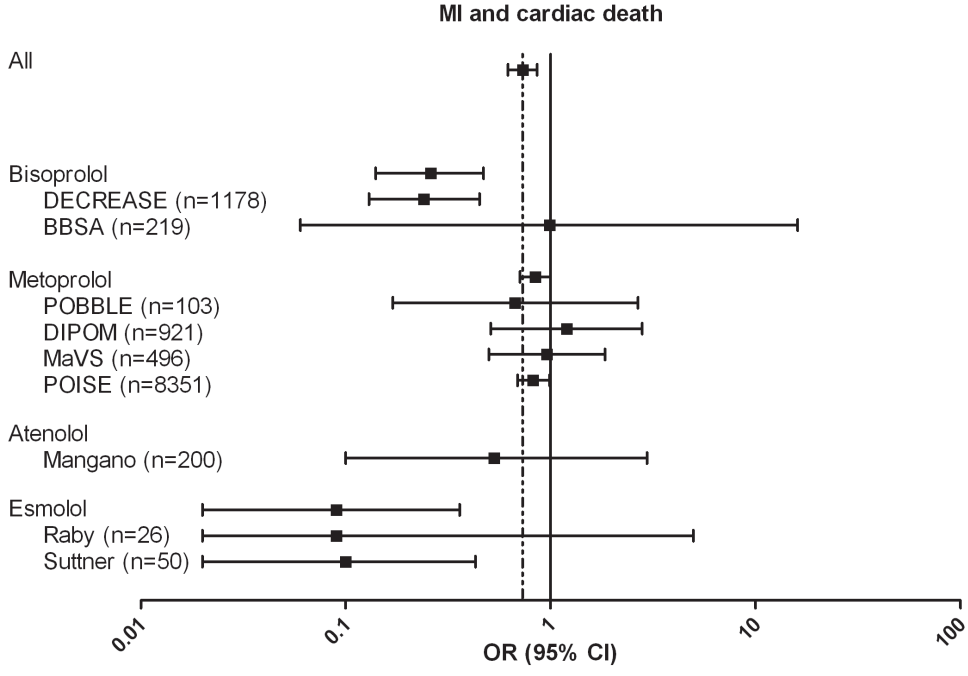

Figure 1. Odds ratios (OR) of randomized beta-blocker trials for perioperative myocardial infarction (MI) and cardiac death. BBSA = Beta Blocker in Spinal Anesthesia; CI = confidence interval; DECREASE = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM = Diabetes Postoperative Mortality and Morbidity; MaVS = Metoprolol after Vascular Surgery; POBBLE = PeriOperative Beta-BlockadE; POISE = PeriOperative Ischemic Evaluation trial.

The Metoprolol after Vascular Surgery (MaVS), PeriOperative Beta-BLockadE (POBBLE) and DIabetic POstoperative Mortality (DIPOM) trials did not find a significant effect of perioperative metoprolol.[30-32] All of these studies included many low-risk patients, in contrast to the DECREASE-I trial which only included patients with inducible ischemia. In a retrospective cohort study of 782,969 patients undergoing major non-cardiac surgery beta-blocker use was associated with a significant beneficial effect in high risk patients but showed no effect or possible harm in low risk patients.[33]

The DECREASE-XIII trial will include only patients undergoing major vascular surgery, including open lower extremity arterial repair, open and endovascular abdominal aortic repair, and open carotid stenosis repair. These patients are all at intermediate or high risk of cardiac complications. Beta-blocker use in these patients was previously demonstrated to be of benefit and is according to the 2009 ESC guidelines on perioperative care.[6,19,23]

Studies by Raby[28] and Feringa[34] observed that higher doses of beta-blockers and lower heart rates were associated with a marked reduction in the incidence of ischemia. These data suggest that early initiation of beta-blocker therapy, monitoring of the heart rate and subsequent dose adjustment are of critical importance for the likelihood that a patient will benefit from beta-blockade.

Controversy exists on the appropriate dosing regimen. In the POISE study patients were randomized for perioperative metoprolol succinate or placebo. Metoprolol succinate was initiated 2-4 hours before surgery in a dose of 100 mg. A second dose of 100 mg was administered if heart rate was >80 and systolic blood pressure was >100 mm Hg anytime within the first 6 hours after surgery. If this situation did not occur, the second dose was administered 6 hours after surgery, if heart rate was 50 BPM or more and systolic blood pressure was greater than 100 mm Hg. Then, a maintenance dose of 200 mg of metoprolol succinate once daily was started 12 hours after the second gift for 30 days. Patients could receive up to 400 mg of metoprolol succinate on the first day of treatment. The incidence of cardiac death, PMI and cardiac arrest in patients randomized to metoprolol compared to placebo was significantly reduced. However, this was offset by an increased incidence of intra-operative hypotension, bradycardia and 30-day stroke and overall mortality in the treatment group when compared to placebo, as shown in Figure 2.[7,35-36] The hypothesis is that the frequently observed ischemic stroke was due to watershed infarction due to hypotension and bradycardia in patients with a diseased cerebrovascular tree.[37-38] In the non-surgical setting, lower starting doses are recommended, for instance an initial daily dose of 25 to 100 mg for hypertension, usually up-titrated at weekly intervals.

