Prognosis of Patients with Peripheral Arterial Disease

Gijs M.J.M. Welten

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Prognose van patiënten met perifeer arterieel vaatlijden
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CONTENTS

Preface

Peripheral arterial disease (PAD) is becoming an increasingly important health issue in Western Society. PAD is affecting approximately 8 to 12 million adults in the USA and more than 30 million adults worldwide[1]. These symptomatic patients represent the 'top of the ice-berg', creating a major health burden. For every patient with symptomatic PAD, 3 to 4 patients have PAD without clinical complaints like claudication intermittens[2]. Especially in patients with PAD undergoing major vascular surgery, a high incidence of coronary artery disease (CAD) has been observed, which also may be asymptomatic or symptomatic. In patients with PAD requiring aortic or lower limb revascularization procedure surgery, the prevalence of CAD is about 50 to 70%[3-5]. Hence, it is not surprising that these patients are at increased risk for perioperatieve and long-term cardiac complications. Cardiac death accounts for approximately 40% of all 30-day mortality after surgery and for 65% of all deaths during long-term follow-up[6]. Importantly, the prognosis of patients with PAD is related to the presence and extent of CAD, as well as the regulation of cardiovascular risk factors.

The goal of preoperative cardiovascular risk stratification is to identify high-risk patients prior to major vascular surgery. These high-risk patients could benefit from medical therapy to improve their postoperative and long-term outcome, undergo less invasive surgery or one might even refrain from the planned intervention. This thesis will give a broad insight of the severity and complexity of patients with peripheral arterial disease undergoing major vascular surgery. It will provide prognostic information based on different cardiovascular risk factors. Furthermore, it attempts to improve the management of this disease through identifying beneficial effects of different pharmacological therapies, like beta-blockers and statins.

OUTLINE OF THE THESIS

Part 1: Prognosis

The main disease process underlying PAD is atherosclerosis. Atherosclerosis is a systemic disease affecting numerous vascular beds, including the coronary and peripheral circulation i.e. cerebrovascular, aortic and lower limb arterial circulation. Patients with multiple affected vascular beds, so-called polyvascular disease, have a worse outcome as was shown in the REACH registry; 1-year event rate from 13% for patients with 1 to 26% for patients with 3 symptomatic affected arterial beds[7]. As PAD is a polyvascular disease, it is of interest to explore the prognosis of patients with PAD undergoing different types of major vascular surgery and isolated CAD to optimize individual risk stratification. Since patients undergoing major vascular surgery are at high risk for perioperatieve and long-term cardiac complications, less invasive surgery (like endovascular procedures) or prophylactic coronary revascularization in high-risk patients seems to be attractive to improve survival. Although endovascular repair improves the short-term outcome in patients undergoing major vascular surgery, the long-term outcome of this technique remains unclear and controversial. In this part of the thesis we will describe the prognosis of PAD undergoing major vascular surgery, compared with CAD. Furthermore, we explore the long-term outcome of endovascular repair.

Chapter 1 is a review of selected publications describing the epidemiology, diagnosis, prognosis and intervention of peripheral arterial disease. It attempts to give a broad insight of the severity of this disease and the complex interactions with coronary artery disease. Furthermore, it can help to identify patients at increased risk and subsequently raise clinical awareness for these patients at high risk and initiate appropriate treatment.

In chapter 2, we compare the prognosis of 2,730 patients undergoing different types of major vascular surgery with 2,730 risk factor matched patients with severe myocardial ischemia without signs or symptoms of PAD. We further compared medication use between these two groups to explain differences in outcome and explored the relationship of pre-operative characteristics and non-fatal perioperative complications with long-term all-cause mortality and cardiac events.

Finally, in chapter 3, the long-term effect of endovascular abdominal aortic aneurysm (AAA) repair in 55 patients with 3 or more clinical cardiac risk factors and a preoperative cardiac stress test is compared to the outcome of 69 patients undergoing open AAA repair.

Part 2: Risk factors

In patients with PAD, the prevalence of cardiovascular risk factors is high, all negatively affecting postoperative outcome of patients undergoing major vascular surgery. Several risk factor indices have been developed to identify vascular patients at high risk for adverse cardiac outcome[8, 9]. As the surgical population is becoming older, we evaluate the influence of aging on the prognostic value of the most widely used cardiac risk index; the Revised Cardiac Risk Index[10]. Furthermore, we study the association of mild renal dysfunction and perioperative renal dysfunction in patients undergoing aortic surgery and its impact on postoperative outcome. Some preoperative variables, like anemia and levels of serum uric acid are not yet included in preoperative cardiac risk factor assessment since the association with postoperative outcome is unclear. The prognostic information of these potential risk factors may further refine preoperative risk assessment and provide the basis of optimal management strategies.

In chapter 4, we describe the impact of mild renal dysfunction on long-term outcome in patients with known or suspected CAD. The effect of mild renal dysfunction in 1,895 patients on long-term all-cause mortality is compared with 3,587 patients with normal renal function at baseline.

In chapter 5, the prognostic value of the Revised Cardiac Risk Index in patients undergoing different types of vascular surgery, among different age categories, is assessed. We further determine whether the predictive value could be improved by the addition of different age categories and additional risk factors.

In chapter 6, we describe the association of temporary perioperative renal dysfunction on outcomes in patients undergoing aortic surgery. The effect on 30-day and long-term mortality of renal function changes within three days after surgery is evaluated in 952 patients.

In chapter 7, we assess the independent contribution of preoperative serum uric acid levels to the risk of 30-day and late mortality and major adverse cardiac events in 936 patients scheduled for open vascular surgery.

Subsequently, in chapter 8 the predictive

value of preoperative anemia on the risk of perioperative and long-term cardiac morbidity and mortality is explored in 1,211 patients undergoing noncardiac vascular surgery.

Part 3: Pharmacological therapy

The cardioprotective effect of some perioperative pharmacological therapies like beta-blockers, has been clearly demonstrated in patients undergoing noncardiac vascular surgery[11, 12]. However, the effect of perioperative beta-blocker therapy in surgical patients with renal dysfunction or chronic obstructive pulmonary disease (COPD) is unclear. Despite fear for possible adverse pulmonary effects, cardioselective beta-blockers seem to be well tolerated in patients with COPD and beta-blocker use has been changed from contra indication to indication in patients with PAD and COPD[13]. Recently, statin therapy has emerged as a promising new cardioprotective therapy in patients with PAD. These lipid-lowering agents have been shown to reduce cholesterol synthesis, lower peripheral vascular resistance, improve endothelial function and even reduce inflammation, all cardiovascular risk factors present in patients with PAD.

Finally, the most important step in the management of patients with PAD is optimal treatment of underlying risk factors in order to reduce cardiac morbidity and mortality associated with PAD. In the final part of this thesis we describe the beneficial effects of beta-blockers and statins on different outcomes in patients undergoing major vascular surgery. We try to encourage intensive cardiovascular medical treatment and physician awareness for optimal care, since patients with PAD are still less likely to receive optimal medical therapy, compared to patients with CAD[14].
In chapter 9, we describe the association of beta-blocker therapy on short-and long-term outcomes of 2,126 patients undergoing major non-cardiac vascular surgery, for different stages of kidney dysfunction.

In chapter 10, we investigate the association between cardioselective beta-blockers and 30-day and long-term mortality in patients with COPD, in a study population of 3,371 consecutive patients who underwent major vascular. Furthermore, we determine the relationship between low and intensified cardioselective beta-blocker dosage and mortality.

Next, in chapter 11 the association of statin therapy on 30-day and long-term all-cause, cardiac and cerebro-cardiovascular outcome of 2,126 patients undergoing major elective vascular surgery, with and without chronic kidney disease is explored.

In chapter 12, we examine the association of pre-operative statin usage on the onset of acute kidney injury within three days after surgery, the recovery of acute kidney injury in the post-operative period and the influence on long-term survival of 1,944 patients undergoing major vascular surgery.

In chapter 13, we evaluate the effect of sudden perioperative statin withdrawal in 70 patients on postoperative adverse cardiac outcomes, compared with continuous use in 228 patients undergoing elective vascular surgery. Additionally, the association of different types of statins on outcome is studied.

Finally, in chapter 14 we highlight the secondary medical intervention of statin, antihypertension and antiplatelet therapy in patients with PAD, to create more aware-

ness of medical therapy in these high-risk patients.

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Part 1

Prognosis

Chapter 1

Prognosis of Patients with Peripheral Arterial Disease

J Cardiovasc Surg 2008, in press

Chapter 2

Long-term Prognosis of Patients with Peripheral Arterial Disease; a Comparison in Patients with Coronary Artery Disease

J Am Coll Cardiol 2008;51:1588-96

Chapter 3

Long-term Cardiac Outcome in High-risk Patients Undergoing Elective Endovascular or Open Infrarenal Abdominal Aortic Aneurysm Repair

Eur J Vasc Endovasc Surg 2008, in press

Chapter 1

Review Article

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J Cardiovasc Surg 2008, in press

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ABSTRACT

The incidence of peripheral arterial disease (PAD) is on the increase and is associated with a major health concern in current practical care. The most common disease process underlying PAD is atherosclerosis. Atherosclerosis is a complex generalized disease affecting several arterial beds, including the peripheral and coronary circulation. Especially in patients with PAD, high incidences of coronary artery disease (CAD) have been observed, which may be asymptomatic or symptomatic. The prognosis of patients with PAD is related to the presence and extent of underlying CAD. In patients with PAD undergoing major vascular surgery, cardiac complications are the major cause of perioperative morbidity and mortality and indicate a high-risk for adverse long-term cardiac outcome. In order to improve outcome for PAD patients, assessment and aggressive therapy of atherosclerotic risk factors and usage of cardio-protective medications is recommended. Unfortunately, substantial differences in risk factor management and treatment and long-term outcome have been reported between PAD and CAD patients.

This review of selected publications will describe the epidemiology, diagnosis, prognosis and intervention of peripheral arterial disease. It attempts to give a broad insight of the severity of this disease and the complex interactions with coronary artery disease. Furthermore, it can help to improve the risk stratification and clinical awareness for these patients at high-risk.

Key words: peripheral arterial diseases, coronary artery diseases, surgery, diagnosis, prognosis, treatment

EPIDEMIOLOGY

Peripheral arterial disease (PAD) is becoming an increasingly important health issue in Western Society. PAD is affecting approximately 8 to 12 million adults in the USA[1]. Some epidemiologic studies suggest a worldwide prevalence of more than 30 million people[2]. In the German Epidemiological Trial on Ankle

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Brachial Index (getABI) study, the prevalence of PAD for women and men was 17% and 20%, respectively in an unselected population of 6,880 patients aged 65 years and older[3].

In the Netherlands, of all 308,828 hospital admissions in 2004 due to cardiovascular disease, 40,304 (14%) admissions were because of PAD[4]. The trend in the number of hospital admissions due to cardiovascular diseases has been increased over time, from 180,411 in 1980 to 308,828 in 2004.

Although there is a larger number of patients at risk for cardiac morbidity and mortality compared to patients presenting with PAD related symptoms, the true population is probably underestimated, as PAD may be asymptomatic or present with atypical symptoms[5-7]. For example, The National Health and Nutrition Examination Survey (NHANES) reported a prevalence of PAD larger than 5 million adults aged 60 and older in the USA between 1999 and 2004. Of these participants, two-thirds of subjects were asymptomatic[8].

Furthermore, PAD increases with age. In The Rotterdam Study the prevalence of PAD increased from 7% in patients aged 55 to 59 years to 52% in those > 85 years [9]. In addition, with improving life expectancy, the prevalence of PAD is increasing, presenting an important public health challenge.

DIAGNOSIS

PAD refers to the presence of atherosclerosis resulting in the progressive narrowing of the arteries distal to the aortic bifurcation. Significant occlusion of the arteries causing clinical symptoms (i.e., claudication, rest pain and reduced walking distance) requiring major vascular surgery indicates the presence of PAD. However, the clinical diagnosis of PAD is made using the ankle-brachial systolic blood pressure index (ABI).

Ankle-brachial systolic blood pressure index

The ABI is a reliable, non-invasive screening tool for lower extremity ischemia and function[10], with a sensitivity of 95% and specificity of 99% for angiographically diagnosed PAD[11]. The ABI is useful in identifying high-risk patients who might otherwise go unrecognized[12]. The ABI is defined as the ratio of the average systolic blood pressure (SBP) in the ankle (dorsalis pedis and posterior tibial arteries) divided by the average SBP in the arm (brachial arteries). In case of differences between the extremities, the highest blood pressure of the arm, and the highest blood pressure of the ankle are taken. The normal range for the ABI is 1.0 to 1.3. In PAD, SBP below the narrowing arterials is reduced, resulting in a fall of ankle SBP below the brachial SBP and the ABI is reduced to less than 1.0. An ABI of 0.9 or less is considered diagnostic of PAD. Hence, the lower ABI levels, the greater the manifestation of PAD[13]. The impact of aging on the severity of PAD is significant, thus with advancing age, ABI decreases. In The Rotterdam Study, the ABI decreased from 1.18 in men aged 55 to 59 to 0.83 in those ≥85 years[9].

The ABI is a well-recognized and significant predictor for cardiovascular mortality and morbidity. In the study of Menke et al, the adjusted odds ratio for the risk of cardiovascular disease (composite of previous diagnosis of coronary heart disease, stroke, congestive

Table I. Relationship between levels of Ankle-Brachial Index (ABI) and risk for long-term mortality.

Source, year	Study population	End-point, follow-up	ABI levels	Adjusted RR or odds ratio (95% CI) for end-point
Diehm et al[15], 2006	N= 6,880, unselected patients aged ≥65 years in Germany	Total mortality during 3 years	<0.5 ≥0.5 and <0.7 ≥0.7 and <0.9 ≥0.9 and <1.1 ≥1.1, ref.	3.59 (2.40 – 5.36) 3.07 (2.01 – 4.68) 1.71 (1.21 – 2.41) 1.26 (0.96 – 1.66) 1.0
McKenna et al[16], 1991	N= 744, university affiliated, community hospitalized population in the USA	Total mortality	<0.4 0.4 – 0.85 >0.85, ref.	3.35 (2.16 - 5.20) 2.02 (1.34 - 3.02) 1.0
McDermott et al[17], 1994	N= 422, patients with ABI <0.92 and no history of lower-extremity vascular procedures in the USA	Total mortality during 4.3 years	≤0.3 0.31 to 0.91, ref.	1.8 (1.2 – 2.9) 1.0
Resnick et al[18], 2004	N= 4,393, American Indians aged 45 to 74 in the USA	Total mortality during 8.3 years	<0.9 ≥0.9 and ≤1.40, ref.	1.69 (1.34 – 2.14) 1.0
Newmann et al[19], 1999	N= 1,446, adults ≥ 65 year and CVD present at baseline in the USA	CVD mortality* during 6 years	<0.9 ≥ 0.9, ref.	1.52 (1.02 - 2.22) 1.0
Leng et al[20], 1996	N= 1,592, unselected men and women aged 45 to 74 in Scotland	Total mortality during 5 years	≤0.9 >0.9, ref.	1.58 (1.14 – 2.18) 1.0
Thatipelli et al[21], 2007	N= 395, patients referred for PAD and CAD evaluation in the USA	Total mortality during 4.7 years	<0.9 ≥ 0.9, ref.	2.34 (1.36 – 4.05) 1.0

*CVD mortality defined as cardiovascular mortality, fatal and nonfatal myocardial infarction, congestive heart failure, angina, stroke, and hospitalized PAD

heart failure, and/or angina) was 1.87 (95% confidence interval (CI) 1.29 to 2.73) for an ABI < 0.90, compared to a normal ABI level (i.e. ABI level of 1.1 to 1.29)[14]. Comparable correlations have been observed between ABI levels and risk of mortality in other studies, which are summarized in Table I[15-21].

Noncompressible calcified arteries, especially in patients with diabetes and kidney disease, result in abnormal high ABI values[22]. Since calcified arteries are correlated with the severity of atherosclerosis, high ABI levels are not reliable for diagnosing PAD. However, Resnick et al found a 1.77 fold increased risk of all-cause mortality during 8.3 years among 4,393 American Indians with an ABI >1.40 or the presence of arterial stiffening (95% CI 1.48 – 2.13)[18].

Non-invasive screening tools

Besides ABI measurement at rest, other non-invasive techniques have been developed, such as ABI measurement with additional exercise testing, segmental pressures and pulse volume recordings and ultrasonic duplex scanning[23]. For the screening of other manifestations of PAD, such as abdominal aortic aneurysms (AAA) or carotid disease,

ultrasound devices are recommended. The recent development of relatively inexpensive, portable hand-held ultrasound devices may have an important role in screening larger number of patients at risk. The correlation between axial computed tomography (CT) diagnosed AAA and a hand-held ultrasound devices is excellent (r= 0.98)[24]. In addition, the correlation coefficient between an ultrasound volume scanner (a newly developed, low-cost, handheld ultrasound volume scanner for 3-dimensional measurements) and CT was 0.86[24]. Of note, an advantage of the volume scanner is the early detection of 3-dimensional changes in aortic size[25].

Symptomatic and Asymptomatic PAD

A major limitation of the diagnosis of PAD is the high incidence of asymptomatic disease manifestation. The clinical expression of symptomatic PAD is claudication intermittens[26]. The prevalence of asymptomatic PAD patients can only be determined by using non-invasive screening tools (like ABI) in the general population. Asymptomatic patients have been found to have a reduced ABI with no claudication pain or other complaints than exertional leg pain. Several studies have looked at the epidemiology of asymptomatic and symptomatic PAD patients[8, 12]. These studies have found that for every patient with symptomatic PAD, 3 to 4 patients have PAD without clinical complaints of claudication. Thus, symptomatic patients represent the 'top of the ice-berg'.

However, the risk for cardiovascular events and death is the same in patients with symptom-free PAD, compared with symptomatic PAD. Leng and colleagues found that in patients with symptomatic PAD (intermittent claudication), the relative risk (RR) of 5-year death from cardiovascular disease (CVD) was 2.67, while patients with asymptomatic PAD have a RR of 2.44, compared with normal subjects in the general population[7].

PROGNOSIS

Peripheral arterial disease and morbidity and mortality

Peripheral arterial disease is associated with significant higher mortality and morbidity, including non-fatal myocardial infarction and stroke[7, 27]. The Cardiovascular Health Study found a two-fold higher risk for cerebrovascular mortality during 6 years follow-up in patients with PAD, with an annual cardiovascular event rate (non-fatal MI, stroke and vascular death) of 4 to 7%[19]. Several studies have also confirmed the association between the presence of PAD and adverse long-term outcome (Table II)[28-32].

Patients with claudication are also at increased risk for severe morbidity. Within five years, the risk of worsening of claudication symptoms in patients with claudication is approximately 25%, approximately 10% for critical limb ischemia and about 5% for amputation. Furthermore, 20% will have a nonfatal cardiovascular event (MI/stroke) and 30% die[33, 34].

Peripheral arterial disease versus coronary artery disease (CAD)

The prognosis of patients with PAD is predominantly determined by the presence and extent of underlying CAD. In patients with PAD requiring major vascular surgery,

Table II. Relationships between the presence of peripheral arterial disease (PAD) and risk for long-term total mortality.

Source, year	Study population	Follow-up	PAD definition	Adjusted RR or hazard ratio (95% CI) for total mortality for PAD, versus no PAD
Newmann et al[28], 1997	N= 1,267, adults ≥ 65 year without clinical CVD at baseline in the USA	4 years	ABI <0.9	2.76 (2.33 – 3.20)
Criqui et al[29], 1992	N= 565, community-dwelling men and women in the USA	10 years	Reduced segmental blood pressure and Doppler flow velocity ultrasound measurement	3.1 (1.9 – 4.9)
Brevetti et al[30], 2006	N= 4,352, adults aged 40 to 80 years from seven general practitioners in Italy	2 years	ABI < 0.90 or reduced Doppler flow velocity measurement	4.03 (1.50 – 10.84)
Voght et al[31], 1995	N= 470, random selected 68 years old adults in Sweden	10 years	ABI <0.9	2.0 (1.3 – 3.0)
Aboyans et al[32], 2005	N= 1,022, consecutive patients undergoing CABG in France	4.4 years	ABI <0.85	3.56 (2.40 – 5.33)

the prevalence of CAD is approximately 50 to 70%[35, 36]. Only 8% of patients undergoing vascular surgery have angiographically normal coronary arteries[37]. In addition, cardiac death accounts for approximately 40% of all 30-day mortality after surgery[38]. In a recent study, outcomes of 2,730 PAD patients was compared with 2,730 CAD patients during 13 years of follow-up[39]. All PAD patients underwent vascular surgery: 560 (20%) patients underwent carotid surgery (CEA), 923 (34%) underwent elective infrarenal AAA surgery (e-AAA), 200 (7%) patients underwent acute repair of a ruptured infrarenal AAA (r-AAA) and 1,047 (38%) patients underwent lower limb reconstruction procedures (LLR). CAD patients were diagnosed as severe myocardial ischemia referred for coronary angioplasty, without signs or symptoms of PAD obtained from review of medical records. All PAD patients were matched for baseline risk factors with 2,730 CAD patients (derived from a large cohort of 15,993 CAD patients). The primary end-point was all-cause mortality. The main finding of this study was that patients with PAD had a significant worse long-term prognosis, compared with CAD patients, unadjusted hazard ratio (HR) 2.40 (95% CI 2.18 – 2.65) (Figure 1).

Polyvascular disease

Polyvascular disease is common in the PAD population. Nearly half of outpatients with PAD have a history of CAD[12]. One out of six patients with PAD, CAD or cerebral arterial disease have symptomatic involvement of one or more arterial beds[40]. In a recent study of 431 patients with symptomatic atherosclerotic disease referred to an university hospital in the Netherlands between March

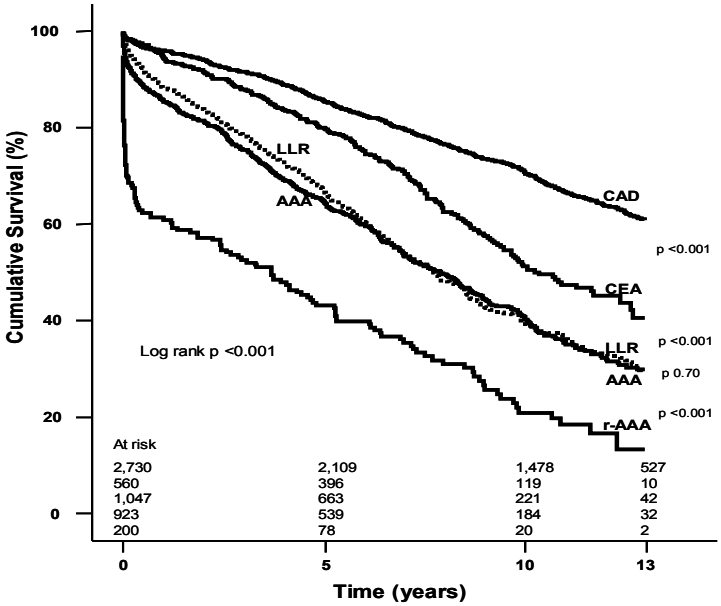

Figure 1 Kaplan-Meier estimate of overall long-term survival of coronary artery disease (CAD) and different types of peripheral surgical patients during 6.37 ± 4.08 years of follow-up[39]

To test for differences between the resulting curves, the overall log-rank test was used.
CEA= carotid endarterectomies surgery; AAA= elective infrarenal AAA surgery; r-AAA= acute infrarenal AAA surgery; LLR= lower limb arterial reconstruction procedures

2006 and September 2007, the prevalence of polyvascular disease (PAD, CAD, carotid artery disease and AAA) was evaluated using ultrasound testing[41]. Vidakovic et al observed that one vascular bed was affected in 29%, two vascular beds in 45%, three vascular beds in 23% and four in 3% of the patient population. Moreover, 38% of these patients had more than one affected peripheral artery territory (abdominal aorta, extra-cranial or lower extremity arteries).