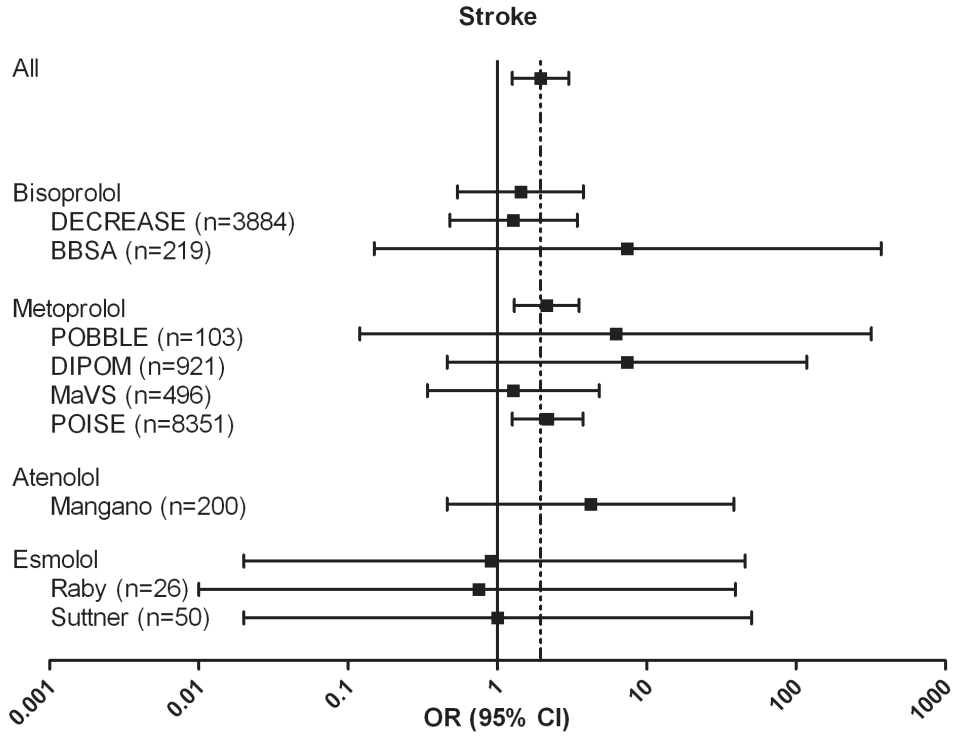

Figure 2. Odds ratios (OR) of randomized beta-blocker trials for stroke. BBSA = Beta Blocker in Spinal Anesthesia; CI = confidence interval; DECREASE = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM = Diabetes Postoperative Mortality and Morbidity; MaVS = Metoprolol after Vascular Surgery; POBBLE = PeriOperative Beta-BlockadE; POISE = PeriOperative Ischemic Evaluation trial.

Feringa et al. demonstrated that a 10 beats per minute increase in both per- and postoperative heart rate is associated with a significantly increased risk of perioperative myocardial ischemia and cardiac Troponin release and long-term cardiac events and mortality (HR ranging from 1.4 to 2.6 per 10 bpm increase, P<0.05 in all cases), after adjusting for risk factors, medication use and preoperative cardiac stress test results.[30]

Both bradycardia and increased heart rate are associated with a significantly increased risk of cardiac complications. These data support the importance of the maintenance of tight heart rate control as a primary endpoint.

A recent meta-analysis by Landoni et al. showed no increase in incidence of hypotension or bradycardia during perioperative esmolol infusion. No data on the incidence of stroke were reported in the trials included in this meta-analysis.[39]

Titration of beta-blocker dose requires that treatment is initiated optimally 30 days prior to surgery, or at least 1 week. Early initiation of beta-blocker therapy poses a logistic difficulty in the United States, where patients are commonly admitted to the hospital only on the day prior to surgery. Perioperative esmolol infusion offers a possibility for tight heart rate control in this clinical condition, although patients do not benefit from the additional cardioprotective anti-inflammatory effect of chronic beta-blocker therapy.

In conclusion, the optimal perioperative beta-blocker dosing regimen is still controversial. Though, proven to be effective in the non-surgical setting in patients with heart failure and coronary artery disease, safety issues such as hypotension and bradycardia leading to stroke are potential deleterious consequences. The use of low-dose regimens with careful up-titration and intraoperative use of ultra-short acting beta-blockers might be the optimal treatment. A sufficiently powered randomized clinical trial is warranted to prove safety and efficacy of these treatment regimens.

Acknowledgements
This study is supported by a research grant from Baxter Healthcare Corporation.
E.J. Bakker, N.J.M. Ravensbergen and M.T. Voute are supported by an unrestricted research grant from “Lijf & Leven” Foundation, Rotterdam, the Netherlands.

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SUMMARY AND CONCLUSION

SAMENVATTING EN CONCLUSIE

CURRICULUM VITAE

DANKWOORD

PORTFOLIO

SUMMARY

This thesis describes preoperative cardiac risk assessment, risk factors for cardiac complications, and cardiac risk reduction strategies in patients undergoing non-cardiac surgery.

Chapter 1 describes a commonly applied step-wise approach to cardiac risk assessment. First, active cardiac conditions, such as decompensated congestive heart failure and unstable coronary artery disease, which require pre-operative assessment and treatment by a cardiologist, have to be excluded. Then, surgical risk, exercise capacity, traditional risk factors for cardiac complications (history of ischemic heart disease, congestive heart failure, renal failure, cerebrovascular disease, and insulin-treated diabetes mellitus), and results of non-invasive testing (electrocardiogram and, when indicated, echocardiography and cardiac stress testing) are assessed. Assessment of biomarkers, such as NT-proBNP, can further improve risk stratification. In patients at increased risk of cardiac complications or with atherosclerotic co-morbidity, the medication regime should be optimized prior to surgery in order to reduce the risk of cardiac complications. The role of perioperative medical therapy with statins, beta-blockers, and aspirin is discussed. The application of non-pharmacological risk reduction strategies, such as myocardial revascularization and the application of cardiac assist devices, may be beneficial in a highly selected group of patients.