Among those patients with symptomatic atherothrombosis (established CAD, PAD, cerebral arterial disease, or with at least three atherosclerotic risk factors), 16% had symptomatic polyvascular disease in the REACH Registry, which was substantial less than the number observed in the study of Vidakovic et al (71%)[42]. A reason for this discrepancy is the diagnostic criteria used for polyvascular disease. In the study of Vidakovic et al, the diagnosis of polyvascular disease was made using ultrasound testing, therefore identifying additional patients with asymptomatic disease (35% of the total), while the diagnosis in the REACH Registry was made according to disease history.

The REACH Registry also observed an increase in the 1-year event rate based on the number of affected arterial beds; from 13% for patients with 1 to 26% for patients with 3 symptomatic arterial disease locations[42]. This

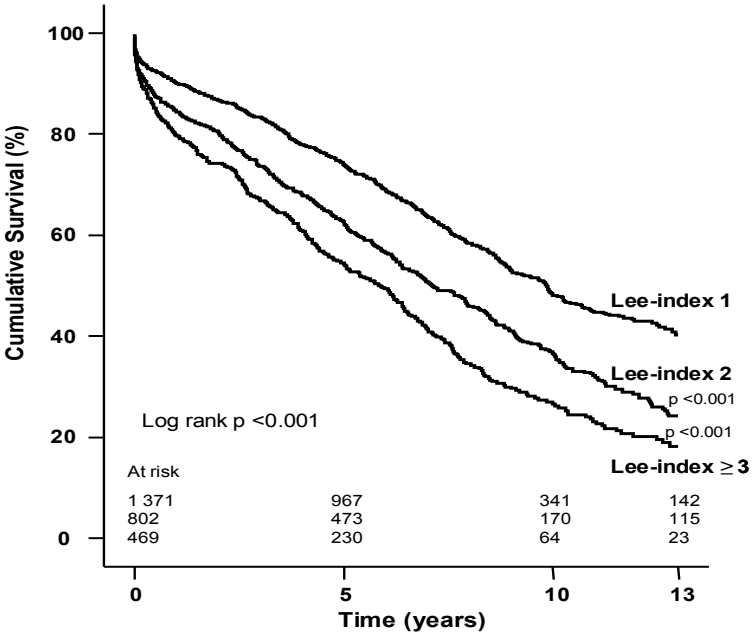

Figure 2 All cause long-term mortality in 2,642 patients who underwent major vascular surgery, according to the Revised Cardiac Risk Index score (Lee-index)[46]

Lee-index that assigns one point to each of the following characteristics: ischemic heart disease, history of heart failure, high-risk surgery, history of cerebrovascular disease, renal insufficiency and diabetes mellitus

indicates that PAD is a systemic disease with great overlap and that the number of beds affected by atherosclerosis is strongly associated with outcome.

Risk factors

The prognosis of patients with PAD is also related to cardiovascular risk factors for coronary artery disease such as diabetes mellitus, smoking, obesity, hypertension, hyperlipidaemia, renal function and chronic obstructive pulmonary disease[43, 44]. In the REACH Registry, the prevalence of hypertension, hyperlipidemia and diabetes mellitus in patients with generalized atherosclerosis is 82%, 72% and 44%, respectively [44]. Thus, treatment and achievement of optimal treatment targets of cardiovascular risk factors is also independently associated with improved long-term outcome.

The Revised Cardiac Risk Index (Lee-index) was introduced to assess perioperative cardiac risk among a large number of patients[45]. The six risk factors included were ischemic heart disease, heart failure, cerebrovascular disease, insulin dependent diabetes mellitus, renal dysfunction, and high-risk surgery. Among 2,642 patients undergoing major vascular surgery, 2 or ≥3 risk factors were independently associated with adverse long-term all cause

mortality during 6.4 ± 3.9 years follow-up, when compared with 1 risk factor (adjusted HRs 2.92 (95% CI 1.92 – 4.44) and 1.94 (95% CI 1.37 – 2.73), respectively)[46]. As shown in Figure 2, annual mortality rates increased by each risk factor added, indicating that the prognosis is related to underlying cardiovascular disease.

Diabetes mellitus

Approximately one third of patients with claudication have diabetes mellitus[12]. These patients had a five times higher mortality rate that non-diabetic patients over a mean follow-up period of 4.5 years and were five times more likely to have an amputation[47]. Since diabetic neuropathy is a common co-morbidity in patients with diabetes mellitus, leading to impaired pain perception, patients with claudication will present themselves late. This late presentation will increase the severity of PAD at the time of diagnosis, resulting in a worse prognosis. Not surprisingly, diabetics with intermittent claudication have an overall amputation risk of 20% and a 5-year mortality of 50%[48].

An oral glucose tolerance test (OGTT) could improve the detection of diabetes in patients with PAD undergoing surgery. In a recent study of 404 patients without signs or histories of impaired glucose tolerance (plasma glucose of 140 to 199 mg/dl) or diabetes undergoing elective vascular surgery, all patients were subjected to OGTT prior to surgery[49]. In this prospective study, 10% of the patients were diagnosed with new-onset diabetes and 26% have impaired glucose tolerance. An OGTT detected 72% of the patients with diabetes and 76% of the patients with impaired glucose tolerance. This simple test should be considered for all patients who undergo elective vascular surgery, since the prevalence of undiagnosted diabetes and impaired glucose tolerance is high in vascular patients.

Renal function

Patients with baseline chronic kidney disease (defined as a glomerular filtration ratio (GFR) or creatinine clearance (CrCl) of <60 ml/min, indirectly calculated from serum creatinine levels) are at high risk for development of PAD. The Atherosclerotic Risk in Communities (ARIC) Study reported a 1.82 (95% CI 1.34 – 2.47) relative risk increase for the development op PAD (defined as a new onset ABI <0.9, new intermittent claudication, or PAD-related hospital discharges) during a mean follow-up time of 13.1 years[50]. In addition, impaired baseline kidney function is also an independent predictor for long-term outcome among patients undergoing major vascular surgery. Patients with a CrCl of ≤30 ml/min, 30 to 59 ml/min, 60 to 89 ml/min had a adjusted HR of 4.00 (95% CI 3.10 – 5.16), 1.63 (95% CI 1.33 – 1.97) and 1.20 (95% CI 1.01 – 1.44), respectively for all-cause mortality during a mean follow-up of 6 years, compared to patients with a baseline CrCl of ≥90 ml/min[51] (Figure 3). In this cohort of PAD patients, even mild renal insufficiency (CrCl 60 to 89 ml/min) was prognostic for long-term outcome. In addition, mild renal insufficiency is also independently associated with adverse long-term outcome among 6,447 patients with known or suspected CAD over a mean follow-up of 7 years[52]. Changes in kidney function in the postoperative period of major vascular surgeries are a significant predictor for adverse outcome. Ellenberger

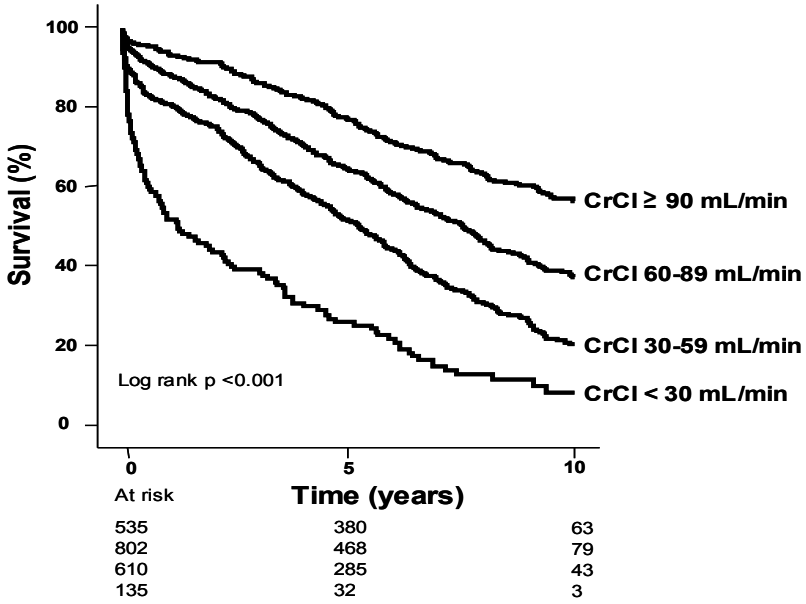

Figure 3 Kaplan-Meier estimate of overall survival by level of kidney function (creatinine clearance, CrCl) during 5.98 ± 3.68 years of follow-up[51]

and colleagues reported an elevated mortality rate within 30-days after elective abdominal aortic surgery in patients with a serum creatinine greater than 0.5 mg/dl within three days after surgery, compared with baseline value[53]. In addition, postoperative worsening of renal function is also related to outcome among PAD patients. Among 1,324 patients undergoing elective infrarenal AAA surgery, postoperative persistent worsening of renal function (>10% decrease in CrCl within three days after surgery) and temporary worsening of renal function (>10% increase at day 1 or 2, then complete recovery within 10% of baseline at day 3) were associated with a adjusted HR for long-term all-cause mortality of 1.7 (95% CI 1.3 – 2.3) and 1.5 (95% CI 1.2 – 1.4), compared to patients with unchanged of improved renal function during 10 years[54].

Biomarkers

Besides traditional cardiovascular risk factors identifying patients at risk for PAD, biomarkers such as N-Terminal pro-B-Type Natriuretic Peptide (NT-proBNP), troponins, uric acid levels and inflammation markers like C-reactive protein (CRP) expand the risk assessment.

Within a large cohort of patients with unstable CAD (n= 6,809), increasing quartiles of NT-proBNP levels were associated with increased 1-year mortality (lowest quartile 1,8%, highest quartile 19,2%, respectively)[55]. Low levels of cardiac troponin elevations in the perioperative period are associated with adverse long-term outcome in patients undergoing major vascular surgery. Among 393 patients undergoing AAA or infrainguinal surgery, elevated cardiac troponin (serum concentrations ≥0.1 ng/ml) was independently associated with

a two-fold increased incidence of all-cause mortality during a median follow-up of 4 years (adjusted HR 1.9, 95% CI 1.1 – 3.1)[56]. In addition, hyperuricemia (serum uric acid level, >7.0 mg/dL) is independently associated with higher risk of PAD[57].

However, from all these markers, CRP has the most emerging roll in risk assessment[58]. CRP plays an important role in the human immune response, which indirectly provides an important plasma biomarker for low-grade systemic inflammation[59]. CRP levels can predict the development of future systemic PAD. In 19,916 men aged 40 to 84 without prior history of cardiovascular disease, CRP was a strong independent predictor for the development of PAD (RR of 2.5 (95% CI 1.3-5.0), highest quartile versus lowest quartile)[60]. PAD was defined as the onset of self-reporting symptomatic PAD. Within patients with severe PAD, CRP levels > 9 mg/L are predictive for the development of myocardial infarction within 24 months[61].

The combined use of biomarkers may offer additive prognostic information for the prediction of adverse outcome. In 1635 patients with acute coronary syndromes, the number of elevated biomarkers (CRP, BNP and troponin) was a significant predictor of adverse outcome[62]. Patients with one, two, and three elevated biomarkers had a 2.1-, 3.1-, and 3.7-fold increase in the risk of death, MI, or congestive heart failure by 6 months, respectively. Unfortunately, data of the prognostic value of combined use of biomarkers is scarce in patients with PAD.

Of note, all these biomarkers have their own limitations and further research is warranted.

INTERVENTION

The selection of the appropriate therapy for PAD should be made after careful review on the patients' risk profile, related to the expected perioperative and late adverse outcome, the anatomical lesion and the expected success rate of the intervention, as the patients should live long enough to enjoy the benefits of surgery.

Surgery

Patients considered for surgical intervention should undergo a thorough risk assessment, since the postoperative and long-term prognosis after vascular surgery is predominantly determined by underlying CAD and should not be overlooked[63].

The perioperative outcome of open vascular surgery is well documented, however, data on the long-term outcome are scarce and often not considered in the immediate preoperative workup. During 13 years of follow-up, the perioperative and long-term risk of all-cause mortality was evaluated among 2,730 patients undergoing four different major vascular procedures. Within 30 days after surgery, the overall mortality rate was 1.4%, 6.3%, 28.5% and 2.9% for elective reconstruction or desobstruction of the carotid artery, elective infrarenal AAA surgery, ruptured-AAA surgery and lower limb reconstruction procedures, respectively[39]. During a mean follow-up of 6.37 ± 4.08 years, the overall mortality rate was 39.1%, 54.3%, 60.8% and 57.0%, respectively.

The perioperative and long-term outcome after non-cardiac surgery is challenged by the introduction of endovascular surgery.

Especially in high-risk cardiac patients, endovascular repair seems suitable, because it's reduced perioperative myocardial stress[64]. Among 683 patients undergoing elective abdominal aneurysm or iliac-femo-popliteal bypass surgery, the perioperative and long-term outcome (defined as cardiac death and myocardial infarction) of endovascular (n= 123) and open (n= 560) vascular surgery was evaluated. A clear benefit of peripoperative survival was observed in endovascular-treated patients (adjusted HR 019, 95% CI 0.07 – 0.53), however, the long-term risk was the same during a mean follow-up of 3.8 years (adjusted HR 0.89, 95% CI 0.52 – 1.52)[65]. Several other studies also concluded that the long-term survival rate (respectively 1-year and 5-year) of high-risk patients undergoing open or endovascular abdominal surgery repair seems to be the same[66, 67].

Aggressive management with preoperative coronary artery revascularization before surgery seems not to be associated with improved perioperative and long-term outcome. In the Coronary Artery Revascularization Prophylaxis (CARP) trial, of the 5,859 patients scheduled for elective vascular surgery, 510 patients were randomly assigned to either coronary-artery revascularization or no revascularization before surgery[68]. The primary end-point was all-cause mortality during a median follow-up of 2.7 years. No significant difference was observed for the long-term outcome (RR 0.98, 95% CI 0.70 – 1.37). In addition, the observed 30-day outcome (postoperative myocardial infarction, defined by elevated troponin levels) was the same (p= 0.4). Same results were observed in the DECREASE-V Study. In total, 101 patients with extensive coronary artery disease were randomly assigned for additional revascularization before major vascular surgery. There were no significant associations between revascularization and improved composites of 30-day and 1-year all-cause death or MI (p=0.3 and p=0.5, respectively)[69]. This is in contrast with the findings of the Coronary Artery Surgery Study (CASS) registry. They reported that preoperative coronary artery bypass grafting (CABG) among patients with PAD (n= 986) was associated with improved long-term outcome, compared to patients with medical treatment preoperatively (n= 848), despite the higher initial risk of perioperative morbidity and mortality[70].

Life style changes

Life style changes as smoking cessation, walking exercise (preferably supervised) and weight reduction are cornerstones in the management of PAD as in CAD.

Exercise training can improve pain free walking time with 180% and maximal walking time with 120% in patients with PAD[71]. Other cardiovascular benefits of regular exercise are an improved cholesterol and triglycerides management and improvement in glucose metabolism[72]. Exercise training is even associated with enhancement of smoking cessation. Smoking cessation is the most important modifiable risk factor in PAD. Continuing smoking increases the risk of amputation within five years in non-diabetic patients with intermittent claudication (11.4% for patients who continued to smoke versus 0% for patients who abstained from smoking)[73]. Furthermore, the patency in lower-extremity bypass grafts is also worse

for smokers, compared to nonsmokers[74]. A systemic review of 20 published articles indicated that smoking cessation was associated with a 36% reduction in risk of mortality for patients with CHD, compared with those patients who continued smoking (RR 0.64, 95% CI 0.58 – 0.71)[75].

Medical treatment

In order to improve outcomes of patients with PAD, assessment and aggressive therapy of atherosclerotic risk factors is recommended. The therapeutic management of the traditional risk factors like hypertension, hyperlipidemia and diabetes mellitus is well described and investigated. Aggressive treatment of hypertension is implemented in guidelines, with a goal of <140/90 mmHg, and <130/80 mmHg in patients with diabetes and renal insufficiency[76]. Thiazides and ACE-inhibitors are first-line drugs. The treatment of hypertension with beta-adrenergic blockage (β-blockers) in PAD patients is to be questioned. Current recommendations for the management of hyperlipidemia is to achieve a LDL cholesterol level of <100 mg/dL[77]. Besides diet modification, pharmacological treatment, like 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors (statins), is very effective[78, 79]. Patients with diabetes should have aggressive control of glucose blood levels with a glycolated hemoglobin goal of <7% with insulin. In patients with type 2 diabetes with evidence of macrovascular disease, pioglitazone seems not to be associated with a lower composite of all-cause mortality, non fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle, compared with placebo-treated patients[80].

However, antiplatelet therapy for secondary prevention of cardiovascular event is the cornerstone of pharmacologic intervention in patients with PAD. Aspirin (75 – 325 mg) have clear benefits in patients with atherosclerotic cardiovascular disease[81]. The risk for nonfatal MI, stroke and vascular death is reduced with approximately 25% in these patients[82]. In addition, clopidogrel (75 mg once daily), a new thienopyridine derivative studied in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial, is effective to reduce stroke, myocardial infarction and vascular death with 8.7% in patients with symptomatic PAD (n= 6452), compared with aspirin 325 mg once daily[83].

Besides the beneficial effect of antiplatelet therapy (like Aspirin and Ticlopidine), they have serious adverse side effects, like gastrointestinal bleeding and development of gastrointestinal ulcers. In the Physicians' Health Study, a randomized, double-blind, placebo-controlled trial, aspirin therapy (325 mg once daily) was accociated with an increased relative risk of ulcer of 1.22 (95% CI 0.98 – 1.53), compared to placebo treatment, during a mean follow-up of 60 months[84]. Since clopidrogel therapy was associated with statistically less severe gastrointestinal bleeding (0.49% vs. 0.71%) and intracranial haemorrhages or haemorrhagic deaths (0.39% vs. 0.53%), compared to aspirin therapy, the CAPRIE trial suggested that clopidogrel is an effective new antiplatelet agent and is indicated in atherothrombotic disease[83].

β-Blockers and statins

To prevent perioperative myocardial ischemia and long-term cardiovascular complications and survival after non-cardiac surgery, guidelines recommend β-blocker therapy in all patients at high-risk for coronary artery disease[85]. Unfortunately, the guidelines for PAD are still not implemented. The main proposed mechanisms underlying the efficacy of β-blockers include decreasing cardiac energy requirements and modification of arrhythmias risk by antagonizing the deleterious effects of the sympathetic nervous system[86]. β-Blockers have recently proven safe for the treatment of coronary artery disease in patients undergoing major vascular surgery, therefore changed from a contra indication to an indication[87]. Among patients undergoing major vascular surgery, β-blocker use was associated with decreased risk for 30-day and long-term all-cause mortality (adjusted HRs 0.39 (95% CI 0.24 – 0.64) and 0.82 (95% CI 0.71 – 0.93), respectively)[51]. Even in patients with chronic kidney disease (CKD) undergoing major vascular surgery, these beneficial effects have been observed[51].

In patients with relative contraindications for β-blocker therapy because of its possible adverse pulmonary effects, the use seems to be well tolerated and associated with improved in-hospital survival among inpatients with exacerbations of chronic obstructive disease[88]. Furthermore, the association between cardioselective beta-blockers and 30-day and long-term mortality in patients with COPD was evaluated in a study population of 3,371 consecutive patients who underwent major vascular[89]. This study concluded that the use of cardioselective beta-blockers was safe and was associated with a reduced 30-day and long-term mortality during a median follow-up of 5 years in patients with COPD who underwent major vascular surgery.

Besides reducing cholesterol synthesis, lipid-lowering agents have been shown to lower peripheral vascular resistance, improve endothelial function and even reduce inflammation in general population[90]. In addition, statins appear to be effective in lowering cardiovascular morbidity and mortality in patients with chronic kidney disease. Among 768 CKD patients undergoing major vascular surgery, statin use was associated with improved perioperative and long-term survival (adjusted HRs 0.39 (95% CI 0.16 – 0.96) and 0.56 (95% CI 0.43 – 0.73), respectively)[91]. In the same study, a 3-fold increase of statin use in the period 1995 – 2006 was observed. Despite the beneficial effect of statins, discontinuation of this lipid lowering agent is associated with higher risks of non-fatal myocardial infarction and cardiovascular death in the postoperative period of patients undergoing vascular surgery (adjusted HR 7.5 (95% CI 2.8 – 20.1))[92].

Cilostazol and pentoxifylline

For patients with claudication, the goal of treatment is to improve symptoms and walking ability. Pharmcacotherapy like cilostazol and pentoxifylline seem to improve pain-free and maximal treadmill walking distance in patients with claudication. Cilostazol is a phosphodiesterase inhibitor leading to peripheral vasodilatation, inhibition of the formation of arterial thrombi and platelet aggregation inhibition[93, 94]. A meta-analysis of 6 double-blind randomized trials compared cilostazol

with placebo[95]. Treatment of cilostazol was associated with improved maximal treadmill walking distance, increased walking distance and health-related quality of life, compared to placebo treatment. Pentoxifylline (a methylxanthine derivate) reduces the viscosity of blood, which can improve peripheral vascular perfusion[96]. Although pentoxifylline can improve walking ability, data from clinical trials are conflicting regarding its use[97-99]. In a randomized, double-blind, placebo-controlled, multicenter trial, 698 patients with claudication were randomized to cilostazol, pentoxifylline or placebo[100]. Mean maximal walking distance was significantly greater of cilostazol-treated patients compared with patients who received pentoxifylline or placebo at 24 weeks. No difference between walking distance was observed between patients receiving pentoxifylline and placebo. Same associations were observed with pain-free walking distance for the three treatment groups. Of note, patients receiving cilostazol experienced more side effects (like headache, palpitations and diarrhea).