Chapters 2-4 assess the value of several possible non-traditional risk factors for cardiac complications.

Chapter 2 focuses on type 2 diabetes mellitus (DM2). DM2 is characterized by insulin resistance, and not primarily by the absolute insulin deficiency characterizing type 1 diabetes. Both types lead to atherosclerosis and atherosclerotic complications, such as myocardial infarction, stroke and renal failure. It is therefore conceivable that diabetes predisposes for cardiac complications. While this relationship is well-accepted for DM1, previous reports show divergent results for DM2. Chapter 2 investigates the relationship between DM2 and cardiac complications in a cohort of 1462 vascular surgery patients, of whom 329 had DM2. The main outcome measure was cardiac complications, a composite of cardiac death, non-fatal myocardial infarction, congestive heart failure, severe arrhythmia, and asymptomatic troponin T release. After adjustment for possible confounding factors, DM2 was significantly associated with cardiac complications, with an odds ratio of 1.80 (95%-CI 1.25 – 2.60). Cardiac event rates were similar in DM2 patients managed with insulin, and those treated with oral medication or diet alone. Chapter 2 demonstrates that all diabetes mellitus, regardless of type of diabetes and the need for insulin therapy, should be considered a risk factor for cardiac complications after vascular surgery.

Chapter 3 describes the relationship between ABO blood type and cardiac complications after vascular surgery. ABO blood type is the major determinant of plasma levels of von Willebrand factor (VWF) and subsequently clotting factor VIII. VWF levels are elevated by 25-30% in patients with non-O blood types, compared with individuals with blood type O. High levels of VWF are associated with an increased risk of arterial and venous thrombosis, resulting in an increased risk of myocardial infarction, ischemic stroke, peripheral arterial disease, and venous thrombo-embolism (with odds ratios of 1.25, 1.14, 1.45, and 1.79, respectively) in people with non-O blood types, compared with those with blood type O. Chapter 3 assesses the prognostic implications of non-O blood type in a cohort of 4679 vascular surgery patients. No significant differences were found between patients with O and non-O blood types regarding 30-day cardiovascular events, 30-day cardiovascular death, 30-day non-fatal myocardial infarction, 30-day non-fatal stroke, and long-term mortality. Possible factors interacting with the relationship between blood type and cardiac events are age, gender, and the use of anti-platelet agents, anti-coagulants and statins. Further analysis however did not reveal an effect of ABO blood type on outcome in any subgroup. The observed paradox (a relatively strong effect of non-O blood types on the occurrence of thrombotic events in the general population, but no effect in a population of vascular surgery patients) might be explained by a phenomenon called 'index event bias'. In conclusion, ABO blood type is not in any way associated with perioperative cardiovascular complications or long-term mortality in patients undergoing vascular surgery.

Chapter 4 investigates the prognostic implications of aortic valve calcification after vascular surgery. Aortic valve calcification was assessed with echocardiography. Aortic valve sclerosis was defined as thickening and/or calcification of one or more leaflets of the aortic valve, without outflow obstruction (peak flow velocity <2.5 m/s), and aortic valve stenosis as the presence of outflow obstruction (peak flow velocity ≥2.5 m/s). Aortic valve calcification was highly prevalent in the study population (36% aortic valve sclerosis and 3% aortic valve stenosis). Aortic valve stenosis was significantly correlated with both perioperative cardiac complications and long-term mortality. This is in accordance with previous studies. Aortic valve sclerosis was not associated with perioperative cardiac events. A univariate relationship between aortic valve sclerosis and long-term mortality was present, but this effect was explained by the increased presence of cardiovascular co-morbidity in these patients; aortic valve sclerosis was not independently associated with long-term mortality. Aortic valve sclerosis is a known risk factor for cardiac mortality in the general population, but chapter 4 demonstrates that it has no impact on prognosis after vascular surgery. The prognostic implications of aortic valve sclerosis are probably attenuated by the presence of extensive generalized atherosclerosis in the study population of vascular surgery patients.

Elderly patients requiring non-cardiac surgery are at increased risk of cardiac complications compared with the younger population, due to the increased presence of cardiovascular co-morbid conditions and reduced cardiac reserve. Chapter 5 analyses the value of several perioperative cardiac risk indices in a population of patients aged 80 years or older. The Revised Cardiac Risk Index (RCRI, which assigns equal value to the traditional risk factors for cardiac complications mentioned earlier) was found to have a moderate discriminatory value in this population. Several factors probably explain this observation, most importantly categorization of surgical risk: the RCRI categorizes surgical risk as either high or non-high. This is probably overly simplified. The Erasmus model (a modification of the RCRI) categorizes surgical risk in four groups, which explains the significantly superior discriminative power of this model compared with the Revised Cardiac Risk Index in the study population of Chapter 5. The discriminatory power of the Erasmus model remains unsatisfactory however, with an area under the ROC-curve of 0.77. Explanations for this moderate discrimination include the fact that 3 further independent predictors for cardiac complications in the study population (peripheral vascular disease, atrial fibrillation, and current inducible myocardial ischemia) are not included in the model. In conclusion, the investigated risk models perform moderately. The need for a more adequate cardiac risk model for elderly surgical patients therefore remains.