Undertreatment of PAD

Although aggressive treatment of risk factors and usage of cardio-protective medications are recommended, several studies observed high rates of undertreatment in patients with PAD[12]. While the secondary prevention of subjects with PAD is similar to patients with CAD, atherosclerotic risk factors are less intensively treated in patients with PAD, compared with patients with CAD[101]. In a risk factor matched population of 2,730 PAD en 2,730 CAD patients, patients with CAD received more cardiac medications, compared with the PAD patients (β-blockers 74% vs. 34%, calcium antagonists 52% vs. 33%, aspirin 88% vs. 40%, nitrates 37% vs. 19%, statins 67% vs. 29% and angiotensin-converting-enzyme inhibitors (ACE-inhibitors) 57% vs. 31%, respectively) (Figure 5)[39]. The reason for this undertreatment seems to be multifactorial. The gap between recommendations in guidelines and clinical practice is highlighted in the REACH study[44]. Besides differences in geographical regions, another reason mentioned is the specialty of the treating physician. For example, statin prescription was 79.1% among cardiologists and 49.2% among vascular surgeons. Same difference in prescription rate was observed for β-blockers (70.1% versus 34.2%, respectively). Furthermore, only a minority of patients with cardiovascular risk factors achieved treatment targets[44]. Regarding patients with diagnosed hypertension (systolic >140 mm Hg and/or diastolic ≥90 mm Hg), blood pressure was still elevated in 54.9%.

IMPLICATIONS

The objective of cardiovascular risk stratification among PAD patients is to identify patients at high risk for adverse long-term cardiovascular outcome. Since the prognosis is related to the presence and extent of underlying coronary artery disease, a careful cardiac risk assessment is recommended. Besides life style changes, PAD patients benefit from long-term atherosclerotic risk factor management and optimal medical treatment. Beta-blocker and statin use seem to play an important role to optimize the secondary treatment of PAD patients. As the number

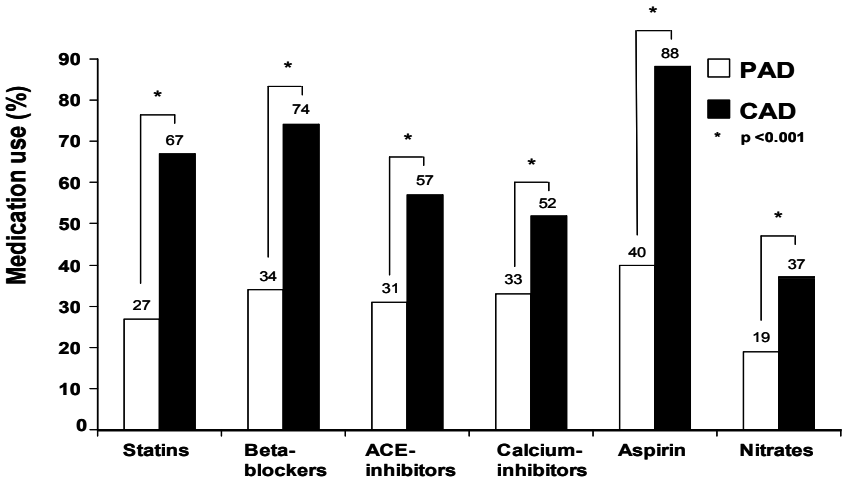

Figure 4 Medication use according to peripheral arterial disease (PAD) and coronary artery disease (CAD) patients[39]

ACE-inhibitors= angiotensin-converting-enzyme inhibitors

of PAD patients in on the increase, physician awareness is necessary for optimal care. When invasive therapy like surgery is required, patients at high risk for major morbidity and mortality in the post-operative period should be considered to undergo less invasive surgery like endovascular treatment, as patients should live long enough to enjoy the benefits of vascular surgery.

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Chapter 2

Long-term Prognosis of Patients with Peripheral Arterial Disease; a Comparison in Patients with Coronary Artery Disease

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Peripheral Vascular Disease

Long-Term Prognosis of Patients With Peripheral Arterial Disease

A Comparison in Patients With Coronary Artery Disease

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Objectives This study was designed to compare the long-term outcomes of patients with peripheral arterial disease (PAD) with a risk factor matched population of coronary artery disease (CAD) patients, but without PAD.

Background The PAD is considered to be a risk factor for adverse late outcome.

Methods A total of 2,730 PAD patients undergoing vascular surgery were categorized into groups: 1) carotid endarterectomy (n = 560); 2) elective abdominal aortic surgery (AAA) (n = 923); 3) acute AAA surgery (r-AAA) (n = 200), and 4) lower limb reconstruction procedures (n = 1,047). All patients were matched using the propensity score, with 2,730 CAD patients who underwent coronary angioplasty. Survival status of all patients was obtained. In addition, the cause of death and complications after surgery in PAD patients were noted. The Kaplan-Meier method was used to compare survival between the matched PAD and CAD population and the different operation groups. Prognostic risk factors and perioperative complications were identified with the Cox proportional hazards regression model.

Results The PAD patients had a worse long-term prognosis (hazard ratio 2.40, 95% confidence interval 2.18 to 2.65) and received less medication (beta-blockers, statins, angiotensin-converting enzyme inhibitors, aspirin, nitrates, and calcium antagonists) than CAD patients did ($p < 0.001$). Cerebro-cardiovascular complications were the major cause of long-term death (46%). Importantly, no significant difference in long-term survival was observed between the AAA and lower limb reconstruction groups (log rank $p = 0.70$). After vascular surgery, perioperative cardiac complications were associated with long-term cardiac death, and noncardiac complications were associated with all-cause death.

Conclusions Long-term prognosis of vascular surgery patients is significantly worse than for patients with CAD. The vascular surgery patients receive less cardiac medication than CAD patients do, and cerebro-cardiovascular events are the major cause of late death. (J Am Coll Cardiol 2008;51:1588–96) © 2008 by the American College of Cardiology Foundation

Atherosclerosis is a systemic disease affecting numerous vascular beds. In patients with peripheral arterial disease (PAD), coronary artery disease (CAD) has a prevalence of 46% to 71% (1,2). Post-operative and long-term prognosis after vascular surgery is predominantly determined by underlying CAD (3). Furthermore, cardiac death accounts for approximately 40% of 30-day mortality, and the 1-year mortality has been estimated at 6% to 10% (4–7). To improve outcomes of patients with PAD requiring surgery, assessment and aggressive therapy of atherosclerotic risk factors is recommended. Hence, the secondary prevention for subjects with PAD is similar to the measures for patients with CAD (8,9). However, data are scarce about the survival and treatment of patients with PAD compared with patients with CAD.

In addition, long-term outcomes in vascular surgery patients with PAD are ill-defined and often not considered in the immediate pre-operative workup. To provide information on long-term prognosis after open vascular surgery repairs among an entire stratum of procedures, it would be

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important to understand the relationship between preoperative characteristics and nonfatal perioperative complications with long-term all-cause mortality and cardiac events in a large cohort of patients with PAD. Therefore, in this analysis, we compared survival and treatment of patients with PAD scheduled for open vascular surgery procedures with a risk factor matched large cohort of patients with documented severe myocardial ischemia referred for coronary angioplasty in the same clinical setting, without signs or symptoms of PAD.

Methods

Study design and patient selection. Between January 1993 and June 2006, 2,730 PAD patients underwent major vascular surgery at the Erasmus Medical Center, Rotterdam, the Netherlands, and were entered into a computerized database. All patients underwent open surgery and were categorized into 4 groups, respectively: 1) carotid endarterectomy (CEA); 2) elective infrarenal abdominal aortic surgery (AAA); 3) acute infrarenal AAA surgery (r-AAA), and 4) lower limb arterial reconstruction procedures (LLR). The medical ethics committee of the Erasmus Medical Center was informed about the study protocol, and per institutional practice, no official approval was requested.

Operation groups. Patients in the CEA group underwent an elective reconstruction or desobstruction of the carotid artery. The AAA group underwent open infrarenal AAA repair (aortic-to-aortic or aortic-bifurcation prostheses procedures, removal of infected prostheses, and other operations of the abdominal aorta). Those with a rupture of the infrarenal abdominal aorta were classified as r-AAA. Finally, patients of the LLR group underwent iliac-femoral, femoral-popliteal, or femoral-tibial artery bypass procedures; removal of infected prostheses; peripheral desobstruction; and other elective peripheral arterial surgical reconstructions.

Propensity score risk factor matched CAD population. To compare the risk of underlying vascular disease (PAD or CAD) on long-term mortality, we compared the prognosis of patients undergoing vascular surgery (PAD patients) with the survival of a separate group of 15,993 patients diagnosed with severe myocardial ischemia (CAD patients), who were referred to the Erasmus Medical Center in the same period (1993 to 2006) for coronary angioplasty without signs or symptoms of PAD obtained from review of medical records. Because of the differences in baseline characteristics between the PAD and CAD populations, propensity score methodology was used to identify comparable patients with the same risk. First, a propensity score for each patient was constructed, providing an estimate of the propensity toward belonging to 1 patient group versus the other using multivariate logistic regression with the type of population as end point (PAD coded as 0, CAD coded as 1). Included in the analysis were the following available cardiovascular risk factors: age, gender, year of operation, hypertension, diabetes mellitus, smoking status, prior percutaneous coronary intervention, prior coronary artery bypass graft, and prior myocardial infarction (MI). Then, each PAD patient was matched with 1 CAD patient with the same propensity score, rounded off at 2 deciles. The graphical method of examination by box plots showed a balance of the estimated propensity score between PAD and CAD patients within each decile of the propensity score. As a result, the matched CAD population resembled the PAD cohort after matching for cardiovascular risk factors (Table 1). Finally, a total of 2,730 PAD patients were matched with 2,730 CAD patients.

In addition, medication use (statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors), aspirin, nitrates, and calcium antagonists) of the CAD

Abbreviations and Acronyms

AAA = elective infrarenal abdominal aortic surgery

ACE = angiotensin-converting enzyme

CAD = coronary artery disease

CCV = cerebro-cardiovascular

CEA = carotid endarterectomy

LLR = lower limb arterial reconstruction procedures

MI = myocardial infarction

PAD = peripheral arterial disease

r-AAA = acute infrarenal abdominal aortic surgery

Table 1 Propensity Score Risk Factor Matched PAD and CAD Population

	Before Matching			After Matching*		
Baseline Risk Factors (%)	PAD (n = 2,730)	CAD (n = 15,993)	p Value	PAD (n = 2,730)	CAD (n = 2,730)	p Value
Age, yrs (± SD)	66 (11)	61 (13)	<0.001	66 (11)	66 (12)	1.0
Males	75	72	<0.001	75	75	1.0
Hypertension	45	33	<0.001	44	45	0.9
Diabetes mellitus	15	11	<0.001	14	12	0.8
Smoking	23	24	0.008	23	21	0.8
Prior PCI	10	11	0.02	10	11	0.9
Prior CABG	19	27	<0.001	19	22	0.4
Prior MI	25	38	<0.001	25	25	1.0

*Matched for age, gender, year of operation, hypertension, diabetes mellitus, smoking status, and prior PCI.

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention.

population was recorded to attempt to explain differences in survival between the PAD and CAD populations.

Patients' characteristics. For all PAD patients, we recorded age, gender, hypertension (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or use of antihypertensive medication), diabetes mellitus (the presence of a fasting blood glucose ≥140 mg/dl or requirement for insulin or oral hypoglycemic agents), smoking status, hypercholesterolemia (total cholesterol of >200 mg/dl and/or the requirement of lipid-lowering medication), chronic obstructive pulmonary disease according to symptoms and pulmonary function tests (i.e., forced expiratory volume in 1 s <70% of maximal age and gender predictive value), body mass index, renal dysfunction (baseline serum creatinine >1.5 mg/dl), the presence of ischemic heart disease (prior MI, prior coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention) and angina pectoris), heart failure (defined according the New York Heart Association functional classification), and medication (statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, beta-blockers, aspirin, and anticoagulants). All prescription and over-the-counter medications were noted on the day of admission.

Clinical follow-up and end points. Post-operative clinical information was retrieved from an electronic database of patients followed in our hospital. On occasion, missing data were abstracted retrospectively by reviewing patients' medical records. Routinely, all vascular surgery patients are screened for adverse post-operative outcome by repeated cardiac isoenzyme measurements and electrocardiographic recording. Additional tests are performed at the discretion of the attending physician. After surgery, patients visit the outpatient clinic regularly and are screened for late cardiac events. From the municipal civil registries, we obtained the survival status. At the reference date, January 2007, follow-up was complete in 99.3% of cases. The mean follow-up of the PAD patients was 6.37 ± 4.08 years, the mean follow-up of the CAD patients was 9.17 ± 4.14 years. The primary end point was long-term all-cause mortality in the PAD and CAD populations. The secondary end point was the composite of perioperative mortality and nonfatal events in the PAD population.

Perioperative and long-term mortality. Perioperative all-cause mortality was defined as death occurring during 30-day in-hospital stay or as death occurring after hospital discharge but within the first 30 days after surgery. Cardiac death was defined as death secondary to MI, heart failure, or arrhythmias. Long-term all-cause mortality was defined as death beyond 30 days after surgery; deaths that occurred in the 30-day period were thus excluded from the long-term period.

The cause of death in the PAD population was grouped into a cerebro-cardiovascular (CCV), a non-CCV, and an

Table 2 Baseline Characteristics of All Patients With PAD, According to Type of Operation

	All Patients n = 2,730 (100%)	CEA n = 560 (21%)	AAA n = 923 (34%)	r-AAA n = 100 (7%)	LLR n = 1,047 (38%)	p Value
Demographics						
Mean age (± SD)	66 (11)	65 (10)	66 (11)	71 (9)	65 (12)	<0.001
Male (%)	75	73	78	88	72	<0.001
Cardiovascular risk factor (%)						
Body mass index (± SD)	25.0 (5)	25.8 (3)	24.9 (5)	25.4 (3)	24.7 (4)	0.006
Current smoker	24	11	28	14	29	<0.001
Hypertension	45	34	53	43	46	<0.001
Diabetes mellitus	15	10	13	10	20	<0.001
Hypercholesterolemia	29	28	37	33	26	<0.001
COPD	18	7	26	20	17	<0.001
Renal dysfunction*	12	5	13	20	14	<0.001
Disease history (%)						
Angina	15	7	17	14	19	<0.001
MI	24	9	30	27	31	0.01
Coronary revascularization	24	19	26	20	28	<0.001
Heart failure	5	1	6	5	7	<0.001
Medication use (%)						
Statins	26	26	33	19	23	<0.001
Diuretics	18	10	18	19	23	<0.001
ACE inhibitors	31	21	35	25	34	<0.001
Calcium antagonists	34	27	43	22	32	<0.001
Nitrates	19	13	21	14	20	<0.001
Beta-blockers	33	26	45	22	29	<0.001
Aspirin	40	73	33	28	32	<0.001
Anticoagulation	20	6	17	10	33	<0.001

*Baseline serum creatinine >1.5 mg/dl.

AAA = elective infrarenal abdominal aortic surgery; ACE = angiotensin-converting enzyme; CEA = carotid endarterectomy; COPD = chronic obstructive pulmonary disease; LLR = lower limb arterial reconstruction procedures; r-AAA = acute infrarenal abdominal aortic surgery; other abbreviations as in Table 1.

unknown cause of death. A CCV death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and included deaths following MI, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular accident or transient ischemic attack), surgery-related bleeding complications (only a post-operative cause of death), and others. Sudden unexpected death was classified as a CCV death. An MI was defined as the presence of 2 out of the following 3 criteria: 1) typical chest pain complaints; 2) electrocardiographic changes including acute ST-segment elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 h, or new ST-segment depression that persisted >24 h; and 3) a positive troponin T (i.e., >0.10 ng/ml) or peak creatinine phosphokinase myocardial band ≥8% of an elevated total creatinine phosphokinase with characteristic rise and fall (10). Non-CCV death was defined as any death with a principal non-CCV cause, including infection, malignancy, respiratory insufficiency, and others. The cause of death was ascertained by reviewing medical records, the computerized hospital database, autopsy reports, or by contacting the referring physician or general practitioner.

Nonfatal perioperative events in the PAD population. We recorded the following nonfatal complications within 30 days after surgery: infection (such as wound infection, pneumonia, sepsis, and urinary tract infection), MI, arrhythmias, heart failure, stroke, reoperation (percutaneous revascularization or bypass surgery to a vessel that has been treated during the index procedure), hemorrhage (arterial bleeding leading to hypotension (systolic pressure of <100 mm Hg) requiring blood transfusion), thrombectomy, amputation (excluded toe amputation), perioperative renal dysfunction (peak post-operative serum creatinine >+0.5 mg/dl within 3 days after surgery compared with pre-operative serum creatinine), and the requirement of hemodialysis (excluding pre-operative hemodialysis).

Statistical analysis. Continuous data are described as mean values and standard deviations, and dichotomous data are described as percentage frequencies. The chi-square test was used for categorical variables, and the analysis of variance test was used for continuous variables.

Kaplan-Meier survival analysis was used to compare survival times between the PAD and CAD patients and the 4 PAD subgroups, stratified by type of surgery. To test for differences between the resulting curves, the log-rank test was used. For the long-term survival analysis using the Kaplan-Meier method, we included those who died within 30 days after surgery.

A univariate Cox proportional hazard regression model was used to explore the association of underlying vascular disease on long-term survival. We used univariate and not multivariate analysis because we matched all PAD and CAD patients for the available baseline cardiovascular risk factors. For this long-term analysis, we included all survivors within 30 days after vascular surgery.

Multivariate logistic regression and Cox proportional hazard regression models were used to explore the relationship of major baseline risk factors of all PAD patients undergoing vascular surgery and perioperative all-cause and cardiac death, respectively. Risk factors entered in the risk model were type of operation, age >70 years, gender, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, smoking status, hypercholesterolemia, prior MI, prior heart failure, prior coronary revascularization, prior angina, and renal dysfunction. For the long-term all-cause and cardiac mortality, multivariate Cox proportional hazards regression analysis was performed and included also all nonfatal perioperative complications.

All univariate risk factors with a p value of <0.10 were entered in the perioperative and long-term multivariate analysis, resulting in an adjusted significant odds and hazard ratios (ORs and HRs) or as not significant. Unadjusted and adjusted ORs and HRs were reported with corresponding 95% confidence intervals (CIs). A p value of <0.05 was considered to be significant. All computations were performed with SPSS software version 12.0.1 (SPSS Inc., Chicago, Illinois), running under Windows 2000 Professional (Microsoft, Redmond, Washington).

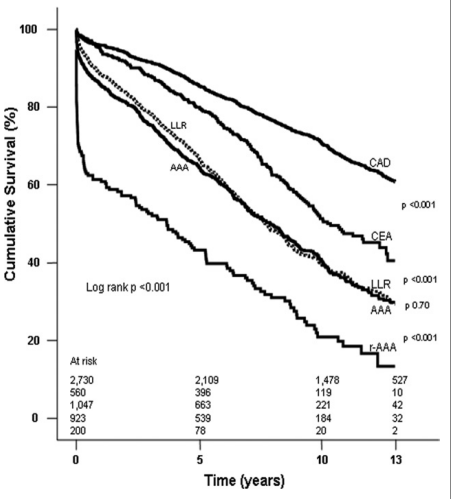

Figure 1 **Kaplan-Meier Estimate of Long-Term Survival of CAD and Different Types of Peripheral Surgical Patients**

To test for differences between the resulting curves, the log-rank test was used. AAA = elective infrarenal abdominal aortic surgery; CAD = coronary artery disease; CEA = carotid endarterectomy; LLR = lower limb arterial reconstruction; r-AAA = acute infrarenal AAA.

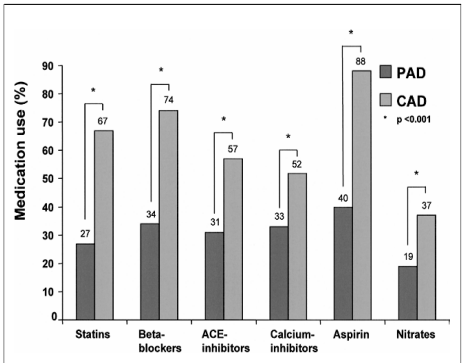

Figure 2 Medication Use According to PAD and CAD Patients

ACE = angiotensin-converting enzyme;
PAD = peripheral arterial disease; other abbreviation as in Figure 1.

Results

Patient characteristics. The mean age of all patients with PAD (n = 2,730) was 64 ± 16 years and 76% were male. A total of 560 patients (20%) underwent CEA surgery; 923 patients (34%) underwent AAA surgery (aortic-to-aortic n = 206, aortic bifurcation n = 624, infected prostheses n = 51, and others n = 42); 200 patients (7%) had a r-AAA; and 1,047 patients (38%) underwent LLR surgery (iliac-femoral n = 208, femoral-popliteal n =6 03, femoral-tibial n = 203, and infected prostheses n = 33). Patient's characteristics are presented in Table 2.

Primary end point. Compared with CAD patients, patients with PAD had a significantly worse long-term prognosis (unadjusted HR 2.40, 95% CI 2.18 to 2.65) (Fig. 1). Annual mortality rates of the PAD and CAD populations were 5.7% and 3.0% per year ($p < 0.001$). Importantly, patients with CAD received more cardiac medications than the PAD patients did (beta-blockers 74% vs. 34%, calcium antagonists 52% vs. 33%, aspirin 88% vs. 40%, nitrates 37% vs. 19%, statins 67% vs. 29%, and ACE inhibitors 57% vs. 31%, respectively) (Fig. 2).

Secondary end point. Within 30 days after surgery, a total of 153 PAD patients (5.6%) died. The overall mortality of the CEA, AAA, r-AAA, and LLR groups was 8 (1.4%), 58 (6.3%), 57 (28.5%), and 30 (2.9%) ($p < 0.001$), respectively. The leading causes of death were CCV events (76%) (Table 3). Specified according to the type of surgery, the leading cause of death at 30 days for CEA patients was stroke (38%), for

Table 3 Cause of Death During the Perioperative and Long-Term Period

	All Patients n = 2,730 (100%)	CEA n = 560 (21%)	AAA n = 923 (34%)	r-AAA n = 200 (7%)	LLR n = 1,047 (38%)	p Value
Perioperative mortality	153 (6)	8 (1)	58 (6)	57 (29)	30 (3)	
Total CCV death n (%)	116 (76)	6 (75)	45 (78)	46 (81)	19 (63)	0.3
MI	28 (18)	2 (25)	14 (24)	6 (11)	6 (20)	0.3
Congestive heart failure	15 (10)	0 (0)	7 (12)	4 (7)	4 (13)	0.5
Arrhythmia	15 (10)	0 (0)	4 (7)	7 (12)	4 (13)	0.5
Stroke	9 (6)	3 (38)	3 (5)	3 (5)	1 (3)	0.001
Fatal bleeding	40 (26)	1 (13)	13 (22)	23 (40)	3 (10)	0.01
Other	9 (6)	0 (0)	5 (9)	3 (5)	1 (3)	0.6
Total n-CCV death n (%)	37 (24)	2 (25)	13 (22)	11 (19)	11 (37)	0.3
Infection	22 (14)	0 (0)	4 (7)	8 (14)	10 (33)	0.005
Malignancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Respiratory insufficiency	9 (6)	2 (25)	4 (7)	2 (4)	1 (3)	0.1
Others	6 (4)	0 (0)	5 (9)	1 (2)	0 (0)	0.1
Unknown n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Long-term mortality*	1,353 (53)	216 (39)	470 (54)	87 (61)	580 (57)	
Total CCV death n (%)	625 (46)	91 (42)	203 (43)	36 (41)	295 (51)	0.03
MI	250 (19)	31 (14)	85 (18)	15 (17)	119 (21)	0.2
Congestive heart failure	168 (12)	28 (13)	41 (9)	10 (12)	89 (15)	0.01
Arrhythmia	26 (2)	2 (1)	11 (2)	3 (3)	10 (2)	0.4
Stroke	96 (7)	22 (10)	33 (7)	5 (7)	35 (6)	0.2
Others	85 (6)	8 (4)	33 (7)	2 (2)	42 (7)	0.1
Total n-CCV death n (%)	412 (31)	66 (31)	150 (32)	30 (35)	166 (29)	0.6
Infection	78 (6)	4 (2)	26 (6)	7 (8)	41 (7)	0.03
Malignancy	153 (11)	32 (15)	54 (12)	7 (8)	60 (10)	0.2
Respiratory insufficiency	85 (6)	9 (4)	31 (7)	10 (12)	35 (6)	0.1
Others	96 (7)	21 (10)	39 (8)	6 (7)	30 (5)	0.09
Unknown n (%)	316 (23)	59 (27)	117 (25)	21 (24)	119 (21)	0.2

*Excluding those patients who died within the post-operative period (n = 153).
CCV = cerebro-cardiovascular; n-CCV = noncerebro-cardiovascular; other abbreviations as in Table 2.

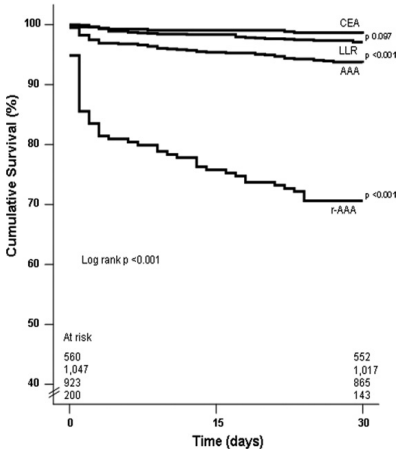

Figure 3 **Kaplan-Meier Estimate of Overall Perioperative (30-Day) Survival of Different Types of Surgical Patients**

To test for differences between the resulting curves, the log-rank test was used. Abbreviations as in Figure 1.

AAA was MI (24%), for r-AAA was fatal bleeding (40%), and for LLR was infection (40%). Outcomes at 30 days of patients undergoing CEA or LLR were superior to patients undergoing AAA surgery (Fig. 3). Patients scheduled for r-AAA surgery had the worst 30-day outcome. Also, in the multivariate Cox proportional hazards regression analysis, the type of operation was an important independent risk factor for perioperative all-cause mortality and cardiac events (Table 4).

A total of 1,353 (52.5%) patients with PAD died during 6.37 ± 4.08 years of follow-up, excluding the 153 patients who died within 30 days post-operatively. Mortality rates among the different surgical procedures were 216 (39.1%), 470 (54.3%), 87 (60.8%), and 580 (57.0%) for CEA, AAA, r-AAA, and LLR, respectively. Annual mortality rates of CEA, AAA, LLR, and r-AAA are 5.0%, 5.9%, 5.9%, and 6.8% per year (log rank $p < 0.001$), respectively. The leading cause of death was CCV (46%). Myocardial infarction accounts for 19% of all causes of long-term mortality. During long-term follow-up, patients of the LLR group had a similar prognosis compared with the AAA group (log rank $p = 0.70$), but patients of the r-AAA group had the worst outcome (Fig. 1). However, the multivariate Cox proportional hazards regression analysis illustrated that, converse to the perioperative outcome, the type of surgery was not related to outcome during long-term follow-up (Table 5). The proportional hazards assumptions were tested by constructing interaction terms between the variables and time to each end point. The Cox proportional hazards regression analyses showed no statistically significant interaction with time (each p value >0.05).

Long-term all-cause outcome was affected by age, smoking, chronic obstructive pulmonary disease, MI, renal dysfunction, and noncardiac complications (infection, stroke, and amputation). Pre-operative cardiac risk factors (age >70 years, diabetes mellitus, prior MI, coronary revascularization, heart failure) and perioperative nonfatal cardiac complications (MI, heart failure, arrhythmia) were the primary determinants of long-term adverse cardiac outcome.

Table 4 **Multivariate Associations of Baseline Characteristics With All-Cause and Cardiac Mortality in the Perioperative Period**

	Perioperative All-Cause Mortality		Perioperative Cardiac Death*	
Risk Factor	**OR Univariate (95% CI)**	**OR Multivariate (95% CI)**	**OR Univariate (95% CI)**	**OR Multivariate (95% CI)**
Operation group				
LLR (reference)	1.0	1.0	1.0	1.0
r-AAA	13.51 (8.40–21.74)	12.22 (7.46–20.04)	6.86 (3.32–14.15)	6.21 (2.94–13.12)
AAA	2.27 (1.45–3.57)	2.00 (1.27–3.16)	2.05 (1.06–3.97)	1.89 (1.01–3.68)
CEA	0.49 (0.22–1.07)	NS	0.26 (0.06–1.17)	NS
Gender	1.19 (0.80–1.77)	NS	1.40 (0.72–2.72)	NS
Age >70 yrs	2.31 (1.66–3.21)	1.55 (1.09–2.21)	2.57 (1.50–4.39)	1.95 (1.12–3.39)
Hypertension	1.50 (1.08–2.09)	1.55 (1.08–2.22)	1.72 (1.02–2.92)	NS
COPD	2.39 (1.68–3.40)	2.05 (1.40–3.01)	2.06 (1.17–3.62)	NS
Diabetes mellitus	1.13 (0.73–1.76)	NS	1.20 (0.60–2.40)	NS
Hypercholesterolemia	0.71 (0.40–1.23)	NS	0.83 (0.36–1.96)	NS
Current smoker	1.10 (0.73–1.68)	NS	0.88 (0.43–1.81)	NS
MI	1.22 (0.80–1.89)	NS	1.41 (0.80–2.47)	NS
Coronary revascularization	0.54 (0.34–0.84)	NS	0.65 (0.33–1.28)	NS
Heart failure	1.26 (0.65–2.34)	NS	2.50 (1.12–5.61)	NS
Angina	1.11 (0.60–2.03)	NS	1.27 (0.55–2.96)	NS
Renal dysfunction†	2.61 (1.77–3.84)	2.09 (1.38–3.18)	2.88 (1.60–5.19)	2.11 (1.15–3.88)

*Death because of MI, heart failure, and arrhythmia. †Baseline serum creatinine >1.5 mg/dl.
CI = confidence interval; NS = not significant; OR = odds ratio; other abbreviations as in Table 2.

Table 5 Multivariate Associations of Baseline Characteristics and Nonfatal Perioperative Complications With Long-Term All-Cause and Cardiac Mortality

	Long-Term All-Cause Mortality		Long-Term Cardiac Death*	
Risk Factor	HR Univariate (95% CI)	HR Multivariate (95% CI)	HR Univariate (95% CI)	HR Multivariate (95% CI)
Baseline risk factors				
Operation group				
LLR (reference)	1.0	1.0	1.0	1.0
r-AAA	1.29 (1.03–1.62)	NS	1.11 (0.75–1.64)	NS
AAA	0.97 (0.86–1.09)	NS	0.75 (0.61–0.93)	NS
CEA	0.66 (0.57–0.78)	NS	0.50 (0.38–0.67)	NS
Gender	1.15 (1.01–1.30)	NS	1.13 (0.91–1.41)	NS
Age >70 yrs	2.18 (1.96–2.43)	2.11 (1.88–2.36)	2.00 (1.65–2.41)	2.02 (1.66–2.47)
Hypertension	1.15 (1.03–1.28)	NS	1.18 (0.98–1.42)	NS
COPD	1.60 (1.41–1.81)	1.49 (1.29–1.71)	1.29 (1.02–1.63)	NS
Diabetes mellitus	1.32 (1.14–1.52)	NS	1.87 (1.50–2.34)	1.47 (1.16–1.87)
Hypercholesterolemia	1.06 (0.93–1.22)	NS	1.38 (1.10–1.72)	NS
Current smoker	1.30 (1.16–1.46)	1.20 (1.06–1.36)	1.44 (1.18–1.76)	NS
MI	1.43 (1.28–1.62)	NS	2.59 (2.15–3.13)	1.59 (1.26–2.01)
Coronary revascularization	1.08 (0.96–1.22)	NS	2.17 (1.80–2.62)	1.61 (1.30–1.99)
Heart failure	1.74 (1.41–2.14)	NS	2.94 (2.19–3.94)	1.45 (1.04–2.01)
Angina	1.26 (1.10–1.45)	NS	2.22 (1.81–2.73)	1.21 (1.01–1.59)
Renal dysfunction†	2.23 (1.83–2.47)	1.72 (1.47–2.02)	2.31 (1.80–2.96)	1.60 (1.22–2.09)
Post-operative complications				
Nonfatal MI	1.45 (1.19–1.76)	NS	4.07 (2.17–7.63)	2.22 (1.15–4.28)
Heart failure	2.20 (1.47–3.29)	NS	3.36 (1.89–5.96)	1.86 (1.01–3.43)
Arrhythmia	2.04 (1.41–2.98)	1.65 (1.12–2.43)	2.41 (1.33–4.40)	1.86 (1.00–3.52)
Infection	1.75 (1.52–2.02)	1.51 (1.31–1.76)	1.51 (1.17–1.96)	NS
Stroke	2.05 (1.55–2.72)	1.98 (1.47–2.67)	1.57 (0.90–2.73)	NS
Amputation	2.03 (1.58–2.61)	1.74 (1.33–2.29)	1.50 (0.84–2.68)	NS
Hemorrhage	1.24 (0.99–1.57)	NS	0.95 (0.60–1.50)	NS
Thrombectomy	1.14 (0.87–1.48)	NS	1.45 (0.96–2.19)	NS
Reoperation	1.30 (0.98–1.74)	NS	1.49 (0.93–2.39)	NS
Acute renal failure‡	1.81 (1.54–2.12)	1.44 (1.21–1.73)	1.73 (1.31–2.29)	1.39 (1.01–1.92)
Hemodialysis§	2.95 (1.98–4.38)	1.67 (1.06–2.63)	3.13 (1.61–6.06)	NS

*Death because of MI, heart failure, and arrhythmia. †Baseline serum creatinine >1.5 mg/dl. ‡Peak post-operative serum creatinine >+0.5 mg/dl (>44 μmol/l) within 3 days after surgery compared with pre-operative serum creatinine. §Excluding patients who were on pre-operative dialysis.

HR = hazard ratio; other abbreviations as in Table 2.

Discussion

Our main finding of this study is that patients with PAD, compared with a matched population for cardiac risk factors and year of treatment with CAD, are at increased risk for long-term mortality. In addition, PAD patients receive less cardiovascular medical therapy (e.g., beta-blockers, statins, ACE inhibitors, calcium antagonists, nitrates, and aspirin) than CAD patients do.

Furthermore, we conclude that CCV death is the major cause of perioperative and long-term mortality among vascular surgical patients with PAD (76% and 46%, respectively). Cardiac risk factors and perioperative cardiac complications are associated with long-term cardiac death, but noncardiac complications including infection, stroke, amputation, acute renal failure, and dialysis dependency are mainly related with all-cause mortality. The type of vascular surgery was found to be an independent risk factor for an adverse outcome in the perioperative period but not during the long-term follow-up. The long-term prognosis of patients undergoing acute repair of the ruptured abdominal aorta is similar to patients undergoing elective AAA surgery, contrary to the perioperative period. Similar results were observed by Soisalon-Soininen et al. (11) among 1,070 patients undergoing repair of ruptured and nonruptured abdominal aorta aneurysms.

Aggressive treatment of atherosclerotic risk factors (i.e., hypertension, diabetes mellitus, smoking, and hypercholesterolemia) and usage of cardioprotective medications (i.e., beta-blockers, statins, aspirin, and ACE inhibitors) are recommended for PAD patients, because they are associated with improved long-term survival (12–14). However, in our matched PAD and CAD population for cardiovascular risk factors, we clearly observed an underuse of cardiac medication among patients with PAD. McDermott et al. (8) reported that patients with CAD, compared with PAD patients, are treated more frequently with aspirin and lipid-lowering medication (82% vs. 37% and 56% vs. 40%, respectively). Overall, the undertreatment of PAD patients

can explain their worse long-term outcome when compared with CAD patients.

Peripheral atherosclerotic disease is becoming an increasingly important health issue in Western society; it affects between 8 to 12 million adults (15). The introduction of endovascular repair has the potential to improve the outcome for PAD patients undergoing noncardiac surgery because of its reduced perioperative myocardial stress (16). This technique is currently considered as a promising alternative, especially in high-risk cardiac patients. In addition, new cardioprotective strategies, including medical therapy (17) and prophylactic coronary interventions (18), are currently being evaluated in these patients. Though the preliminary results of endovascular repair are promising and associated with improved immediate post-operative outcome, the beneficial effect on long-term survival remains controversial (3,19,20). We described the results of open surgery in a tertiary hospital in relation to long-term outcome of patients undergoing different types of vascular surgery. The results of this study will provide useful information to compare long-term outcome between open and endovascular surgery.

We do think that propensity matching is appropriate in this study setting. In this study, we deal with patients with the same underlying disease, namely generalized atherosclerosis. However, patients with PAD present themselves with different clinical symptoms (e.g., claudication), compared with the more cardiac-related complications (e.g., angina) observed in CAD patients. We used the propensity score to compare survival of patients with generalized atherosclerosis with the same risk profile with 2 different treatments (PAD or CAD).

Study limitations. First, the study is not a randomized clinical trial but an observational study of a propensity-matched cohort. Despite using propensity to adjust as much as possible for the bias inherent in the decision about being PAD or CAD patients, we cannot exclude the possibility of residual confounding. As can be seen in Table 1, the PAD and CAD populations differed significantly, and by using the propensity score matching procedure, the resulting matched CAD cohort ultimately reassembled the PAD cohort. We did not match the PAD and CAD database with the risk factor hypercholesterolemia, because of the inconsistency of the CAD database regarding the reporting of hypercholesterolemia during the early stage of our study period. Second, although data were prospectively collected, this analysis is retrospective. Because of the acute setting of r-AAA patients, not all the baseline characteristics were completely recorded in the admission data, which might result in an underdiagnosis of some risk factors. Third, changes in the perioperative management have evolved markedly over time and were not taken into account in our analysis. These include multiple factors ranging from preoperative management, such as drug therapy, to anesthesiological and surgical techniques to intensive post-surgical care management. We tried to adjust for this confounding by adding the year of operation in our multivariate analysis (as a categorical variable per 2 years). We did not investigate our results across different time periods, because we did not observe different perioperative (30-day) outcomes in the PAD database over time. Finally, in our cohort, we found a remarkably low incidence of diabetes mellitus (15%). The diagnosis of diabetes mellitus was based on the requirement for insulin therapy, hypoglycemic agents, or as fasting blood glucose ≥140 mg/dl. In patients qualified as nondiabetics with PAD, fasting glucose levels may be normal, and the diagnosis of diabetes is only made after a glucose loading test. Unfortunately, we did not routinely perform a loading test for patients with a normal fasting glucose. Therefore, the number of diabetics might be underestimated.

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Chapter 3

Long-term Cardiac Outcome in High-risk Patients Undergoing Elective Endovascular or Open Infrarenal Abdominal Aortic Aneurysm Repair

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Long-term cardiac outcome in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair.

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ABSTRACT

Objectives: To assess long term outcome of patients at high cardiac risk undergoing endovascular or open AAA repair.

Methods: Patients undergoing open or endovascular infrarenal AAA repair with ≥ 3 cardiac risk factors and preoperative cardiac stress testing (DSE) at 2 university hospitals were studied. Main outcome was cardiac event free and overall survival. Multivariate Cox regression analysis was used to evaluate the influence of type of AAA repair on long-term outcome.

Results: In 124 patients (55 endovascular, 69 open) the number and type of cardiac risk factors, medication use and DSE results were similar in both groups. In multivariable analysis, adjusting for cardiac risk factors, stress test results, medication use, and propensity score endovascular repair was associated with improved cardiac-event free survival (HR 0.54; 95%CI 0.30-0.98) but not with an overall survival benefit (HR 0.73; 95%CI 0.37-1.46). Importantly, statin therapy was associated with both improved overall survival (HR 0.42; 95%CI 0.21-0.83) and cardiac event free survival (HR 0.45; 95%CI 0.23-0.86).

Conclusions: The perioperative cardiac benefit of endovascular AAA repair in high cardiac risk patients is sustained during long-term follow-up provided patients are on optimal medical therapy but it is not associated with improved overall long-term survival.

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INTRODUCTION

Patient undergoing abdominal aortic aneurysm repair are at significant risk for both perioperative and long term cardiovascular events. In particular patients at high cardiac risk might benefit from endovascular AAA repair. However, no randomized trials

comparing open and endovascular treatment have been reported on patients at high cardiac risk. For example, less than half of the patients in the DREAM trial (44%) and EVAR-1 trial (43%) had a history of cardiac disease[1,2]. A major limitation of non-randomized comparative studies between open and endovascular surgical procedures conducted so far is the lack of objective criteria for baseline cardiac condition[3].

Preoperative cardiac stress testing such as dobutamine stress echocardiography (DSE) provides an objective assessment of the presence and extent of coronary artery disease[4]. In a previous study we used this modality to compare perioperative outcome after open or endovascular AAA repair and found that endovascular repair was superior in terms of cardiovascular outcome[5]. The long-term outcome of these high-risk patients however remained ill-defined.

Therefore we expanded the study population of the previous study and conducted long term follow-up of these patients. The aim of the present study was to evaluate the long-term effect of endovascular AAA repair compared to open AAA repair in patients at clinical high cardiac risk on cardiac complications and mortality.

METHODS

Patients

The study population was composed of patients with 3 or more cardiac risk factors who underwent elective abdominal aneurysm repair between January 2000 and January 2006 at two tertiary referral centers, Erasmus University Medical Center Rotterdam, the Netherlands and University Medical Center Utrecht, the Netherlands and had a preoperative cardiac stress test. The choice for either repair method was at the discretion of the treating vascular surgeon and was mainly based on anatomical considerations. The study was approved by the Erasmus MC medical ethics committee.

Preoperative cardiac risk assessment

All patients were routinely screened for cardiac risk factors, including age over 70 years, history of or presence of angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure (serum creatinine > 170 umol/l), and diabetes mellitus. The presence of hypertension and chronic obstructive pulmonary disease (COPD) was noted as well. A patient was classified as having COPD at the preoperative screening visit according to symptoms and pulmonary function test (i.e. FEV1 <70% of maximal age and gender predictive value). According to the ACC/AHA guidelines all patients with 3 or more risk cardiac risk factors underwent cardiac stress testing prior to surgery.

Perioperative medication use was noted including ACE-inhibitors, platelet aggregation inhibitors, beta-blockers, calcium antagonists, cumarin derivatives, diuretics, nitrates, and statins. Patients unable to take medication orally perioperatively were switched to intravenous formula. If no intravenous formula was available, i.e. statins and ACE-inhibitors, oral medication was restarted as soon as possible after surgery.

Cardiac stress testing

Resting echocardiography was used to estimate the left ventricular ejection fraction using the Simpson rule. Cardiac stress testing was performed by dobutamine echocardiography as previously described[6]. Myocardial stress induced ischemia was assessed using a semi-quantitative evaluation; a 5-point score in a 17-segement model. Limited ischemia was defined by the presence of 1-4 ischemic segments, while extensive ischemia was defined by ≥ 5 ischemic segments.

Outcome

All patients were monitored for cardiac events after abdominal aortic aneurysm repair. Twelve-lead ECG and serum troponin-T levels were systematically determined on day 1, 3, and 7 postoperatively or at discharge. The primary outcome of the study was the incidence of myocardial infarction and the combination of myocardial infarction and all-cause death during long-term follow-up. Myocardial infarction was defined as the presence of 2 out of the following 3 criteria: (1) Characteristic ischemic symptoms lasting > 20 minutes, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists > 24 hours, and (3) a positive troponin T, i.e. >0.10 ng/ml, or peak CK-MB ≥8% of an elevated total creatinine phosphokinase with characteristic rise and fall[7]. Survival status was confirmed by contacting the civil service registry.

Statistical analysis

Continuous data are presented as median values and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical characteristics between patients undergoing endovascular repair or open repair were evaluated by Wilcoxon's nonparametric tests, Chi-square tests or Fisher's exact tests, as appropriate. The incidence of events over time was further examined by the Kaplan-Meier method, whereas a log-rank test was applied to evaluate differences between the two treatment modialities. We developed a propensity score for the likelihood of undergoing either open or endovascular AAA repair and used applied multivariate logistic regression analysis to calculate the propensity score. The association of type of AAA repair, cardiovascular risk factors and medication use with long-term events was assessed via multivariate Cox regression analysis, including the propensity score, with stepwise backward removal. The limit of statistical significance was set at $P = .05$ (two sided). All analysis was performed using the statistical software SPSS for Windows 12.0.1 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patient characteristics

A total of 124 patients with 3 or more clinical cardiac risk factors were included in this study. Of these, 69 patients underwent open AAA repair and 55 patients underwent endovascular AAA repair. Clinical baseline characteristics of these patients are shown in table 1. Almost

all (92%) patients were male, their mean age was 74 ± 6 years, and the median AAA diameter was 60 mm (interquartile range 55-70 mm). There were no statistically significant differences between patients undergoing open or endovascular AAA repair in terms of clinical characteristics or medication use. During non-invasive stress testing approximately half (47%) of all patients had stress inducible myocardial ischemia. A total of 46 (37%) patients had mild myocardial ischemia while another 12 (10%) patients had extensive myocardial ischemia. There was no difference in no, mild or extensive myocardial ischemia between the open and endovascular group (respectively 54% vs 53%, 35% vs 40% and 12% vs 7%).

Perioperative outcome

Overall 30 day mortality was 4.3% for the open group and 0% for the endovascular group. An additional 3 (4.3%) patients in the open group died during hospitalization but after 30 days of the index procedure. The combined 30-day endpoint of non-fatal myocardial infarction and all-cause death was 12 (17%) in the open and 2 (4%) in the endovascular group (p=0.02). The length of hospital stay was significantly shorter in patients treated endovascular (median 3 vs 11 days, p<0.001).