Chapters 6 and 7 focus on cardiac risk reduction strategies.

Endovascular therapy greatly reduces the physiological stress and the risk of cardiac complications associated with aortic aneurysm repair, compared with the conventional open approach. The performance of endovascular aneurysm repair (EVAR) was demonstrated to be feasible under multiple types of anesthesia. Chapter 6 investigates the risk of cardiac complications after EVAR under general versus locoregional anesthesia. In this retrospective cohort study, general anesthesia was associated with a significantly higher risk of cardiac complications compared with locoregional anesthesia. A possible explanation can be found in the stronger attenuation of the physiological stress response to surgery by locoregional compared with general anesthesia. Multivariable analyses were adjusted for the propensity of receiving locoregional versus general anesthesia. However, this does not rule out the possibility of selection bias, as one cannot correct for unkown confounders. This stresses the need for a randomized trial to provide definite evidence regarding the optimal anesthetic technique for EVAR.

Tachycardia has detrimental effects in patients with coronary artery disease: the myocardial oxygen demand rises, while the oxygen supply to (parts of) the myocardium fails to increase sufficiently or even decreases, resulting in oxygen supply-to-demand mismatch.

The subsequent myocardial ischemia often precedes major cardiac complications such as myocardial infarction. It is therefore of the utmost importance to prevent this cascade, that is initiated by tachycardia. Beta-blockers are usually prescribed to maintain adequate heart rate control in high-risk surgical patients. While a low dose is oftentimes insufficient, pre-operative initiation of high-dose beta-blocker therapy is the cause of increased incidence of bradycardia, hypotension, (watershed-type) cerebral infarction, and all-cause mortality. Chapter 7 describes the design of a randomized study of perioperative esmolol infusion. The intravenous beta-blocker esmolol is a very short acting agent with a halve-life of 2-9 minutes. It is therefore easily titratable in the perioperative phase, which is characterized by rapid hemodynamic fluctuations. The aim of the study was to prevent the occurrence of tachycardia without increasing the incidence of bradycardia and hypotension, by titrating esmolol to achieve a heart rate of 60-80 beats per minute in the perioperative phase. The intended study population consisted of patients undergoing major vascular surgery, who are all treated with a low dose of a long-acting oral beta-blocker. Patients are then randomized to esmolol or placebo infusion, initiated during surgery or at extubation, for 24 hours from initiation of surgery. The primary endpoint was heart rate control: the amount of time that a patient has a heart rate outside the target window of 60-80 beats per minute. Secondary endpoints included safety measures (bradycardia, hypotension, stroke) and efficacy measures (myocardial infarction). Unfortunately, the trial was terminated prematurely because of a slow inclusion rate. Only 7 of the intended 260 patients were included in the first year of the study, without a realistic potential for reaching that number of study subjects in the 3 years of the study period. The vital factors limiting inclusions were a relatively low number of eligible patients and the logistics required for the study: all patients need postoperative monitoring for 24 hours on an intensive or high care level. Attempts to perform postoperative monitoring and esmolol dose titration on the (medium care) vascular surgery step-down unit were not successful. This left no other option then termination of the trial.

DISCUSSION

It is well established that vascular surgery patients suffer of severe generalized atherosclerosis. Angiographic evidence of coronary artery disease is present in over 90% of these patients. [1] Symptomatic atherosclerotic disease of another vascular bed, such as a history of cerebrovascular disease, coronary artery disease (CAD), or renal disease is common. [2] This leads to an impaired prognosis of patients with peripheral arterial disease (PAD) compared with their unaffected counterparts of similar age. [3] The prognosis of PAD patients is even worse than that of patients who present with CAD. [4] This is thought to arise from a larger atherosclerotic burden in PAD patients, and, probably more importantly,

from inadequate secondary prevention measures. [2] This remains a problem despite the availablity of guidelines addressing medical care for PAD patients. [5]

Cardiovascular events are the leading cause of death in PAD patients. [4] The highest risk of cardiovascular complications in PAD patients is observed in the period during and shortly after vascular surgery. Depending on the definition of cardiac events, the specific procedure, and the risk profile, cardiac complications occur in up to >25% of patients. [6]

The most important complications are myocardial infarction, congestive heart failure, and hemodynamically important arrhythmias. Asymptomatic troponin release (defined as at least one troponin measurement above the 99th percentile of normal without clinical or electrocardiographic signs of myocardial ischemia) can be considered a major cardiac complication as well, although it is clinically silent. The main reason for this is the detrimental effect of asymptomatic troponin release on long-term survival. [7] This effect is comparable to that of the previously mentioned complications such as myocardial infarction. It may be prudent to subject patients who suffered any postoperative cardiac event (including troponin release) to vigorous long-term surveillance on an outpatient basis to ascertain adequate control of risk factors.

Not all PAD patients are at equal risk of perioperative and long-term cardiac complications and mortality. In order to identify the patients that will benefit the most of vigorous secondary prevention and follow-up, and to aid decision making regarding the surgical and anesthesiological strategy to be followed, it is important to be able to identify the patient at highest risk for cardiac events, both perioperative and on the long-term. While involvement of other vascular beds, impaired cardiac and renal function, and poor control of the classic atherosclerotic risk factors are well-known predictors of poor outcome, none of the available risk prediction scores are (near-) perfect. This thesis adds information on the prognostic value of several non-traditional risk markers in PAD patients. It is highly unlikely that all risk factors for poor outcome in this population are now known. This stresses the need for future research on this topic. Eventually, this should lead to comprehensive risk models for the prediction of perioperative cardiac events and for long-term prognosis in PAD patients. Such models should include at least data regarding age, exercise capacity, cardiovascular co-morbidity, (non-invasive) cardiac testing, and various biomarkers. The area under the ROC-curve of such a model will never be 1.0, but significant improvement from where we are today can be made. Adequate risk stratification will facilitate further improvement of care for PAD patients.