Long-term outcome

Type of repair

During a median follow-up of 3.3 years (interquartile range 1.8 – 5.6 years) a total of 39 (31%) patients died and a total of 55 (45%) patients reached the combined endpoint of all-cause death and MI. As is shown in figure 1a, during long-term follow-up there was no significant difference in overall survival between endovascular and open AAA repair (p=0.38). Also in multivariate analysis patients treated endovascular had no significant better survival rate (HR 0.73, 95%CI 0.37 – 1.46, table 2). However, patients who underwent endovascular AAA repair did have a statistically significant better cardiac event free survival as compared to patients treated with open repair (figure 1b, HR 0.54, 95% CI 0.30 – 0.98, table 3). It should be noted however that this benefit was mainly driven by the 30-day events. If the first 30 days after surgery are not taken into account there would have been a similar cardiac event free survival among patients treated by endovascular or open repair (HR 0.89, 95% CI 0.44 - 1.77, p=0.73).

Medical therapy

While type of AAA repair did not have a significant impact on overall long-term survival aggressive medical therapy did seem to be associated with improved overall-survival. Patients on statin therapy had a significant survival benefit over patients not on statin therapy; 5 year overall survival 77% vs 53% respectively (HR 0.42, 95% CI 0.21-0.83, table 2). Also cardiac event free was significantly better in patients on statin therapy (HR 0.45, 95% CI 0.23-0.86, table 3). As is shown in figures 2a and 2b the perioperative benefit of endovascular repair was only sustained in patients on statin therapy in contrast to patients not on statin therapy. The prescription rate of statins gradually increased over the studied years, from 38% in 2001/2002 to 67% in 2003/2004 and 88% in 2005/2006 (p<0.001). The vast majority of patients were

Table 1. Baseline clinical characteristics of patients undergoing open and endovascular abdominal aneurysm repair.

	All patients (N =124)	Open (N = 69)	Endovascular (N = 55)	P
Men	114 (92%)	64 (93%)	50 (91%)	0.75
Age (mean, SD)	74 ± 6	74 ± 6	74 ± 7	0.66
Heart rate prior to surgery	65 ± 12	66 ± 13	64 ± 9	0.23
Risk factors				
Previous angina pectoris	77 (62%)	41 (59%)	36 (64%)	0.71
Previous myocardial infarction	107 (86%)	60 (87%)	47 (84%)	0.80
Previous heart failure	25 (20%)	12 (17%)	13 (23%)	0.50
Previous CABG or PTCA	60 (48%)	33 (48%)	27 (48%)	0.99
CVA or TIA	46 (37%)	29 (42%)	17 (30%)	0.20
Diabetes Mellitus	18 (14%)	10 (15%)	8 (14%)	0.95
Renal failure	28 (22%)	14 (20%)	14 (25%)	0.67
Systemic hypertension	52 (42%)	32 (46%)	20 (36%)	0.28
COPD	48 (38%)	28 (41%)	20 (36%)	0.57
Stress echocardiography				
No ischemia	66 (53%)	37 (54%)	29 (53%)	0.66
Limited ischemia	46 (37%)	24 (35%)	22 (40%)	
Extensive ischemia	12 (10%)	8 (12%)	4 (7%)	
Medication at screening				
Platelet aggregation inhibitors	90 (72%)	40 (73%)	40 (71%)	0.84
ACE-inhibitors	51 (41%)	32 (47%)	19 (34%)	0.15
Diuretics	42 (34%)	25 (59%)	17 (41%)	0.57
Nitrates	35 (28%)	19 (27%)	16 (29%)	0.95
Beta-blockers	108 (86%)	60 (87%)	48 (86%)	0.88
Statins	78 (63%)	41 (59%)	37 (67%)	0.46
Calcium-antagonists	42 (34%)	24 (35%)	18 (32%)	0.85

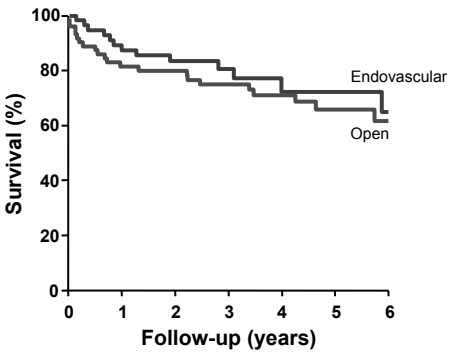

Figure 1a. Overall survival of patients undergoing endovascular or open AAA repair.

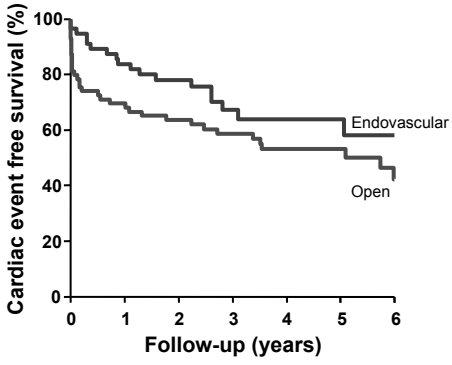

Figure 1b. Cardiac event free survival of patients undergoing endovascular or open AAA repair.

Table 2. Significant predictors of long-term overall survival status when clinical characteristics, propensity score for type of surgery, medication use and year of surgery were entered as independent variables into a Cox regression model with stepwise backward removal.

	HR	95% CI	P-value
Endovascular treatment	0.73	0.37 – 1.46	0.37
Age (per year increase)	1.10	1.03 – 1.17	0.003
Stress inducible myocardial ischemia	1.95	1.03 – 3.89	0.04
Statin use	0.42	0.21 – 0.83	0.01
Heart rate < 70 bpm	0.26	0.13 – 0.54	<0.001
Platelet aggregation inhibitor	0.47	0.23 – 0.97	0.04

Table 3. Significant predictors of long-term cardiac event free survival status when clinical characteristics, propensity score for type of surgery, medication use and year of surgery were entered as independent variables into a Cox regression model with stepwise backward removal.

	HR	95% CI	P-value
Endovascular treatment	0.54	0.30 – 0.98	0.04
Age (per year increase)	1.05	1.01 – 1.10	0.03
Stress inducible myocardial ischemia	2.60	1.45 – 4.67	0.001
Statin use	0.45	0.23 – 0.86	0.02
Heart rate < 70 bpm	0.53	0.29 – 0.97	0.04

on beta-blocker therapy. Importantly the mean heart rate prior to surgery was 65 beats per minute, indicating adequate beta-blocker dosing in most patients. However, 35 (28%) patients had inadequate heart rate control with a rate of > 70 beats per minute. Patients not on adequate beta-blocker therapy had a significantly worse overall survival (HR 0.26, 95% CI 0.13-0.54, table 2) and cardiac event free survival (HR 0.53, 95% CI 0.29-0.97, table 3). Importantly, there was no significant interaction between statin use and adequate beta-blocker dosing. Furthermore, as shown in table 2 patients who were on platelet aggregation inhibitors had a better overall survival than did patients who were not on antiplatelet therapy (HR 0.47; 95%CI 0.23 – 0.97, p=0.04).

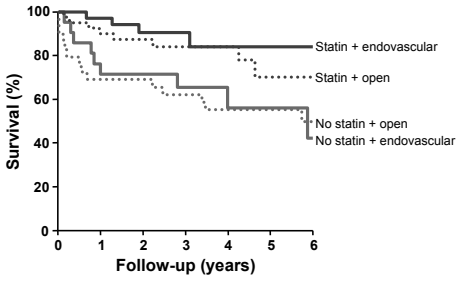

Figure 2a. Overall survival of patients undergoing endovascular or open AAA repair, divided into statin users or non-users.

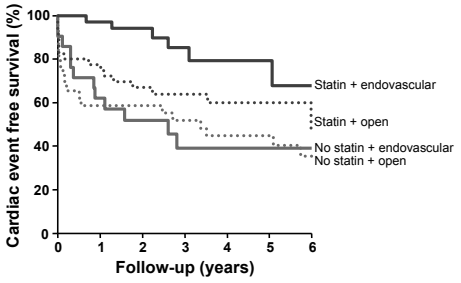

Figure 2b. Cardiac event free survival of patients undergoing endovascular or open AAA repair, divided into statin users or non-users.

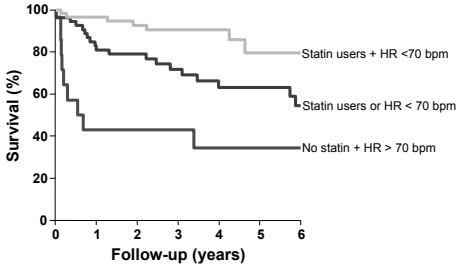

Figure 3. Overall survival of patients undergoing endovascular or open AAA repair, divided into patients not on adequate beta-blocker therapy and statin therapy, patients on either adequate beta-blocker therapy or statin therapy, and patients on both adequate beta-blocker therapy and statin therapy.

Discussion

This study showed that, despite a reduced incidence of adverse perioperative events, endovascular repair of elective infrarenal AAA in cardiac high-risk patients has a similar long-term survival, compared to patients undergoing open AAA repair. However, the perioperative cardiac benefit is sustained during a median follow-up of 3.3 years in this high risk population provided patients are on optimal medical therapy. Furthermore, aggressive medical treatment seems to have more impact on overall and cardiac event free survival than does the choice of AAA treatment modality.

Patients undergoing major noncardiac surgery are at significant risk of cardiovascular morbidity and mortality. The prognosis after vascular surgery is predominantly determined by the presence and extent of underlying coronary artery disease[8]. In the landmark study performed over 20 years ago Hertzer et al. found that only 8% of a group of 1000 patients undergoing noncardiac vascular surgery had normal coronary angiography results[9]. This high prevalence of underlying cardiac disease has later also been confirmed by functional tests such as dobutamine stress echocardiography[10]. Considering this high prevalence of coronary artery disease in vascular surgery patients it is hardly surprising that cardiac death after AAA repair accounts for approximately 40% and 65% of all 30-day and long-term mortality, respectively[11]. It might be argued that optimal medical therapy is warranted to sustain the initial cardiovascular survival benefit in patients who underwent endovascular AAA repair.

In previous studies perioperative and long-term statin therapy have been associated with improved outcome in patients undergoing AAA repair. Several recent retrospective studies have shown a beneficial effect of statins on perioperative cardiac outcome with adjusted hazard ratio's ranging from 0.20 to 0.62[12]. Importantly, Kertai et al also found the effect of statins to be independent of β-blocker use[13]. So far only one placebo-controlled, randomized trial has investigated the influence of statin use on perioperative cardiovascular complications. In a group of 100 patients treatment with 20 mg of atorvastatin was associated with a significant 3.1-fold (p=0.022) reduction in cardiovascular complications within 6 months after vascular surgery[14]. Kertai et al. described the influence of statin use on long-term outcome after open AAA repair in 570 patients with a median follow-up of 4.7 years[15]. It was shown that, in this group of unselected AAA patients, statin use was associated with a 2.5-fold reduction in the risk of all-cause mortality (HR 0.4; 95%CI 0.3-0.5) and a 3-fold reduction in the risk of cardiovascular mortality (HR 0.3; 95%CI 0.2-0.6). Interestingly,

the present study included only high-cardiac risk patients but the reduction in the risk for mortality and cardiovascular complications was similar to the reported figures of Kertai et al.

Importantly statin use is advocated in the recent TASC II document[16]. Patients with symptomatic or asymptomatic peripheral arterial disease should have their LDL lowered to less than 2.59 mmol/L. Patients with multiple vascular beds affected should be treated even more aggressively with a target LDL <1.81 mmol/l. It should be noted that the cardioprotective effect of statins might not only be by reducing LDL levels but statins might also exert their protective effects by so-called pleiotropic effects.

Another medical intervention that has been proven successful in high risk patients undergoing major vascular surgery is beta-blocker therapy. In the DECREASE I trial patients with preoperative stress inducible myocardial ischemia had a mere 10-fold reduction in perioperative cardiac events compared to patients who received placebo treatment[17]. Additionally, during a median follow-up of 22 months only 12% of patients on beta-blocker therapy experienced a cardiac event versus 32% of the patients who were not on beta-blocker therapy (p=0.025)[18]. This treatment effect was later confirmed in the DECREASE I registry patients in which 1299 survivors of vascular surgery were followed for a median duration of 23 months[19]. In multivariable analysis the 360 patients on beta-blockers had a significant risk reduction for cardiac events (HR 0.3; 95% CI 0.2-0.6; P<.001). However, recently some trials were published that questioned the potential benefit of beta-blockers in vascular surgery patients. In particular the POISE trial might have a negative impact on the willingness to prescribe beta-blockers to patients undergoing major vascular surgery. In the POISE trial the investigators found an increased risk for all-cause death in patients using beta-blockers, in particular driven by an excess in perioperative strokes[20]. There are several explanations for the findings in POISE related to dosing, duration of therapy, beta-blocker withdrawal and adequate titration[21]. When keeping this in mind, beta-blocker therapy still is safe and effective, in particular in patients at high cardiac risk as in the current study.

It should be noted that the patients in the current study were considered to be at high cardiac risk which does not imply that they were considered to be unfit for surgery in general. The term cardiac high risk in this study is based on our observations in the DECREASE I and II trials[22]. Patients with 3 or more risk factors as in the present study had a 4-fold and 28-fold increased risk for perioperative cardiac events as compared to patients at intermediate or low risk respectively. In terms of overall survival, patients in the current study had a worse outcome compared to patients in EVAR-1 and DREAM but a much better outcome compared to patients in EVAR-2[1,23,24]. Furthermore, the current study is not a randomized trial and as such has obvious limitations related to the nature of the study. However, keeping these limitations in mind, and using multivariable regression analysis with propensity scoring, the results of this study are in line with previous published studies. It reemphasizes the need for optimal medical therapy in high risk

patients scheduled for AAA repair irrespective of the choice of treatment modality. Physicians should not be pacified by the thought that endovascular treatment is a less invasive treatment, therefore being less stressful for the heart and hence requiring less aggressive medical therapy. On the contrary, in the end patients undergoing endovascular AAA repair could even benefit more from aggressive medical therapy as the initial benefit of endovascular repair might be sustained in these patients.

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Part 2

Risk factors

Chapter 4

Renal Insufficiency and Mortality in Patients with Known or Suspected Coronary Artery Disease

*J Am Soc Nephrol 2008;*19:158-63

Chapter 5

Temporary Worsening of Renal Function after Aortic Surgery is associated with Higher Long-term Mortality

Am J Kidney Dis 2007;50:219-28

Chapter 6

The Influence of Aging on the Prognostic Value of the Revised Cardiac Risk Index for Postoperative Cardiac Complications in Vascular Surgery Patients

Eur J Vasc Endovasc Surg 2007;34:632-8

Chapter 7

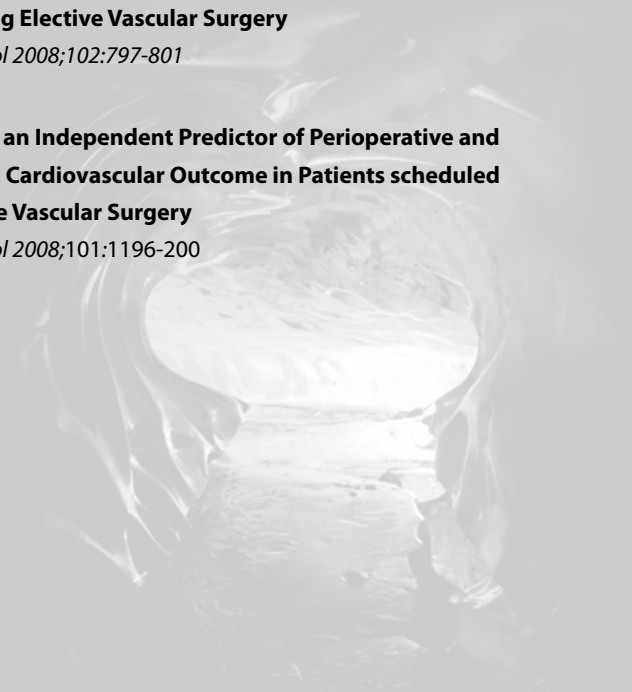
Association between Serum Uric Acid and Perioperative and Late Cardiovascular Outcome in Patients with Suspected or Definitive Coronary Artery Disease undergoing Elective Vascular Surgery

Am J Cardiol 2008;102:797-801

Chapter 8

Anemia as an Independent Predictor of Perioperative and Long-term Cardiovascular Outcome in Patients scheduled for Elective Vascular Surgery

*Am J Cardiol 2008;*101:1196-200



Chapter 4

Renal Insufficiency and Mortality in Patients with Known or Suspected Coronary Artery Disease

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Renal Insufficiency and Mortality in Patients with Known or Suspected Coronary Artery Disease

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ABSTRACT

It remains unclear whether mild renal dysfunction is associated with adverse cardiovascular outcome. We investigated whether estimated glomerular filtration rate (eGFR) was associated with mortality and cardiac death among 6447 patients with known or suspected coronary artery disease over a mean follow-up of 7 yr. Cumulative 5- and 10-yr survival rates decreased in a graded fashion from 88% and 70%, respectively, for those with normal renal function to 43% and 33% for those with eGFR <30 ml/min. Compared with patients with normal renal function, the multivariable adjusted hazard ratios for all-cause mortality among patients with mild, moderate, and severe renal impairment were 1.33 (95% confidence interval [CI], 1.21–1.48), 1.67 (95% CI, 1.44–1.93), and 3.38 (95% CI, 2.73–4.19), respectively. Similar relationships between cardiac death and decreasing renal function were found. In conclusion, renal function is a graded and independent predictor of long-term mortality in patients with known or suspected coronary artery disease. Intense treatment and close surveillance of these patients is encouraged.

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Chronic renal dysfunction has been shown to be an independent risk factor for cardiovascular mortality and morbidity in patients with coronary artery disease (CAD).[1–7] Population-based studies have shown discordant results regarding the association of mild renal dysfunction,[8–10] cardiovascular disease events, and all-cause mortality. Serum creatinine >1.5 mg/dl (133 μmol/L) was associated with a 70% increase in risk for all-cause mortality in participants who were followed for 5 yr in the Cardiovascular Health Study[11]; however, the Framingham Study did not show an association between baseline renal function and incident cardiovascular disease events.[12] Furthermore, the results of the National Health and Nutrition Examination Survey (NHANES) study did not support moderate renal insufficiency as an independent risk factor for cardiovascular disease in the general population.[13] It remains unclear whether mild renal dysfunction is related to adverse cardiovascular outcomes; therefore, the purpose of this study was to determine the association between mild renal dysfunction and mortality during long-term follow-up.

RESULTS

Mean age was 63 yr, and 26% were women (Table 1). Renal function was normal (GFR >90 ml/

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Table 1. Clinical characteristics stratified by the creatinine clearance (GFR)[a]

Variable	Total (n = 6447)	GFR				P for Trend
		Normal (>90 ml/min; n = 3587; 56%)	Mild (60 to 90 ml/min; n = 1895; 29%)	Moderate (30 to 60 ml/min; n = 720; 11%)	Severe (<30 ml/min; n = 245; 4%)	
Age (mean ± SD)	61 ± 11	60 ± 18	64 ± 10	61 ± 12	58 ± 13	<0.0001
Male (%)	67	66	75	69	73	0.1
History (%)						
MI	33	35	30	22	22	<0.0001
CABG	13	17	19	13	9	<0.0001
PCI	17	18	17	11	10	0.4
heart failure	15	13	16	26	31	<0.001
angina	24	27	23	13	7	0.2
Risk factors (%)						
diabetes	15	14	15	19	23	<0.005
hypertension	45	39	55	64	72	<0.0001
dyslipidemia	36	35	37	45	44	<0.001
smoking	28	30	25	21	23	<0.0001
Cardiac medication (%)						
β blockers	42	36	46	60	63	<0.0001
nitrates	17	16	19	23	28	<0.0001
calcium antagonists	30	30	29	27	34	0.3
diuretics	11	9	15	15	11	<0.0001
ACEI	13	10	21	18	22	<0.0001
digitalis	3	3	3	4	4	0.5
Serum creatinine (μmol/L; mean ± SD)	105 ± 16	71 ± 14	101 ± 14	152 ± 30	346 ± 81	<0.0001
GFR (ml/min; mean ± SD)	89 ± 16	122 ± 21	75 ± 8	47 ± 8	15 ± 8	<0.0001

[a]CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

min) in 3587 (56%) patients, whereas 720 (11%) had moderate impairment (GFR 30 to 60 ml/min) and 245 (4%) patients had severe impairment (GFR <30 ml/min). A mild degree of renal dysfunction (GFR 60 to 90 ml/min) was present in 1895 (29%) patients. The mean follow-up time was 7 yr (range 6 mo to 12 yr). During follow-up, 37,392 patient-years were collected. Death occurred in 2007 (31%) patients, 54% of which were cardiac. The GFR (mean ± SD 83.1 ± 16) ranged from 3.8 to 265.3 ml/min per 1.73 m^2.

After adjustment for all baseline clinical and demographic characteristics, the risk for all-cause mortality and cardiac death was significantly increased in all three groups of renal impairment compared with the group with normal renal function (Table 2). Patients with mild impaired renal

Table 2. HR for the incidence of all-cause mortality, cardiac death, and hard cardiac events (cardiac death or nonfatal MI) associated with renal function estimated by levels of the creatinine clearance (GFR).

Parameter	Events (%)	HR (95% CI)	
		Unadjusted	Adjusted[a]
All-cause mortality			
normal renal function	25	1.0	1.0
mild impaired renal function	36	1.49(1.35to1.65)	1.33(1.21to1.48)
moderate impaired renal function	45	2.07(1.80to2.37)	1.67(1.44to1.93)
severe impaired renal function	47	4.00(3.26to4.93)	3.38(2.73to4.19)
Cardiac death			
normal impaired renal function	13	1.0	1.0
mild impaired renal function	18	1.39(1.20to1.61)	1.46(1.25to1.71)
moderate impaired renal function	26	2.31(1.93to2.78)	2.31(1.90to2.81)
severe impaired renal function	40	6.28(5.00to7.89)	5.57(4.38to7.08)

[a]Adjusted for age, gender, previous MI, previous CABG, previous PCI, history of heart failure, history of typical angina, diabetes, hypertension, dyslipidemia, and current smoking.

function had 33% increased risk for mortality (hazard ratio [HR] 1.33; 95% confidence interval [CI] 1.21 to 1.48) as compared with patients with normal renal function. The risk for mortality was increased 1.5-fold with moderate renal insufficiency (HR 1.67; 95% CI 1.44 to 1.93) and threefold with severe renal impairment (HR 3.38; 95% CI 2.73 to 4.19). Although renal function is related to age, no significant interaction was found. Similar strong relations with cardiac death with decreasing renal function were found. The adjusted HR for GFR as a continuous variable for all-cause mortality or cardiac death were 0.82 (95% CI 0.80 to 0.84) and 0.85 (95% CI 0.82 to 0.88), respectively.

Age-adjusted cumulative Kaplan-Meier survival curves for all-cause mortality according to renal function were 88, 83, 68, and 43% for normal, mild, moderate, and severe, respectively, at 5 yr and 70, 58, 51, and 33%, respectively, at 10 yr ($P < 0.0001$; Figure 1). Similar relations with cardiac death with decreasing renal function were found.