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SAMENVATTING

Deze thesis beschrijft preoperatieve cardiale risico inschatting, risicofactoren voor cardiale complicaties en strategieën voor cardiale risico reductie in patiënten die een niet-cardiale operatie ondergaan.

Hoofdstuk 1 beschrijft een veelgebruikte stapsgewijze benadering voor cardiale risico inschatting. Als eerste is het van belang om actieve cardiale problemen uit te sluiten, die preoperatieve beoordeling en behandeling door een cardioloog behoeven, zoals gedecompenseerd hartfalen of onstabiel coronairlijden. Vervolgens worden het chirurgische risico, de inspanningstolerantie, traditionele risicofactoren voor cardiale complicaties (voorgeschiedenis van ischemisch hartlijden, hartfalen, nierfalen, cerebrovasculair lijden, en met insuline behandelde diabetes), en de uitslagen van niet-invasieve cardiale onderzoeken (electrocardiogram, en indien geïndiceerd echocardiogram en stresstest) in kaart gebracht. Het bepalen van biomarkers, zoals NT-proBNP, kan bijdragen aan een verfijning van de risico inschatting. Het medicamenteuze beleid moet vóór de operatie geoptimaliseerd worden om het risico op cardiale complicaties te verkleinen in patiënten met een verhoogd risico op deze complicaties of met atherosclerotische comorbiditeit. De rol van perioperatieve medicamenteuze therapie met beta-blockers en statines wordt besproken. In een zeer specifieke groep patiënten kunnen niet-farmacologische risico reductie strategieën van nut zijn, zoals coronaire revascularisatie en cardiale assist devices.

Hoofdstukken 2-4 brengen de waarde van enkele mogelijke niet-traditionele cardiale risicofactoren in kaart.

Hoofdstuk 2 richt zich op type 2 diabetes mellitus (DM2). DM2 wordt gekenmerkt door de aanwezigheid van insuline resistentie, en niet primair door de absolute insuline deficiëntie die kenmerkend is voor type 1 diabetes. Beide typen leiden tot atherosclerose en atherosclerotische complicaties, zoals myocardinfarcten, herseninfarcten, en nierfalen. Het is daarmee goed voorstelbaar dat beide typen leiden tot een verhoogd risico op postoperatieve cardiale complicaties. Hoewel dit voor type 1 DM een geaccepteerd gegeven is, blijft er onduidelijkheid over de rol van DM2. Hoofdstuk 2 onderzoekt de relatie tussen DM2 en postoperatieve cardiale complicaties in een cohort van 1462 vaatchirurgische patiënten, van wie er 329 DM2 hebben. De belangrijkste uitkomstmaat was cardiale complicaties, een samengesteld eindpunt van cardiale dood, niet-fataal myocardinfarct, hartfalen, ernstige ritmestoornissen, en asymptomatische troponine T stijging. Na correctie voor mogelijke confounders was DM2 significant geassocieerd met het optreden van cardiale complicatie met een odds ratio van 1.80 (95%-CI 1.25 – 2.60). Het risico op cardiale

complicaties was vergelijkbaar in DM2 patiënten die met insuline behandeld werden en die met orale medicatie of een dieet behandeld werden. Hoofdstuk 2 toont aan dat alle diabetes mellitus, ongeacht het type en de behoefte aan insuline therapie, als risicofactor voor het optreden van cardiale complicaties na vaatchirurgie gezien moet worden.

Hoofdstuk 3 beschrijft de relatie tussen ABO bloedgroep en cardiale complicaties na vaatchirurgie. ABO bloedgroep is de belangrijkste determinant van de plasma spiegels van von Willebrand factor (VWF) en daarmee stollingsfactor VIII. VWF spiegels zijn 25-30% verhoogd bij mensen met een niet-O bloedgroep vergeleken met degenen met bloedgroep O. Hoge VWF spiegels zijn geassocieerd met een verhoogd risico op arteriële en veneuze trombose, leidend tot een verhoogd risico op myocard infarcten, hersen infarcten, perifeer vaatlijden, en veneuze thrombo-emboliën in mensen met niet-O bloedgroepen, vergeleken met mensen met bloedgroep O (met odds ratio's van respectievelijk 1.25, 1.14, 1.45 en 1.79). Hoofdstuk 3 onderzoekt de prognostische implicaties van niet-O bloedgroepen in een cohort van 4679 vaatchirurgische patiënten. Er werd geen verschil gevonden tussen patiënten met niet-O en O bloedgroepen met betrekking tot het optreden van cardiale complicaties, myocard infarcten, hersen infarcten, en cardiale dood binnen 30 dagen na operatie, en lange-termijn overleving. Mogelijke factoren die van invloed zijn op de relatie tussen uitkomst en bloedgroep zijn leeftijd, geslacht, het gebruik van anti-plaatjes- en antistollingsmedicatie en statines. Verdere analyse gaf in geen van de onderzochte subgroepen enig effect van ABO bloedgroep aan. Deze paradox (een relatief sterke relatie tussen ABO en een eerste athero-thrombotische complicatie, maar geen effect op het optreden van een volgende gebeurtenis) wordt mogelijk verklaard door de aanwezigheid van 'index even bias'. Concluderend, ABO bloedgroep is op geen enkele manier geassocieerd met perioperatieve cardiovasculaire complicaties of lange-termijn overleving na vaatchirurgie.

Hoofdstuk 4 onderzoekt de relatie tussen aortaklep calcificatie en uitkomst na vaatchirurgie. Calcificatie van de aortaklep werd beoordeeld middels echocardiografie, en gedefinieerd als verdikking of calcificatie van 1 of meer bladen van de aortaklep zonder aanwijzingen voor outflow obstructie (piek stroomsnelheid <2.5 m/s). Aortaklep stenose was gedefinieerd als uitstroom obstructie (piek stroomsnelheid >2.5 m/s). Aortaklep calcificatie komt veel voor in de studie populatie (sclerose 36%, stenose 3%). Aortaklep stenose was significant gecorreleerd aan zowel perioperatieve cardiale complicaties als aan lange-termijn overleving. Dit is in overeenkomst met eerdere studies. Aortaklep sclerose was niet geassocieerd met perioperatieve cardiale complicaties. Er was wel een univariate relatie tussen aortaklep sclerose en lange-termijn overleving, maar dit effect werd verklaard door de toegenomen aanwezigheid van andere cardiale risicofactoren in de mensen met een sclerotische aortaklep; aortaklep sclerose was niet onafhankelijk gecorreleerd aan lange-termijn

overleving. Aortaklep sclerose is een bekende risicofactor voor cardiale mortaliteit in de algemene populatie, maar hoofdstuk 4 toont aan dat het geen invloed heeft op de prognose van vaatchirurgische patiënten. Het is waarschijnlijk dat de aanwezigheid van uitgebreide atherosclerose in de studiepopulatie zorgt dat de aanwezigheid van aortaklepsclerose geen verdere invloed heeft op de prognose.

Ouderen die een niet-cardiale operatie moeten ondergaan hebben een verhoogd risico op cardiale complicaties vergeleken met de jongere populatie, door de aanwezigheid van meer comorbiditeit en een kleinere cardiale reserve. Hoofdstuk 5 beoordeelt de waarde van enkele perioperatieve cardiale risico indices in een populatie van 80-plussers. De Revised Cardiac Risk Index (RCRI, die 1 punt toekent aan de eerder genoemde traditionele risicofactoren voor cardiale complicaties) bleek een matige discriminatoire waarde te hebben in deze populatie. Er zijn meerdere verklaringen voor deze bevinding. De belangrijkste daarvan betreft waarschijnlijk de classificatie van het chirurgische risico: dit wordt als hoog of niet-hoog ingeschat. Die indeling is waarschijnlijk over gesimplificeerd. Het Erasmus model (een modificatie van de RCRI) classificeert het chirurgische risico in vier groepen. Dit verklaart waarschijnlijk de significant betere discriminatie van dit model vergeleken met de RCRI in de studie populatie van hoofdstuk 5. De discriminatieve kracht van het Erasmus model blijft echter onbevredigend, met een oppervlakte onder de ROC-curve van 0.77. Een verklaring voor dit matige presteren is het ontbreken in het model van een aantal onafhankelijke voorspellers van cardiale complicaties in de studie populatie, te weten perifeer vaatlijden, atriumfibrilleren en huidige induceerbare cardiale ischemie. In conclusie, de onderzochte risicomodellen presteren matig. Daarom blijft er behoefte aan een adequaat model voor het voorspellen van cardiale complicaties na niet-cardiale chirurgie in 80-plusseres.

Hoofdstukken 6 en 7 kijken naar cardiale risico reductie strategieën.

Vergeleken met de conventionele open benadering, verlaagt endovasculaire behandeling de fysiologische stress en het risico op cardiale complicaties gerelateerd aan chirurgie voor abdominale aorta aneurysmata. Endovasculair aneurysma herstel (EVAR) is mogelijk onder meerdere typen anesthesie. Hoofdstuk 6 onderzoekt het risico op cardiale complicaties bij EVAR onder algehele versus locoregionale chirurgie. In deze retrospectieve analyse bleek algehele anesthesie gepaard te gaan met een significant verhoogd risico op cardiale complicaties na EVAR, vergeleken met locoregionale technieken. Een mogelijke verklaring ligt in het feit dat locoregionale anesthesie een sterker dempend effect op de fysiologische stress respons op de ingreep heeft dan algehele anesthesie. In multivariabele analyse werd gecorrigeerd voor de kans een locoregionale techniek versus algehele anesthesie te ondergaan. Dit sluit echter niet uit dat er sprake is van selectie bias, aangezien het niet

mogelijk is te corrigeren voor confounders die onbekend zijn. Hoofdstuk 6 geeft het belang aan van het verrichten van een gerandomiseerde studie naar het effect van anesthesie type op de cardiale uitkomst na EVAR.