DISCUSSION

The main finding of this study is that mild renal dysfunction defined as a GFR of 60 to 90 ml/min is a graded and independent predictor of long-term outcome of mortality and hard cardiac events. Mild or moderate impairment of renal function has also been shown to be associated with worse prognosis in patients with congestive heart failure,[14] those with myocardial infarction (MI),[15] and those in a normal population[16]; however, why even a mild renal dysfunction is related with worse prognosis is not known. One possibility might be that renal dysfunction may be a pathogenetic factor in causing the progression of cardiac deterioration. Furthermore, cardiac pump failure may lead to diminished renal function, and thus early renal dysfunction may be a marker of increased cardiac function; however, we still observed an independent association between renal function and all-cause mortality and cardiac death after adjusting for cardiovascular risk factors. Therefore, renal impairment itself might initiate and accelerate adverse cardiac events.

Usually, kidney disease is defined as GFR <60 ml/min per 1.73 m^2, a cutoff value recently proposed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Advisory Board to identify patients who have moderate renal impairment[17] and American Heart Association's Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention.[5]The results of this study show an increased risk for mortality and hard cardiac events, starting at earlier stages of renal dysfunction than commonly thought. This mildly decreased renal dysfunction, one quarter of this study, represent patients without symptoms and signs of renal dysfunction. As patients get older, mild degrees of renal insufficiency will become progressively more important because renal function declines with elderly age; therefore, early recognition of renal dysfunction may be a key target to prevent worsening renal function.

Treatment of patients with impaired renal function and CAD is problematic. Evidence of medical therapy both in trials and in clinical practice is limited and frequently sub-

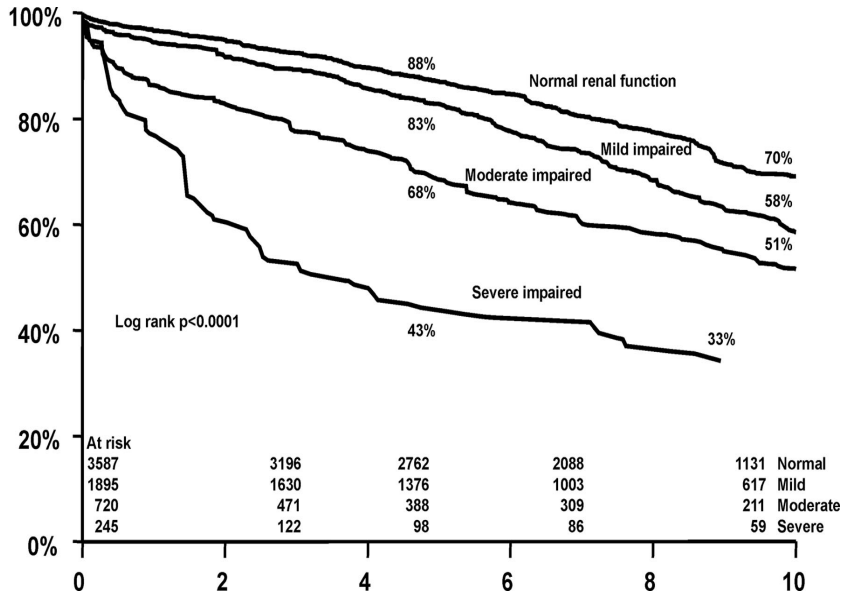

Figure 1. Age-adjusted all-cause mortality in 6447 patients with known or suspected CAD according to the GFR.

optimal. Acetylsalicylic acid (ASA)[18] and β blockers[19] were shown to reduce mortality among patients with CAD and may also reduce mortality and morbidity in asymptomatic patients who are at increased risk for CAD. Also evidence continues to accrue that angiotensin-converting enzyme inhibitors ACEI reduce vascular morbidity and mortality.[20–22] Furthermore, a systematic review demonstrated in patients who had renal insufficiency and were treated with ACEI a strong association between creatinine levels and slowing of the renal disease progression in the long term.[8] The authors concluded that ACEI therapy should be offered to all patients with left ventricular systolic dysfunction and renal insufficiency, and also the sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommends use of ACEI for control of hypertension in patients with renal insufficiency.[9] The use of statins has also been shown to reduce mortality. Although there might be a slight increase of myositis, statins are generally considered safe for use in patients with renal insufficiency[9]; however, these therapies are still underused among patients with renal impairment. Although there may be exceptions, therapies that have been beneficial at normal levels of kidney function are increasingly being shown also to be beneficial at lower levels of kidney function[23]; therefore, intensive medical treatment, especially in patients with only mild renal dysfunction and without any signs of renal disease, including β blockers, ACEI, and statins, should be considered.

Although data were prospectively collected, this analysis is retrospective. Only patients for whom a single baseline creatinine value was available were included in this study, which may have introduced a selection bias in the analysis. Thus, this study cohort was per definition a preselected one, already having a higher risk for death earlier than an average population. This includes the renal reference group; therefore, all conclusions regarding the outcome of the four GFR groups must take this into account. Another limitation is the lack of data on albuminuria, which may contribute to the cardiovascular effects of renal dysfunction.[24]

This study shows that renal function is a graded and independent predictor of long-term adverse cardiac outcome. In particularly, even mild renal dysfunction is an important predictor of all-cause mortality and cardiac death. Intense treatment and close surveillance of these patients is warranted.

CONCISE METHODS

Study Design and Patient Selection

We studied a cohort of 6447 patients who had known or suspected CAD, had had baseline serum creatinine determined, and were referred to the outpatient clinics of the Erasmus University Medical Center between January 1993 and January 2005. Patients who were included in our analysis were intermediate- to high-risk patients who had atherosclerotic disease and were referred for cardiac evaluation, management of underlying risk factors, or follow-up of their known ischemic heart condition.

Patients who presented at the time of examination with a history of angina, previous MI, or myocardial revascularization (*i.e.*, previous percutaneous coronary intervention and/or coronary artery bypass graft) were considered as CAD patients. Patients with atypical chest pain, dyspnea, atypical electrocardiogram abnormalities (ST-T changes without Q-waves), or multiple risk factors for coronary disease were considered to have suspected CAD. Patients who were on hemodialysis therapy or had undergone a renal transplant were excluded. The study protocol was approved by the local medical ethics committee and was conducted in accordance with the Declaration of Helsinki.

Renal Function Assessment

Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method.[25] GFR was estimated by using the Modification of Diet in Renal Disease (MDRD) equation[26]: GFR (ml/min per 1.73 m^2 body surface area) = $175 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female).

Clinical Follow-up and End Points

In-hospital clinical information for patients was retrieved from an electronic database that is maintained in our hospital and by review of hospital records. Survival status was obtained from the municipal civil registries. Follow-up was performed by mailed questionnaires and telephone interviews. Patients who were lost to follow-up were considered at risk until the date of last contact, at which point they were censored. When needed, referring physicians and institutions were contacted for additional information. Events and cause of death were verified by contacting the patient's primary physician and reviewing medical records. The follow-up was complete in 98.3%. The end points considered were all-cause mortality and cardiac death. Death was considered cardiac when it was caused by acute MI, significant arrhythmias, or refractory heart failure. Sudden unexpected death occurring without another explanation was included as cardiac death.

Statistical Analyses

Continuous variables are presented as the mean ± SD or as a percentage. Patients were subsequently categorized as having normal renal function (GFR >90 ml/min), mild renal impairment (GFR 60 to 90 ml/min), moderate impairment (GFR 30 to 60 ml/min), and severe impairment (GFR <30 ml/min).[5] Tests of trend were performed using the four GFR groups as a categorical measurement. Continuous variables are presented as the mean ± SD or as a percentage. Cox proportional hazard regression analysis was used to investigate the independent effect of renal function on the outcome events. Analyses were conducted for crude values and adjusted for age; gender; previous MI; previous percutaneous coronary intervention; previous coronary artery bypass graft surgery; history of typical of angina; history of heart failure (defined according the New York Heart Association classification); diabetes (defined as the presence of a fasting blood glucose ≥126 mg/dl or

requirement for insulin or oral hypoglycemic agents); hypercholesterolemia (defined as total cholesterol of >200 mg/dl); hypertension (defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication); smoking; and the use of statins, β blockers, nitrates, calcium antagonists, ACEI, digitalis, and diuretics. The association between GFR and outcome events was also assessed with GFR as a continuous variable. To investigate the relation between GFR and age, we performed a test for interaction in the Cox regression. Using Cox regression, age-adjusted Kaplan-Meier survival curves of the four GFR groups in relation to all-cause mortality were constructed and examined using the log-rank test.

DISCLOSURES

None.

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Chapter 5

Temporary Worsening of Renal Function after Aortic Surgery is associated with Higher Long-term Mortality

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Temporary Worsening of Renal Function After Aortic Surgery Is Associated With Higher Long-Term Mortality

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Background: Little is known about acute changes in renal function in the postoperative period and the outcome of patients undergoing major vascular surgery. Specifically, data are scarce for patients in whom renal function temporarily decreases and returns to baseline at 3 days after surgery.

Study Design: Retrospective cohort study.

Setting & Participants: 1,324 patients who underwent elective open abdominal aortic aneurysm surgery in a single center.

Predictor: Renal function (creatinine clearance was measured preoperatively and on days 1, 2, and 3 after surgery. Patients were divided into 3 groups: group 1, improved or unchanged (change in creatinine clearance, ±10% of function compared with baseline); group 2, temporary worsening (worsening > 10% at day 1 or 2, then complete recovery within 10% of baseline at day 3); and group 3, persistent worsening (>10% decrease compared with baseline).

Outcomes & Measurements: All-cause mortality.

Results: 30-day mortality rates were 1.3%, 5.0%, and 12.6% in groups 1 to 3, respectively. Adjusted for baseline characteristics and postoperative complications, 30-day mortality was the greatest in patients with persistent worsening of renal function (hazard ratio [HR], 7.3; 95% confidence interval [CI], 2.7 to 19.8), followed by those with temporary worsening (HR, 3.7; 95% CI, 1.4 to 9.9). During 6.0 ± 3.4 years of follow-up, 348 patients (36.5%) died. Risk of late mortality was 1.7 (95% CI, 1.3 to 2.3) in the persistent-worsening group followed by those with temporary worsening (HR, 1.5; 95% CI, 1.2 to 1.4).

Limitations: No steady state was achieved to assess renal function.

Conclusion: Although renal function may recover completely after aortic surgery, temporary worsening of renal function was associated with greater long-term mortality.

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INDEX WORDS: Renal dysfunction; survival; aortic surgery; cardiovascular disease.

Atherosclerosis is a generalized disease with symptoms ranging from angina pectoris, myocardial infarction, and stroke to claudication. The major cause of abdominal aortic aneurysm (AAA) is atherosclerosis, frequently associated with impaired organ function, a true determinant of long-term survival after surgery.[1] Renal dysfunction with or without symptoms often is present and is considered to be a marker for the presence and severity of underlying vascular disease.[2-4] Postoperative decreased renal function is a well-known feared complication after major vascular surgery associated with increased long-term mortality.[5,6] The incidence rate varies from 2% to 45% (ranging from mild renal dysfunction to long-term hemodialysis therapy).[6-9] The pathogenesis of postoperative decreased renal function is multifactorial.[10] Poor baseline renal function, perioperative blood loss, use of nephrotoxic agents, suprarenal aortic cross-clamping time, high intra-abdominal pressure, systemic or regional hypoperfusion, temporary hypotension, and ligation of renal veins during surgery all negatively affect postoperative renal

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function. All these factors combined can cause acute renal failure with a high periprocedural mortality rate of 50% to 80%.[11-13] In patients with abnormal kidney function at baseline, postoperative chronic renal dysfunction requiring renal replacement therapy is common. To prevent this devastating complication, it is recommended to take every possible measure to minimize the risk.[5,11,14] Importantly, even subtle changes in postoperative renal function might identify patients at risk.

However, little is known about acute changes in renal function in the postoperative period and their short- and long-term outcomes in patients undergoing major vascular surgery. Specifically, data are scarce for patients in whom renal function temporarily decreases and returns to baseline value within 3 days after surgery; ie, temporary worsening of renal function. Hence, the purpose of this observational study is to describe the predictive value of postoperative renal function changes, especially for patients with temporary worsening of renal function, in patients undergoing AAA surgery.

METHODS

Study Design and Patient Selection

From January 1995 to June 2006, a total of 1,324 patients underwent open infrarenal AAA repair at the Erasmus Medical Centre, Rotterdam, The Netherlands, and were entered into a computerized database. Exclusion criteria were baseline creatinine clearance (CrCl) less than 30 mL/min (<0.5 mL/s), long-term hemodialysis therapy, death within 3 days after surgery, endovascular surgery, and requirement of additional renal revascularization.

Renal Function Assessment

Serum creatinine was assessed by means of a nonkinetic alkaline picrate (Jaffé) method.[15] Renal function, or CrCl, was computed using the Cockcroft-Gault formula from serum creatinine level, age, sex, and body weight. The following equation was used[16]:

$$\text{CrCl (mL/min/1.73 m}^2) = (140 - \text{age [years]}) * (\text{body weight [kg]})/72 * \text{serum creatinine (mg/dL)} \times 0.85 \text{ in women}$$

This equation gives a more accurate assessment of renal function than serum creatinine level alone.[17-19]

Renal Function Groups

Serum creatinine (in milligrams per deciliter) was measured preoperatively at baseline and postoperatively at days 1, 2, and 3. Patients were divided into 3 groups based on changes in estimated CrCl from baseline to day 1 or 2 and from day 1 or 2 to day 3: group 1, improved or unchanged renal function (change in CrCl, −10% to +10% function compared with baseline); group 2, temporary worsening in renal function (temporarily worsening >10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3); and group 3, persistent worsening in renal function (>10% decrease compared with baseline). Baseline CrCl is defined as the value recorded just before surgery. When data were not available, measurements in the days preceding surgery were used.

Clinical Follow-Up and End Points

Perioperative clinical information was retrieved from an electronic database of patients maintained in our hospital. On occasion, missing data were abstracted retrospectively by reviewing patients' medical records. From the municipal civil registries, we obtained survival status. Follow-up was complete in 98.2%.

The primary outcome is overall 30-day and long-term all-cause mortality after AAA surgery, verified by contacting the patient's primary physician and reviewing medical records. Mortality at 30 days is defined as all deaths occurring during the postoperative in-hospital stay or after hospital discharge, but within the first 30 days after surgery. Long-term mortality is defined as death occurring in the first 10 years after surgery. Causes of death were grouped into 3 different categories: (1) cerebrocardiovascular death [CCVD], (2) non-CCVD, and (3) unknown cause. CCVD is defined as any death with a cerebrocardiovascular complication as the primary or secondary cause and includes deaths after myocardial infarction, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular accident or transient ischemic attack), surgery-related fatal bleeding complications, and others. Sudden unexpected death is classified as a CCVD. Non-CCVD is defined as any death with a principal noncerebrocardiovascular cause, including infection, malignancy, respiratory insufficiency, and others. Cause of death was ascertained by reviewing medical records, the computerized hospital database, and autopsy reports or contacting the referring physician or general practitioner.

The secondary outcome is short-term complications (perioperative and during postoperative in-hospital stay within 30 days or after hospital discharge, but within the first 30 days after surgery). The complications noted are infection, stroke, coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention), heart failure, limb amputation, limb necrosis, hemorrhage (vascular bleeding leading to a hypotensive state [systolic blood pressure < 100 mm Hg] and requirement of blood transfusions), and new postoperative dialysis therapy (temporary or persistent).

Statistical Analyses

Continuous data are described as mean ± SD or median ± SD, and dichotomous data are described as percentage frequencies. Analysis of variance with Bonferroni test was used for continuous variables, and chi-square test was used for categorical variables. The probability of all-cause mortality was calculated by means of the Kaplan-Meier method, and the resulting curves were compared using log-rank test. We performed multivariate Cox regression analyses to investigate the indepen-

dent value of CrCl for perioperative and long-term mortality after adjustment for age, sex, cardiovascular risk factors (eg, hypertension [defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of cardiovascular medication], diabetes mellitus [fasting blood glucose ≥ 140 mg/dL (≥7.8 mmol/L) or requirement for insulin or oral hypoglycemic agents], smoking status, hypercholesterolemia [total cholesterol > 200 mg/dL (>5.2 mmol/L)], chronic obstructive pulmonary disease [according to symptoms and pulmonary function test results; ie, forced expiratory volume in 1 second < 70% of maximal age and sex predictive value], body mass index, and medication use [statins, diuretics, angiotensin-converting enzyme inhibitors, calcium antagonists, nitrates, β-blockers, digitalis, and aspirin]), presence of ischemic heart disease (prior myocardial infarction, prior coronary revascularization, and angina pectoris), heart failure (defined according to the New York Heart Association classification), baseline CrCl, and short-term complications (infection, stroke, coronary intervention, heart failure, amputation, limb necrosis, hemorrhage, and dialysis requirement). All prescription and over-the-counter medications were noted on the day of admission. Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). *P* less than 0.05 is considered significant. Proportional hazards assumptions were tested by constructing interaction terms between the variables and time to each end point. Cox regression analyses showed no statistically significant interaction with time (each $P > 0.05$). All computations were performed using SPSS software, version 12.0.1 (SPSS Inc, Chicago, IL) running under Windows 2000 Professional (Microsoft Corp, Redmond, WA).

RESULTS

Patient Characteristics

A total of 1,324 patients underwent AAA surgery. After exclusion of patients with a preoperative CrCl less than 30 mL/min (<0.5 mL/s; n = 86), those on long-term hemodialysis therapy (n = 8), patients who underwent endovascular surgery (n = 236), patients who died within 3 days after surgery (n = 31), and those who required additional renal revascularization (n = 11), 952 patients were included in the analysis. For 28 patients (2.9%), missing data were abstracted by reviewing patients' medical records.

Mean age was 66 ± 14 years, and 80% were men. Improved or unchanged renal function, temporary worsening of renal function, and persistent worsening of renal function were present in 56%, 27%, and 17% of the patient population, respectively. In the entire population, a slight decrease in CrCl was observed within 3 days after surgery (mean CrCl on day 1 or 2 after surgery, 76 ± 40 mL/min [1.27 ± 0.67 mL/s]; on day 3, 77 ± 44 mL/min [1.28 ± 0.73 mL/s] compared with a preoperative CrCl of 81 ± 34 mL/min [1.35 ± 0.57 mL/s]; Fig 1). Mean changes in CrCl on day 1 or 2 and day 3 for the groups with temporary and persistent worsening of renal function were −30% and −7% and −35% and −46% compared with baseline values, respectively (Fig 2). Baseline characteristics in the 3 groups were similar for renal function and cerebrocardiovascular risk factors (Table 1). Only a greater incidence of hypertension was observed in the groups with temporary and persistent worsening renal function. A significant association between total perioperative blood loss (milliliters) and suprarenal aortic cross-clamping time (minutes) was found with worsening of renal function ($P < 0.001$). No significant difference in aortic cross-clamping time between the groups with temporary and persistent worsening of renal function was observed ($P = 0.3$).

Short-Term Outcome

Overall 30-day (mean, 29 ± 3.2 days) mortality rates were 1.3%, 5.0%, and 12.6% in the 3 renal function groups, respectively. Survival was significantly worse in the groups with temporary and persistent worsening renal function compared with the group with improved or unchanged renal function ($P < 0.001$), as shown by means of Kaplan-Meier (Fig 3). Both unadjusted and adjusted regression analyses showed a significant difference in risk of 30-day mortality (Table 2). HRs of the groups with temporary and persistent worsening of renal function were compared with those of the group with improved or unchanged renal function. Unadjusted HRs were 4.0 (95% CI, 1.6 to 10.2) followed by 10.9 (95% CI, 4.5 to 26.2). After adjustment, HRs were 3.7 (95% CI, 1.4 to 9.9) and 7.3 (95% CI, 2.7 to 19.8), respectively. The adjusted HR for baseline CrCl was 0.975 (95% CI, 0.958 to 0.993; $P = 0.007$) per 1-mL/min (0.02-mL/s) increase in CrCl. Other important adjusted risk factors were hemorrhage (HR, 3.3; 95% CI, 1.3 to 8.3), chronic obstructive pulmonary disease (HR, 3.0; 95% CI, 1.4 to 6.4), myocardial infarction (HR, 7.5; 95% CI, 2.1 to 27.1), and dialysis therapy (HR, 6.3; 95% CI, 1.9 to 21.3). β-Blocker use was associated with improved short-term outcome (HR, 0.3; 95% CI, 0.1 to 0.9).

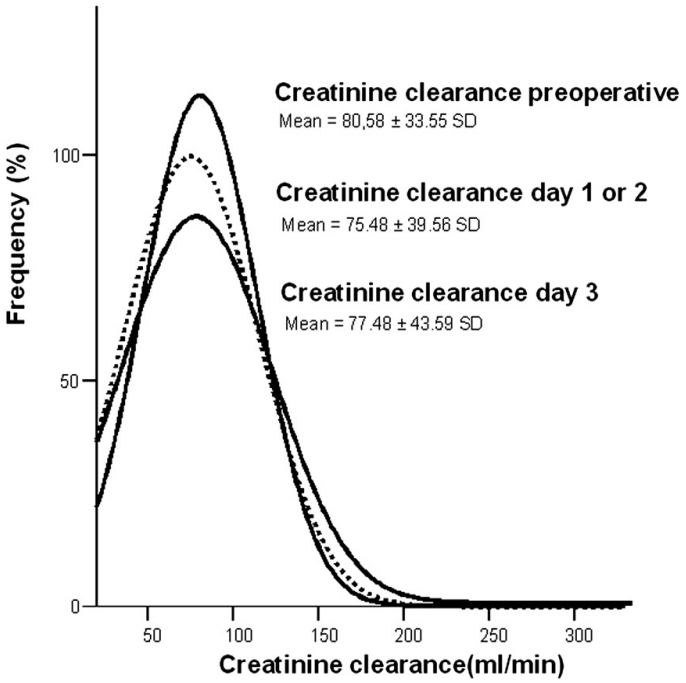

Figure 1. Distribution of observed changes in estimated creatinine clearance (CrCl; mL/min) in all patients (normal curves). To convert CrCl in mL/min to mL/s, multiply by 0.01667.

Patients with persistent worsening of renal function more frequently had hemorrhages ($P < 0.001$) and required postoperative initiation of dialysis therapy compared with the other 2 renal function groups (Table 3).