Tachycardie heeft een nadelig effect bij patiënten met coronairlijden: de myocardiale zuurstofvraag stijgt, terwijl het zuurstofaanbod aan (delen van) het myocard niet evenredig stijgt of zelfs daalt. De resulterende myocard ischemie gaat vaak vooraf aan ernstige cardiale complicaties, zoals myocardinfarcten. Het is daarmee van groot belang deze cascade, die begint met tachycardie, te voorkomen. In patiënten met een hoog cardiaal risico worden hier vaak beta-blockers voor voorgeschreven. Hoewel een lage dosis vaak onvoldoende effect heeft, is van hoog gedoseerde beta-blockers bekend dat het risico op bradycardie, hypotensie, (waterscheidings-) herseninfarcten en overlijden toeneemt. Hoofdstuk 7 beschrijft het ontwerp van een gerandomiseerde studie naar perioperatieve esmolol titratie. De intraveneus toegediende beta-blocker esmolol is een zeer kort werkend middel met een halfwaarde tijd van 2-9 minuten. Het is daarmee makkelijk te titreren in de perioperatieve fase, die gekenmerkt wordt door snelle hemodynamische fluctuaties. Het doel van de studie is het voorkómen van tachycardie zonder het risico op bradycardie en hypotensie te verhogen, door esmolol te titreren om een hartslag van 60-80 slagen per minuut te bereiken in the perioperatieve fase. De studiepopulatie zou bestaan uit patiënten die een grote vaatingreep moeten ondergaan en behandeld worden met een lage dosis lang werkende orale beta-blokker. De patiënten worden gerandomiseerd naar esmolol of placebo infusie, te initiëren tijdens de operatie of ten tijde van de extubatie, gedurende 24 uur vanaf het begin van de operatie. Het primaire eindpunt was hartslag controle: de tijd waarin een patiënt een hartslag heeft buiten het target window van 60-80 slagen per minuut. Secundaire eindpunten waren onder andere veiligheidsparameters (bradycardie, hypotensie, herseninfarcten) en effectiviteitsparameters (myocardinfarcten). Helaas is de trial voortijdig beëindigd in verband met een laag tempo van includeren. Slechts 7 van de voorgenomen 260 Patiënten werden geïncludeerd in het eerste jaar van de studie, zonder realistisch vooruitzicht om binnen de 3-jarige studie periode het benodigde aantal proefpersonen te includeren. De limiterende factoren voor het includeren waren een relatief laag aantal voor de studie geschikte vaatchirurgische patiënten en de logistieke vereisten voor deelname aan de studie: het infunderen van esmolol vereist 24 uur monitoring op intensive of high care niveau. Pogingen om postoperatieve monitoring en het titreren van esmolol op de afdeling vaatchirurgie (medium care) te laten plaatsvinden waren niet succesvol. Hierdoor was er geen andere mogelijkheid dan het voortijdig beëindigen van de trial.

DISCUSSIE

Het is bekend dat vaatchirurgische patiënten lijden aan ernstige generaliseerde atherosclerose. Meer dan 90% van deze patiënten vertoont angiografische tekenen van coronairlijden (CAD). [1] Symptomatische atherosclerose van een ander vaatbed, zoals een voorgeschiedenis van cerebrovasculair lijden, CAD of nierfunctiestoornissen, komt veel voor. [2] Dit leidt tot een verslechterde prognose van patiënten met perifeer vaatlijden (PAD) vergeleken met onaangedane leeftijdsgenoten. [3] De prognose van PAD patiënten is zelfs slechter dan die van patiënten die zich presenteren met CAD. [4] Dit komt waarschijnlijk door een meer uitgebreide atherosclerose in PAD patiënten en, waarschijnlijk belangrijker, door inadequate secundaire preventie. [2] Dit blijft een probleem ondanks de beschikbaarheid van richtlijnen voor de behandeling van patiënten met PAD. [5]

Cardiovasculaire voorvallen zijn de belangrijkste doodsoorzaak in PAD patiënten. [4] Het hoogste risico op cardiovasculaire complicaties wordt gezien rondom vaatchirurgische ingrepen. Cardiale complicaties treden op bij >25% van de patiënten, afhankelijk van de specifieke operatie, het cardiale risicoprofiel en de definitie van cardiale complicaties. [6]

De belangrijkste cardiale complicaties zijn myocardinfarcten, hartfalen en haemodynamisch belangrijke ritmestoornissen. Asymptomatische troponine stijging (gedefinieerd als ten minste 1 troponine meting boven het 99ste percentiel van normaal zonder electrocardiografische of klinische tekenen van myocardischemie) kan ook als een ernstige cardiale complicatie gezien worden, hoewel dit klinisch stil verloopt. De belangrijkste reden hiervoor is het negatieve effect van asymptomatische troponine release op de langetermijn overleving. [7] Dit effect is vergelijkbaar met dat van de eerder genoemde complicaties, zoals het myocardinfarct. Mogelijk is het verstandig om patiënten die een postoperatieve cardiale complicatie doormaken te onderwerpen aan een intensief en levenslang regime van poliklinische controles om zorg te dragen voor adequate controle van risicofactoren.

Niet alle PAD patiënten hebben een gelijk risico op perioperatieve en langetermijn cardiale complicaties en overlijden. Het is belangrijk om in staat te zijn de patiënten met het hoogste risico te identificeren, teneinde zo de patiënten te selecteren die het meeste baat kunnen hebben bij intensieve controle en secundaire preventie, en om beslissingen omtrent de te volgen chirurgische en anesthesiologische behandelstrategie te verbeteren. Hoewel van betrokkenheid van andere vaatbedden, verminderde cardiale en renale functie, en slechte controle van de klassieke atherosclerotische risicofactoren alom bekende risicofactoren zijn voor een slechte uitkomst, presteert geen van de beschikbare risicomodellen (bijna) perfect. Dit proefschrift voegt informatie toe over de prognostische waarde van enkele mogelijke