Long-Term Outcome

A total of 348 patients (36.5%) died during the 10-year follow-up (mean, 6.0 ± 3.4 years). In the group with improved or unchanged renal function, 30.8% of patients died, followed by 43.4% and

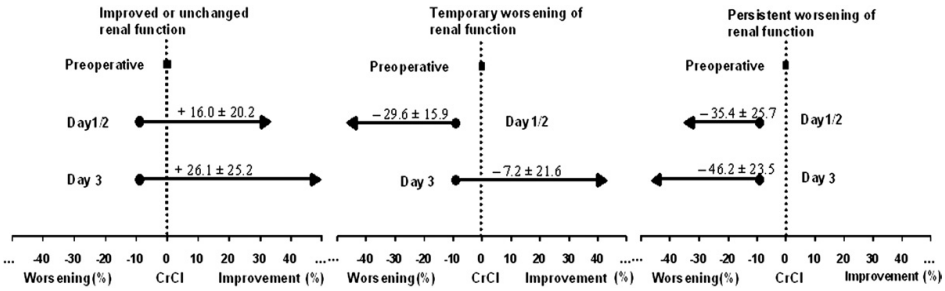

Figure 2. Subdivision of renal function groups based on creatinine clearance (CrCl) response, with mean changes (Δ) in CrCl (% ± SD). Improved or unchanged renal function, ΔCrCl of −10% to +10% function compared with baseline; temporary worsening of renal function, temporarily worsening greater than 10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3; and persistent worsening of renal function, greater than 10% decrease compared with baseline.

Table 1. Baseline Characteristics of the Abdominal Aortic Aneurysm Group

	All Patients (952; 100%)	Improved or Unchanged Renal Function (535; 56%)	Temporary Worsening of Renal Function (258; 27%)	Persistent Worsening of Renal Function (159; 17%)	*P*
Demographics					
Mean age (y)	66 ± 14	65 ± 14	67 ± 14	66 ± 14	0.1
Men (%)	79	80	76	83	0.2
Cardiovascular risk factor (%)					
Hypertension	41	36	47	50	<0.001
Diabetes mellitus	6	6	5	9	0.3
Current smoker	31	30	33	31	0.8
Increased cholesterol	23	23	28	16	0.1
Chronic obstructive pulmonary disease	21	19	23	26	0.1
Body mass index (kg/m^2)	25 ± 4	25 ± 4	25 ± 4	26 ± 3	0.1
Baseline serum creatinine (mg/dL)	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	1.1 ± 0.3	0.5
Baseline creatinine clearance (mL/min)	81 ± 34	80 ± 30	80 ± 36	83 ± 41	0.7
Disease history (%)					
Previous myocardial infarction	30	28	31	37	0.3
Previous coronary artery bypass grafting	14	14	16	12	0.5
Previous percutaneous coronary intervention	6	6	7	5	0.8
Previous heart failure	5	5	4	6	0.6
Angina	15	15	12	16	0.6
Medication use (%)					
Statins	23	22	27	23	0.3
Diuretics	12	10	14	13	0.2
Angiotensin-converting enzyme inhibitors	24	22	25	29	0.2
Calcium antagonists	30	27	35	33	0.07
Nitrates	15	16	13	17	0.4
β-Blockers	34	34	33	37	0.7
Digitalis	3	2	4	3	0.6
Aspirin	21	22	22	18	0.6
Surgery parameters					
Median total blood loss (mL)	2,250 ± 2,720	2,000 ± 1,946	2,500 ± 2,449	3,200 ± 4,356	<0.001
Median suprarenal aortic cross-clamping time (min)	51 ± 29	40 ± 21	54 ± 28	63 ± 30	<0.001

Note: Values expressed as mean or median ± SD or percent. Creatinine clearance (mL/min/1.73 m^2) estimated by means of the Cockcroft-Gault formula. Improved or unchanged renal function, change in creatinine clearance from −10% to +10% function compared with baseline; temporary worsening of renal function, temporarily worsening greater than 10% at day 1 or 2, then complete recovery within 10% of baseline at day 3; and persistent worsening of renal function, greater than 10% decrease compared with baseline. To convert serum creatinine in mg/dL to umol/L, multiply by 88.4; creatinine clearance in mL/min to mL/s, multiply by 0.01667.

46.5% in the groups with temporary and persistent worsening of renal function. During long-term follow-up, patients with temporary worsening of renal function had the same long-term prognosis as patients with persistent worsening of renal function (log rank $P = 0.18$; Fig 4).

In adjusted analysis, significant risk factors for long-term all-cause mortality included age (HR, 1.02; 95% CI, 1.006 to 1.03 per 1-year increase in age), chronic obstructive pulmonary disease (HR, 1.8; 95% CI, 1.4 to 2.3), baseline CrCl (HR, 0.992; 95% CI, 0.988 to 0.997 per 1 mL/min [0.02 mL/s] increase in CrCl), stroke (HR, 1.5; 95% CI, 1.1 to 2.0), dialysis therapy (HR, 2.6; 95% CI, 1.5 to 4.6), and hemorrhage (HR, 1.5; 95% CI, 1.01 to 2.2). Statin use was associated with improved long-term outcome (HR, 0.69; 95% CI, 0.5 to 0.96).

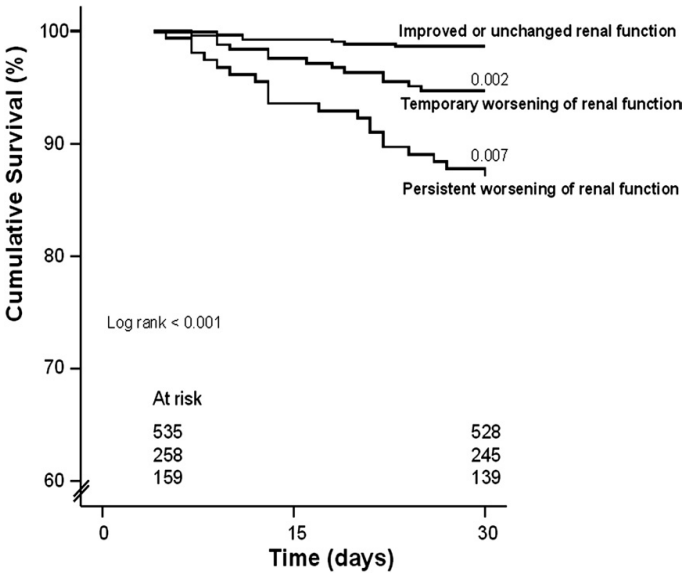

Figure 3. All-cause short-term mortality in 952 patients who underwent abdominal aortic aneurysm surgery according to 3 renal function groups: improved or unchanged renal function, change (Δ) in CrCl of −10% to +10% function compared with baseline; temporary worsening of renal function, temporarily worsening greater than 10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3; and persistent worsening of renal function, greater than 10% decrease compared with baseline.

Cerebrocardiovascular events (157 events; 45%) were the major cause of death and included myocardial infarction (19%), congestive heart failure (9%), arrhythmia (2%), stroke (7%), fatal bleeding (5%), and others (3%). Noncerebrocardiovascular events (115 events;

Table 2. Unadjusted and Adjusted Predictors of Estimate Risk of Short- and Long-Term Mortality in the Abdominal Aortic Aneurysm Group

	Unadjusted Hazard Ratios (95% confidence interval)	Adjusted* Hazard Ratios (95% confidence interval)
30-Day outcome		
Improved or unchanged renal function	1.0	1.0
Temporary worsening of renal function	4.0 (1.6-10.2)	3.7 (1.4-9.9)
Persistent worsening of renal function	10.9 (4.5-26.2)	7.3 (2.7-19.8)
10-Year outcome		
Improved or unchanged renal function	1.0	1.0
Temporary worsening of renal function	1.7 (1.3-2.1)	1.5 (1.2-1.9)
Persistent worsening of renal function	2.1 (1.6-2.7)	1.7 (1.3-2.3)

Note: N = 952. Improved or unchanged renal function indicates change in creatinine clearance from −10% to +10% function compared with baseline value; temporary worsening of renal function, temporarily worsening greater than 10% at day 1 or 2, then complete recovery within 10% of baseline at day 3; and persistent worsening of renal function, greater than 10% decrease compared with baseline.

*Adjusted for age, sex, hypertension, diabetes mellitus, smoking, hypercholesterolemia, chronic obstructive pulmonary disease, body mass index, prior myocardial infarction, prior coronary revascularization (percutaneous coronary intervention and coronary artery bypass grafting), angina pectoris, heart failure, baseline creatinine clearance, medication (statins, diuretics, angiotensin-converting enzyme inhibitors, calcium antagonists, nitrates, β-blockers, digitalis, and aspirin), and short-term complications (infection, stroke, coronary intervention, heart failure, amputation, limb necrosis, hemorrhage, and dialysis therapy).

Table 3. Short-Term Complications After Abdominal Aortic Aneurysm Surgery

	All Patients (952; 100%)	Improved or Unchanged Renal Function (535; 56%)	Temporary Worsening of Renal Function (258; 27%)	Persistent Worsening of Renal Function (159; 17%)	*P*
Complications					
Infection	177 (19)	88 (16)	57 (22)	32 (20)	0.1
Wound	25 (3)	14 (3)	8 (3)	3 (2)	0.7
Pneumonia	91 (10)	39 (7)	32 (14)	20 (13)	0.02
Sepsis	11 (1)	4 (1)	2 (1)	5 (3)	0.05
Urinary tract infection	32 (3)	22 (4)	10 (4)	0 (0)	0.03
Rest	18 (2)	9 (2)	5 (2)	4 (3)	0.8
Stroke	21 (2)	8 (2)	6 (2)	7 (4)	0.1
Coronary intervention	13 (1)	5 (<1)	3 (1)	5 (3)	0.2
Heart failure	20 (2)	9 (2)	5 (2)	6 (4)	0.3
Amputation	12 (1)	4 (1)	3 (1)	5 (3)	0.06
Limb necrosis	23 (2)	10 (2)	7 (3)	6 (3)	0.5
Hemorrhage	60 (6)	24 (4)	14 (5)	22 (14)	<0.001
Dialysis*	26 (3)	1 (<1)	3 (1)	22 (14)	<0.001
Temporary	23 (2)	1 (<1)	3 (1)	19 (12)	<0.001
Persistent	3 (1)	0 (0)	0 (0)	3 (2)	0.001

Note: Values expressed as number (percent). Coronary intervention indicates coronary artery bypass grafting or percutaneous coronary intervention; hemorrhage, vascular bleeding leading to a hypotensive state (systolic pressure < 100 mm Hg) and requirement of packet cells; and dialysis, requirement of new postoperative temporary or persistent dialysis. Improved or unchanged renal function indicates change in creatinine clearance from −10% to +10% function compared with baseline value; temporary worsening of renal function, temporarily worsening greater than 10% at day 1 or 2, then complete recovery within 10% of baseline at day 3; and persistent worsening of renal function, greater than 10% decrease compared with baseline.

*Excluding 8 patients on long-term hemodialysis.

33%) included infection (7%), malignancy (9%), respiratory insufficiency (7%), and others (10%). An unknown cause of death was determined in only 76 patients (22%).

DISCUSSION

The main finding of our study is that renal function changes within the first 3 days after AAA surgery are a predictor for perioperative and long-term mortality. Although renal function may recover completely after aortic surgery with a more or less favorable 30-day outcome, patients are at high risk of long-term mortality, whereas patients with persistent worsening of renal function are most likely to have poor 30-day and long-term prognoses.

The groups with temporary and persistent worsening renal function had a greater incidence of hypertension compared with the improved or unchanged group. Also, total blood loss and suprarenal aortic cross-clamping time as postoperative complications were significantly greater. All these risk factors combined indicate that these 2 groups are predisposed to a greater risk of postoperative renal failure and thereby mortality.[11,20-22]

As mentioned, the cause of developing postoperative renal failure after aortic surgery is multifactorial. Renal function before surgery, total blood loss, use of nephrotoxic agents, preexisting atherosclerosis, hypertension, suprarenal aortic cross-clamping time, and ligation of renal veins during the operation all negatively affect postoperative renal function and, in turn, lead to death.[20,23-25]

Suprarenal aortic cross-clamping is required in approximately 15% of operations for infrarenal vascular disease, resulting in renal hypoxia reperfusion injury, which is an inevitable consequence. When limb ischemia also is present, muscle necrosis and myoglobinuria also might be present, all negatively affecting renal function.[26] A safe renal ischemia time was determined to be 45 to 50 minutes.[20,27] Median cross-clamping times of the groups with temporary and persistent worsening renal function were higher than the described cutoff value; however, there was no significant difference in clamping times

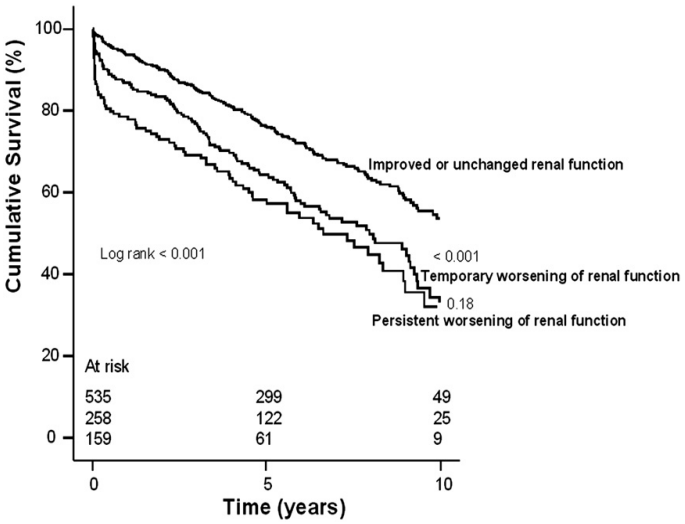

Figure 4. All-cause long-term mortality in 952 patients who underwent abdominal aortic aneurysm surgery according to 3 renal function groups: improved or unchanged renal function, change (Δ) in CrCl of −10% to +10% function compared with baseline; temporary worsening of renal function, temporarily worsening greater than 10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3; and persistent worsening of renal function, greater than 10% decrease compared with baseline.

between these groups. Intraoperative blood loss exceeding 2,000 mL also was found to be an independent predictor of 30-day mortality in patients with a ruptured AAA.[22] Because the groups with temporary and persistent worsening of renal function had total blood loss greater than 2,000 mL, they were at high risk of increased 30-day mortality.

Lassnigg et al[21] suggested that patients who survived the first 30 days after cardiothoracic surgery and had sufficient recovery of renal function regained the same long-term prognosis as patients without temporary impaired renal function. In our study, patients with temporary renal function changes had worse 30-day survival than patients without renal function changes (log rank $P = 0.002$), but they never regained the same long-term (10-year) prognosis (log rank $P < 0.001$). The trend is that patients with temporary renal function changes had an even worse long-term outcome than those with persistent worsening of renal function. High-risk patients with persistent worsening of renal function died mainly within the first 30 days; thus, the diluting effect of renal function changes was less for the long-term mortality outcome. The risk of developing severe nonrenal complications that might lead to death increased further more by the renal injury itself[8] and can be explained by the extent and pattern of preexisting comorbidities.

The effect of acute changes (within the first 3 days) in renal function after AAA surgery also was investigated by Ellenberger et al.[6] They reported the greatest mortality rate within 30 days in patients with a serum creatinine level greater than 0.5 mg/dL (>44 μmol/L) compared with baseline, again indicating that renal function changes within 3 days after surgery were a strong predictor of perioperative mortality. However, long-term mortality was not evaluated and serum creatinine level was used as a marker for renal function. Although serum creatinine level is considered a practical and reasonable approach to use for evaluation of renal dysfunction, we chose CrCl as a more accurate measure of renal function, as recommended by the recent National Kidney Foundation guidelines.[28]

In our cohort, we found a remarkably low incidence of diabetes mellitus (6%). Earlier cohorts with AAA repair reported an incidence of 12% to 13%.[29,30] Diagnosis of diabetes mellitus was based on requirement for insulin therapy or

hypoglycemic agents or a fasting blood glucose level of 140 mg/dL or greater (≥7.8 mmol/L). However, fasting glucose concentrations were not assessed routinely and may have caused underdiagnosis of diabetes.

A major limitation of our study is the retrospective analysis of data. In addition, not all perioperative data (duration of aortic cross-clamping, transfusion requirements, need for additional surgical interventions, time to extubation, admission in intensive care unit, and use of medication) were available to implement these parameters in our analysis. Furthermore, changes in perioperative management have evolved markedly over time and were not taken into account in our analysis. These include multiple factors ranging from preoperative management, such as drug therapy and anesthesiological and surgical techniques, to intensive postsurgical care management.

It is well established that a key impediment in the field of acute renal failure is a lack of uniform definition of changes of kidney function. Current definitions that rely on changes in serum creatinine levels and urine output are neither sensitive nor specific. In a recent publication,[31] the investigators were able to describe 19 different definitions of acute renal failure (ranging from −20% to −100% changes in serum creatinine levels or increases in serum creatinine levels ranging from ≥0.3 mg/dL [≥27 μmol/L] to ≥1.0 mg/dL [≥88 μmol/L]). Although none of these cutoff values were evaluated, comparing our arbitrary definition of change of kidney function with most other published definitions, we found that our cutoff value is extremely conservative. Because the main objective of this study is to evaluate the association between small changes in renal function in relation to outcome, we chose a cutoff value of 10% change. Furthermore, kidney function estimating equations (eg, Cockcroft-Gault) are derived in patients in a steady state. Because we reported perioperative estimated CrCl changes (within 3 days after surgery) by definition, such a steady state is difficult to establish, which might underestimate true changes in kidney function. Unfortunately, there are no practical ways to readily measure kidney function in the acute setting. The strength of our retrospective study is that it covers a long period (6.0 ± 3.4 years) and includes a large number of patients. Few studies focused on the long-term outcome of a temporary decrease in renal function shortly after surgery. In conclusion, patients with temporary worsening of renal function are at high risk of poor long-term outcome, suggesting that these patients may need closer medical follow-up than suggested previously.

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Chapter 6

The Influence of Aging on the Prognostic Value of the Revised Cardiac Risk Index for Postoperative Cardiac Complications in Vascular Surgery Patients

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The Influence of Aging on the Prognostic Value of the Revised Cardiac Risk Index for Postoperative Cardiac Complications in Vascular Surgery Patients

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Objective. *The Lee-risk index [Lee-index] was developed to predict major adverse cardiac events [MACE]. However, age is not included as a risk factor. The aim was to assess the value of the Lee-index in vascular surgery patients among different age categories.*
Methods. *Of 2 642 patients cardiovascular risk factors were noted to calculate the Lee-index. Patients were divided into four age categories; ≤ 55(n = 396), 56–65 (n = 650), 66–75 (n = 1 058) and >75 years (n = 538). Outcome measures were postoperative MACE (cardiac death, MI, coronary revascularization and heart failure). The performance of the Lee-index was determined using C-statistics within the four age groups.*
Results. *The incidence of MACE was 10.9%, for Lee-index 1, 2 and ≥3; 6%, 13% and 20%, respectively. However, the prognostic value differed among age groups. The predictive value for MACE was highest among patients under 55 year (0.76 vs 0.62 of patients aged > 75). The prediction of MACE improved in elderly (aged > 75) after adjusting the Lee-index with age, revised risk of operation (low, low-intermediate, high-intermediate and high-risk procedures) and hypertension (0.62 to 0.69).*
Conclusion. *The prognostic value of the Lee-index is reduced in elderly vascular surgery patients, adjustment with age, risk of surgical procedure, and hypertension improves the Lee-index significantly.*

Keywords: Cardiac Risk; Vascular surgery; Prognosis; Elderly.

Introduction

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

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Method

Study design and patient selection

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

Revised Cardiac Risk Index factors

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

Other risk factors

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

Procedures

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

Clinical follow-up and end points

Perioperative clinical information was retrieved from an electronic database of patients maintained in our hospital. From the municipal civil registries, we obtained the survival status. The follow-up was complete in 98.2%. The primary outcomes were major adverse cardiac event [MACE] and all-cause mortality, occurring within 30 days after surgery. The secondary outcome was all-cause mortality during long-term follow-up. MACE within 30-days after surgery, was defined as cardiac death (which was defined as any death with a cardiac complication as the primary or secondary cause, including deaths following myocardial infarction, cardiac arrhythmia and heart failure), myocardial infarction or coronary revascularization (PCI or CABG). Sudden death in a previously stable patient was considered as cardiac death. Myocardial infarction was defined as the presence of 2 out of the following 3 criteria: (1) typical chest-pain complaints, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, or new left bundle branch block, or new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists >24 hours, and (3) a positive troponin T, ie >0.10 ng/ml (>0.1 ug/L), or peak creatinine phosphokinase -MB >8% of an elevated total creatinine phosphokinase with characteristic rise and fall. Heart failure was defined according the New York Heart Association classification. In addition, the causes of death

occurring within 30 days after surgery were grouped into three different categories: (1) cerebro-cardiovascular death [CCVD], (2) non-cerebrocardiovascular death [non-CCVD] and (3) unknown cause of death. Cerebro-cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and included deaths following myocardial infarction (MI), serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke [cerebro vascular accident (CVA) or transient ischemic attack (TIA)], surgery-related fatal bleeding complications and others. Non-CCVD was defined as any death with a principal non-cerebro-cardiovascular cause, including infection, malignancy, respiratory insufficiency and others. The cause of death was ascertained by reviewing medical records, the computerized hospital database, autopsy reports, or by contacting the referring physician or general practitioner.

Statistical analysis

Continuous data are described as mean values and its standard deviation [± SD], and dichotomous data are described as percentage frequencies. The chi-square test was used for categorical variables and the analysis of variance [ANOVA] was used for continuous variables. Univariable logistic regression analysis was used to evaluate the relation between the Lee-index and MACE for each age category. Multivariable logistic analysis was performed to evaluate whether the predictive power of the Lee-index could be improved by adding age, hypertension and more detailed information on the type of surgery (low risk (CEA), low-intermediate risk (LLR), high-intermediate risk (AAA) and high risk (r-AAA)). The performance of the risk model was determined by the C-statistics and its resulting area under the receiver operating characteristics [ROC] curve [AUC], which indicates how well a model rank orders patients with respect to their outcome (where 0.5 indicates no predictive value and 1.0 indicates perfect performance). Kaplan-Meier survival analysis was used to compare survival of patients, according to the three Lee-index categories. To test for differences between the resulting curves, the log-rank test was used. A p value of <0.05 was considered to be significant. All computations were performed with SPSS software version 12.0.1 (SPSS Inc., Chicago, Illinois, USA), running under Windows 2000 Professional.

Results

Patient characteristics

A total of 2642 procedures were performed (21% CEA, 8% r-AAA, 34% AAA and 38% LLR). The mean age was 66 ± 11 years and 75% of the patients were men. Of these patients, 396 (15%) were ≤55, 650 (25%) were 56–65, 1058 (40%) were 66–75 and 538 (20%) were > 75 years. Men were 0.97 years older than were female (p 0.052). With increase of age, higher incidences of hypertension, COPD, ischemic heart disease and r-AAA and AAA surgery were observed (Table 1). No patients were reported with a Lee-index score of 0, as all patients with CEA had a positive history of cerebrovascular disease and/or presence of another risk factor used in the Lee risk index. The majority of patients had a score of 1 point (52%), followed by 30% and 18%, respectively 2 and ≥3 points (Table 2).