niet-traditionele risicofactoren in PAD patiënten. Het is desondanks onwaarschijnlijk dat op dit moment alle risicofactoren voor een slechte uitkomst bekend zijn. Dit geeft het belang aan van toekomstig onderzoek op dit gebied. Uiteindelijk zou dat moeten leiden tot de ontwikkeling van uitgebreide risicomodellen voor het voorspellen van perioperatieve cardiale complicaties en langetermijn prognose in PAD patiënten. Zulke modellen zullen in ieder geval gegevens moeten bevatten met betrekking tot leeftijd, inspanningstolerantie, cardiovasculaire comorbiditeit, (niet-invasieve) cardiale testen, en verschillende biomarkers. De oppervlakte onder de ROC-curve van zo'n model zal nooit 1.0 zijn, maar er kunnen nog grote verbeteringen plaatsvinden ten opzichte van de huidige situatie. Adequate risicostratificatie zal het mogelijk maken de zorg voor PAD patiënten verder te verbeteren.

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CURRICULUM VITAE

Erik Jan Bakker werd op 5 april 1985 geboren te Nieuwegein. Na het behalen van het eindexamen gymnasium begon hij in 2003 met de studie geneeskunde aan de Erasmus Universiteit Rotterdam. Na het cum laude behalen van het artsexamen in 2009 werkte hij een jaar als arts-assistent cardiologie in het Maasstad Ziekenhuis te Rotterdam. In 2010 startte hij zijn promotieonderzoek naar cardiale risicoschatting en risicoreducerende strategieën rondom niet-cardiale chirurgie in het Erasmus MC te Rotterdam (promotoren: Prof. dr. R.J. Stolker en Prof. dr. H.J.M. Verhagen), leidend tot dit proefschrift. Vanaf juni 2012 is hij werkzaam als arts-assistent niet in opleiding op de afdeling cardiologie van achtereenvolgens het st. Antonius Ziekenhuis te Nieuwegein en het Ziekenhuis Rivierenland te Tiel. In 2014 begint Erik Jan aan de opleiding tot cardioloog in het st. Antonius Ziekenhuis te Nieuwegein (opleider: dr J.M. ten Berg).

DANKWOORD

De totstandkoming van dit proefschrift zou niet mogelijk zijn geweest zonder hulp van de vele mensen die mij geholpen en gesteund hebben. Een aantal personen wil ik in het bijzonder bedanken.

Allereerst mijn promotoren, prof. dr. R.J. Stolker en prof. dr. H.J.M. Verhagen. Beste Robert Jan en Hence, dankzij jullie geweldige begeleiding en toewijding is dit proefschrift tot stand gekomen. Ik ben jullie erg dankbaar voor de fijne samenwerking.

Daarnaast wil ik graag dr. Don Poldermans bedanken. Met uw creativiteit en gedrevenheid stond u aan de basis van dit proefschrift.

Uiteraard ben ik mijn collega's uit de onderzoeksgroep dankbaar: Koen, Tabita, Sanne, Frederico, Michiel, Felix, Niels, Jan Peter. Ik wil jullie bedanken voor alle steun, hulp en gezelligheid.

Mijn paranymfen Imre Yousef Yengej en Anne Marijn Bakker bedank ik voor hun bijdrage aan de dag van de verdediging van dit proefschrift.

Natuurlijk bedank ik ook Malou, mijn familie, vrienden en collega's voor alles wat ze de afgelopen jaren voor me betekend hebben.

PORTFOLIO OF AWARDED ECTS POINTS

Erasmus MC courses (Central courses and courses organized by other Research Schools):

1. Principles of Research in Medicine (NIHES – ESP01)	13-08-'10	0.7
2. Introduction to Data-analysis (NIHES - ESP03)	03-09-'10	1.0

Other activities:	**Date**	**ECTS**
REVEAL Course, Medtronic, Maastricht,	15-09-2011	0.5
Clinical training for vascular surgery ward nurses (3 sessions)	09-2011	1.5

Other seminars:	**Date**	**ECTS**
1. Journal club, Rotterdam (weekly)	2010-2011	1.0
2. Research meeting, Rotterdam (weekly)	2010-2011	1.0
3. Vascular clinical meeting, Rotterdam (weekly)	2010-2011	1.0
4. Vascular rounds, Rotterdam region (6 per year)	2010-2011	1.0
5. Anesthesiology rounds, Rotterdam region (6 per year)	2010-2011	1.0

Lectures:	**Date**	**ECTS**
1. Dutch Society of Anesthesiology annual meeting 2011 (2 lectures)	19/20 april '11	1
2. Vascular rounds, Rotterdam region	16 may '11	0.5
3. European Society of Cardiology annual meeting 2011 (2 lectures)	27-31 aug '11	1
4. Dutch Society of Anesthesiology research meeting 2011	30 sept '11	0.5
5. American Society of Anesthesiologists annual meeting 2011 (3 lectures)	15-19 oct '11	1.5
6. Dutch Society of Vascular Surgery annual meeting 2013	22 april '13	0.5

Symposia and congresses (0.3 ECTS points/day):	**Date, location and number of days:**	**ECTS**
1. Dutch Society of Anesthesiology annual meeting 2011	19/20 april '11, Maastricht, 2 days	0.6
2. European Society of Cardiology annual meeting 2011	27-31 aug '11, Paris, 5 days	1.5
3. Dutch Society of Anesthesiology research meeting 2011	30 sept '11, Ede, 1 day	0.3
4. American Society of Anesthesiologists annual meeting 2011	15-19 oct '11, Chicago, 5 days	1.5