Primary end-point

A total of 287 (10.9%) patients had a major adverse cardiac event, for Lee-index 1, 2 and ≥3 respectively 6.2%, 13.2% and 20.5%. Increasing rates of MACE were found with increased age, with a slight drop of incidences within patients aged >75 years. Within each age category, the Lee-index was significantly associated with incidences of MACE. A correlation of all-cause mortality and Lee-index was found in all patients (p 0.03). However, no correlation of the Lee-index and all-cause mortality was found within each age category. Cerebro-cardiovascular events (116 (76%)) were the major cause of death which included: MI 19%, heart failure 10%, cardiac arrhythmia 10%, stroke 6%, fatal bleeding 26% and others 5%. The non-cerebro-cardiovascular (36 (24%)) events included: infection 14%, malignancy 0%, respiratory insufficient 6% and others 4%. None patients had an unknown cause of death. In total, 58 (39%) patients died because of cardiac complications within 30 days after surgery.

In univariate analysis, the Lee-index was associated with an increased risk of MACE as its individual components (Table 3). The prospective C-statistic for the prediction of MACE was 0.65. The predictive value of the Lee-index was significantly superior in patients aged ≤55 years compared to patients aged >75 years (area under the curve 0.76 vs. 0.62, $p < 0.01$). When more detailed information, including type of surgery (low, low-intermediate, high-intermediate and high risk of surgery), age (≤55, age 56–65, age 66–75 and

Table 1. Baseline characteristics of all patients undergoing major vascular surgery, grouped into four age categories

	All [2642 (100%)]	Age ≤ 55 [396 (15%)]	Age 56–65 [650 (25%)]	Age 66–75 [1058 (40%)]	Age > 75 [538 (20%)]	*P* value
Demographics						
Mean age (± SD)	66 (± 11)	47 (± 8)	61 (± 3)	70 (± 3)	79 (± 4)	<0.001
Male (%)	75	68	79	77	74	<0.001
Revised Cardiac Risk Index factors (%)						
Ischemic heart disease	30	25	31	29	32	0.05
Heart failure	5	6	5	5	7	0.5
High-risk surgery	79	79	77	77	87	<0.001
Abdominal aortic surgery	34	30	32	36	36	0.06
Acute aortic surgery	8	3	5	9	13	<0.001
Lower limb reconstruction	37	47	40	32	39	<0.001
Renal insufficiency	6	7	5	6	5	0.4
Insulin dependent diabetes mellitus	15	17	12	14	17	0.08
Cerebrovascular disease	31	27	34	34	25	<0.001
Other risk factors (%)						
COPD[a]	18	11	15	21	23	<0.001
Current smoker	24	25	27	23	22	0.2
Hypercholesterolemia	18	25	19	16	13	<0.001
Body mass index (± SD)	25.1 (± 5)	25.4 (± 5)	25.3 (± 6)	24.9 (± 4)	24.7 (± 3)	0.02
Hypertension	46	39	44	47	48	0.02
Medication use:						
Statins	26	31	31	26	16	<0.001
Diuretics	18	13	15	19	23	<0.001
ACE-inhibitors[b]	31	28	34	31	33	0.2
Calcium antagonists	34	33	33	35	31	0.4
Nitrates	19	15	19	19	21	0.2
Beta-blockers	33	31	35	35	31	0.3
Aspirin	40	37	40	42	40	0.3
Anti-coagulation	20	18	22	20	18	0.4

[a] COPD = chronic obstructive pulmonary disease.
[b] ACE-inhibitors = angiotensin-converting-enzyme inhibitors.

>75 years) and history of hypertension, was added to the model, the overall C-statistics improved to 0.71. Importantly, after the introduction of these additional risk factors no difference in the C-statistics was observed between each age category ≤55, age 56–65, age 66–75 and >75 years), respectively 0.71, 0.71, 0.69 and 0.69. The prediction of MACE in elderly patients improved from 0.62 to 0.69 ($p = 0.02$).

Important differences in incidence of MACE were observed in relation to type of surgery. Overall incidences of MACE according to low-risk (CEA), low-intermediate (LLR), high-intermediate (AAA) and high-risk (r-AAA) surgery were 2.4%, 11.6%, 12.3% and 24.0%, respectively ($p < 0.001$) (Fig. 1). Within each type of surgery, the Lee-index was significantly associated with risk of MACE.

When we perform our analysis applied only to patients having a single procedure ($n = 2298$, 66 ± 11 years, 75% were men), our results remained the same. For example, incidences of hypertension were 38%, 43%, 46% and 47% for age category ≤ 55, 56–65, 66–75 and > 75 years respectively (p 0.03). The prospective C-statistic for the prediction of MACE was also 0.65 (0.76, 0.66, 0.64 and 0.62 for each age category (≤55, age 56–65, age 66–75 and > 75 years)). After the introduction of our additional risk factors no difference in the C-statistics was observed between each age category, respectively 0.74, 0.73, 0.71 and 0.71. The multivariate analysis showed the same results as presented in Table 3. Because of these findings, we concluded that the influence of patients with multiple procedures on the overall results does not have an important impact on our results.

Secondary end-point

Although the Lee-index was originally developed to predict perioperative cardiac complications, a clear association was found between the Lee-index and all-cause mortality during follow-up (Fig. 2). A total of 1454 (55%) patients died during mean period of 6.4 ± 3.9 years. Annual mortality rates of patients with a Lee-index score of 1, 2 and ≥ 3 were 5.2%/year, 6.4%/year and 7.3%/year respectively ($p < 0.001$). In multivariate analysis, adjusting for the four age categories, risk of surgery (low, low-intermediate, high-intermediate and high risk), year of operation,

Table 2. Incidences of major adverse cardiac events and all-cause mortality, according to the Revised Cardiac Risk score[a]

	All	Lee-index 1	Lee-index 2	Lee-index ≥ 3	*P* value	Area under the curve	Area under the curve[b]
All							
Incidences *n* (%)	2 642 (100)	1 371 (52)	802 (30)	469 (18)			
All-cause death *n* (%)	152 (5.8)	63 (4.6)	55 (6.9)	34 (7.2)	0.03		
MACE *n* (%)	287 (10.9)	85 (6.2)	106 (13.2)	96 (20.5)	<0.001	0.65	0.71
Age ≤ 55							
Incidences *n* (%)	396 (100)	234 (59)	94 (24)	68 (17)			
All-cause death *n* (%)	10 (2.5)	5 (2.1)	3 (3.2)	2 (2.9)	0.84		
MACE *n* (%)	17 (4.3)	3 (1.3)	5 (5.3)	9 (13.2)	<0.001	0.76	0.71
Age 56–65							
Incidences *n* (%)	650 (100)	346 (53)	200 (31)	104 (16)			
All-cause death *n* (%)	22 (3.4)	10 (2.9)	7 (3.5)	5 (4.8)	0.63		
MACE *n* (%)	60 (9.2)	21 (6.1)	17 (8.5)	22 (21.2)	<0.001	0.64	0.71
Age 66–75							
Incidences *n* (%)	1 058 (100)	543 (51)	335 (32)	180 (17)			
All-cause death *n* (%)	68 (6.4)	30 (5.5)	23 (6.9)	15 (8.3)	0.38		
MACE *n* (%)	144 (13.6)	43 (7.9)	59 (17.3)	43 (23.9)	<0.001	0.64	0.69
Age > 75							
Incidences *n* (%)	538 (100)	248 (46)	173 (32)	117 (22)			
All-cause death *n* (%)	52 (9.7)	18 (7.3)	22 (12.7)	12 (10.3)	0.17		
MACE *n* (%)	66 (12.3)	18 (7.3)	26 (15.0)	22 (18.8)	0.003	0.62	0.69

MACE = major adverse cardiac event.
[a] Index that assigns one point to each of the following characteristics: ischemic heart disease, history of heart failure, high-risk surgery, history of cerebrovascular disease, renal insufficiency and diabetes mellitus.
[b] Adjusted for type of surgery (low, low-intermediate, high-intermediate and high risk of surgery), age (≤ 55, 56–65, 66–75 and >75 years) and history of hypertension.

chronic obstructive pulmonary dysfunction, hypercholesterolemia, smoking status, body mass index, gender, hypertension and cardiovascular medication, the risk of all-cause mortality was 1.45 (95% CI: 1.28–1.65) for Lee-index 2 and 1.90 (95% CI: 1.63–2.22) for Lee-index ≥ 3, compared with Lee-index 1. When analysis was performed to patients with a single procedure, the risk of all-cause mortality was 2.01 (95% CI: 1.37–2.94) for Lee-index 2 and 3.11 (95% CI: 1.94–4.97) for Lee-index ≥ 3, compared with Lee-index 1.

Table 3. Unadjusted and adjusted predictors of estimate risk of major adverse cardiac events

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

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

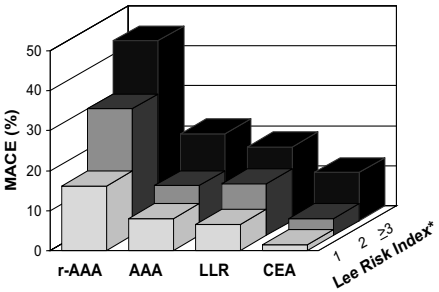

Fig. 1. Incidences of major cardiac events, according to type of operation and the Revised Cardiac Risk score. MACE = major adverse cardiac events; r-AAA = acute infrarenal AAA surgery; AAA = elective infrarenal abdominal aortic surgery; LLR = lower limb arterial reconstruction procedures; CEA = carotid endarterectomy, *Lee-index that assigns one point to each of the following characteristics: ischemic heart disease, history of heart failure, high-risk surgery, history of cerebrovascular disease, renal insufficiency and diabetes mellitus.

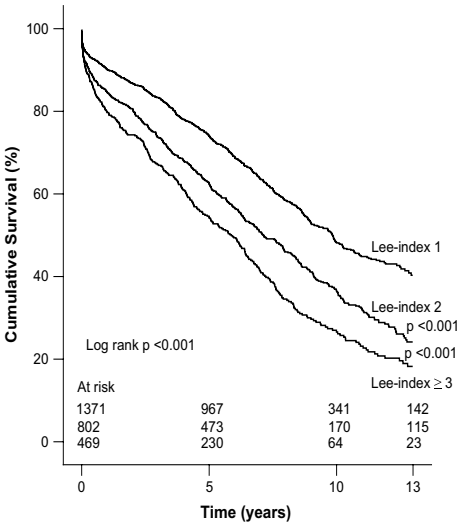

Fig. 2. All cause long-term mortality in 2642 patients who underwent major vascular surgery, according to the Revised Cardiac Risk score. Lee-index that assigns one point to each of the following characteristics: ischemic heart disease, history of heart failure, high-risk surgery, history of cerebrovascular disease, renal insufficiency and diabetes mellitus.

Discussion

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

The Lee-index is a modification of the original Goldman risk index,[8] developed in the 1990s and validated in numerous clinical studies and is currently considered the best available risk model. Although the Lee-index was developed using clinical data of 4315 consecutive patients undergoing non-cardiac surgery, the model has shortcomings for vascular surgery patients. Of all patients, only 21% underwent vascular surgery and all procedures were considered as high-risk. However, postoperative morbidity and mortality varied considerably among different vascular surgical procedures.[9–11] In order to improve the predictive value of the Lee-index, we specified the type of vascular surgery into four categories; low, low-intermediate, high-intermediate and high-risk.

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

Several risk indices have been developed to stratify vascular surgery patients based on age and clinical cardiac risk factors. In 1994, Samy *et al.* developed a scoring system in 500 patients scheduled for abdominal aortic aneurysm surgery for the prediction of postoperative mortality; the Glasgow aneurysm score.[13] This score included myocardial disease, cerebrovascular disease, renal dysfunction and age as a continuous variable as risk factors. Age was an independent risk factor for postoperative mortality ($p = 0.02$). Steyerberg *et al.* constructed the Leiden Risk Model in 246 patients undergoing abdominal aortic aneurysm surgery and included age per decade (<60, 60–70 and >70 years) as a risk factor.[14] Age had only a moderate predictive value for all-cause perioperative mortality (OR 1.9; 95% CI: 0.9–4.2). In addition, L'Italien *et al.* developed a risk model among 1081 patients undergoing different vascular surgical procedures, with an overall predictive value for cardiac death and non-fatal myocardial infarction of 0.74 (C-statistic).[15] They included advanced age (>70 years) as a dichotomous risk factor. The limitations of these studies are the low number of patients included, none of the studies had MACE as their end-point and the focus is predominantly on aortic surgery.

Preoperative cardiovascular risk stratification has been an area of intense interest for identifying patients at higher cardiac risk. Patients classified as high risk can be refrained for surgery or should be considered to undergo less invasive surgery (like endovascular procedures). Additional cardio protective therapy in elderly (like beta-blockers and statins[16–18]) in reduction of perioperative cardiac complications has improved in recent years. In addition to the immediate postoperative outcome, prognostic indices should be considered to assess long-term prognosis, as patients should live long enough to enjoy the benefits of surgery. As shown in the follow-up of patients undergoing major vascular surgery with

different cardiac risk index scores, annual mortality rates increased by each risk factor added, ranging from 5.2%/year in patients with 1 risk factor, to 6.4%/year and 7.3%/year for 2 and ≥3 risk factors respectively. This indicates that the prognosis is related to underlying cardiovascular disease. Post-operative surveillance of patients among the high-risk scores with aggressive anti-ischemic therapy is indicated to improve long-term outcome.

A major limitation of our study is the retrospective analysis of prospectively collected data. Changes in the perioperative management have evolved markedly over time and were not taken into account in our analysis. These include multiple factors ranging from preoperative management, such as drug therapy, anesthesiological and surgical techniques to intensive post-surgical care management. We tried to adjust for this confounding to add the year of operation in our multivariate analysis, resulting in Table 3.

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

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Chapter 7

Association between Serum Uric Acid and Perioperative and Late Cardiovascular Outcome in Patients with Suspected or Definitive Coronary Artery Disease undergoing Elective Vascular Surgery

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Association Between Serum Uric Acid and Perioperative and Late Cardiovascular Outcome in Patients With Suspected or Definite Coronary Artery Disease Undergoing Elective Vascular Surgery

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The role of uric acid as an independent marker of cardiovascular risk is unclear. Therefore, our aim was to assess the independent contribution of preoperative serum uric acid levels to the risk of 30-day and late mortality and major adverse cardiac event (MACE) in patients scheduled for open vascular surgery. In total, 936 patients (76% male, age 68 ± 11 years) were enrolled. Hyperuricemia was defined as serum uric acid >0.42 mmol/l for men and >0.36 mmol/l for women, as defined by large epidemiological studies. Outcome measures were 30-day and late mortality and MACE (cardiac death or myocardial infarction). Multivariable logistic and Cox regression analysis were used, adjusting for age, gender, and all cardiac risk factors. Data are presented as odds ratios or hazard ratios, with 95% confidence intervals. Hyperuricemia was present in 299 patients (32%). The presence of hyperuricemia was associated with heart failure, chronic kidney disease, and the use of diuretics. Perioperatively, 46 patients (5%) died and 61 patients (7%) experienced a MACE. Mean follow-up was 3.7 years (range: 0 to 17 years). During follow-up, 282 patients (30%) died and 170 patients (18%) experienced a MACE. After adjustment for all clinical risk factors, the presence of hyperuricemia was not significantly associated with an increased risk of 30-day mortality or MACE, odds ratios of 1.5 (0.8 to 2.8) and 1.7 (0.9 to 3.0), respectively. However, the presence of hyperuricemia was associated with an increased risk of late mortality and MACE, with hazard ratios of 1.4 (1.1 to 1.7) and 1.7 (1.3 to 2.3), respectively. In conclusion, the presence of preoperative hyperuricemia in vascular patients is a significant predictor of late mortality and MACE. **(Am J Cardiol 2008;xx:xxx)**

Uric acid is the major product of purine metabolism and is formed from xantine, a reaction catalyzed by dehydrogynase/oxidase.[1] The association between serum uric acid levels and the risk of cardiovascular disease has been confirmed by numerous epidemiological studies.[2–6] However, it remains disputed whether uric acid is an independent risk factor for cardiovascular disease; several studies have suggested that hyperuricemia is merely associated with cardiovascular disease because of confounding risk factors.[7,8] To our knowledge, no studies have investigated the role of preoperative hyperuricemia as a risk marker for cardiac outcome in vascular surgery patients. In conclusion, the goal of the present study was to assess the independent contribution of serum uric acid levels to the risk of 30-day and late mortality and major adverse cardiac events (MACEs) in patients scheduled for open vascular surgery.

Methods

In a retrospective study, a series of 936 patients scheduled for elective noncardiac vascular surgery with known or suspected coronary artery disease who were referred for preoperative testing between February 1990 and February 2007 to the Erasmus Medical Center, Rotterdam, the Netherlands were analyzed. Patients undergoing endovascular procedures were excluded from the study. Preoperative testing included laboratory measurement and echocardiography as well as assessment of baseline characteristics. The study protocol was approved by the hospital ethics committee, and all patients gave informed consent.

At study enrollment, a detailed cardiac history was obtained and all clinical risk factors were noted. Hypertension was defined as blood pressure ≥140/90 mm Hg or medical treatment for hypertension, and diabetes mellitus was defined as a fasting glucose level of ≥7.0 mmol/L (126 mg/dL) or the use of insulin or oral glucose lowering agents. Coronary heart disease was defined as an angina pectoris and/or myocardial infarction; stroke was defined as a history

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Table 1
Baseline characteristics according to uric acid levels

Variable	Uric Acid			
	Total (936)	Normal (637)	Abnormal (299)	p Value
Age (yrs) (SD)	67.7 (10.9)	68.1 (10.5)	67. (12.3)	0.74
Men	76.0%	74.6%	81.4%	0.06
Diabetes mellitus	22.9%	22.7%	23.5%	0.82
Ischemic heart disease	54.7%	55.3%	52.5%	0.50
Heart failure	21.2%	19.2%	28.7%	0.006
Previous coronary revascularization	14.4%	14.3%	15.1%	0.80
Hypertension	54.9%	54.8%	55.2%	0.90
Stroke	17.2%	17.4%	16.7%	0.82
Chronic kidney disease	30.6%	25.1%	49.5%	<0.001
Chronic obstructive pulmonary disease	41.0%	39.6%	46.3%	0.11
Hypercholesterolemia	41.5%	40.1%	47.0%	0.09
Central arterial surgery	58.4%	58.9%	56.3%	0.52
β blocker	55.4%	55.1%	56.3%	0.78
Aspirin	38.7%	39.0%	37.7%	0.75
Angiotensin-converting enzyme inhibitors	40.4%	39.7%	43.2%	0.40
Calcium antagonist	39.0%	38.7%	39.9%	0.77
Warfarin	30.8%	30.3%	32.8%	0.52
Diuretics	28.7%	25.2%	42.1%	0.001

Table 2
Thirty-day and late mortality and major adverse cardiac events, according to uric acid levels

Variable	Uric Acid			
	Total	Normal	Abnormal	p Value
30-day mortality	4.9 (%)	3.9 (%)	7.0 (%)	0.050
30-day MACE	6.5 (%)	4.9 (%)	9.8 (%)	0.006
Late mortality	43.8 (%)	41.2 (%)	49.1 (%)	0.026
Late MACE	24.2 (%)	20.5 (%)	32.1 (%)	<0.001

of either a cerebral vascular accident or a transient ischemic attack; chronic obstructive pulmonary disease was defined as a forced expiratory volume in 1 second (FEV1) <70% of age- and gender-predicted value or medication use; hypercholesterolemia was defined as a plasma low-density lipoprotein (LDL) cholesterol >200 mg/dl or medication use; and smoking was noted in patients who currently smoked or had a history of smoking. Patients underwent a resting 2-dimensional echocardiographic examination. Left ventricular end-diastolic and end-systolic volumes were obtained from the apical 4- and 2-chamber views by using the Simpson's rule formula, from which the ejection fraction was calculated. The presence of heart failure was defined as a left ventricular ejection fraction of <35%. Preoperative serum creatinine levels were used to estimate the glomerular filtration rate according to the equation from the Modification of Diet in Renal Disease study. Chronic kidney disease was defined as glomerular filtration rate <60. Finally, preoperative blood samples were used to determine hyperuricemia, which was defined as serum uric acid exceeding 0.42 mmol/L in men and 0.36 mmol/L in women, as defined by large epidemiological studies.[2–3]

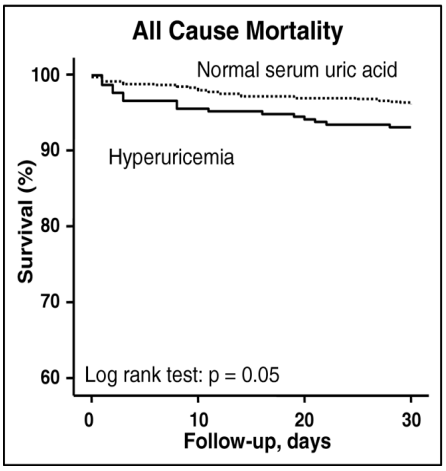

Figure 1. Thirty-day all-cause, mortality-free survival for serum uric acid levels.

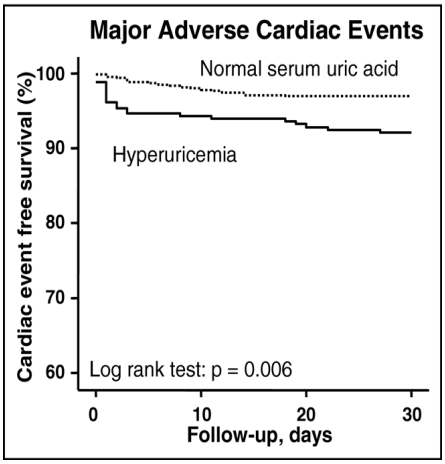

Figure 2. Thirty-day MACE-free survival for serum uric acid levels.

Follow-up data collection was performed by review of hospital records, contacting the patients' general practitioners, and obtaining the patients' vital status from the Office of Civil Registry. Clinical information was obtained by outpatients' visits and reviewing hospital records. Nonfatal myocardial infarction was diagnosed when at least 2 of the following were present: elevated cardiac enzyme levels (creatine kinase [CK] level >190 U/L and CK-MB >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/mL), development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms), and typical symptoms of angina pectoris. Death certificates and autopsy reports were reviewed, and general practitioners were approached to ascertain the cause of death. Car-

Table 3
Multivariable associations between hyperuricemia and risk of 30-day mortality and MACE

Variable	30-Day Outcome	
	All-cause Mortality	MACE
	Odds Ratio* (95% Confidence Interval)	Odds Ratio* (95% Confidence Interval)
Abnormal uric acid	1.46 (0.77–2.82)	1.66 (0.95–2.95)
Age	1.04 (1.01–1.09)	1.02 (1.00–1.05)
Men	0.90 (0.43–1.93)	0.77 (0.39–1.49)
Central arterial surgery	1.62 (0.81–3.26)	1.15 (0.64–2.09)
Chronic kidney disease	1.65 (0.68–4.01)	1.79 (0.83–3.87)
Heart failure	2.24 (1.12–4.47)	2.78 (1.53–5.08)
Diabetes mellitus	1.56 (0.76–3.23)	1.66 (0.88–3.12)
Hypertension	1.36 (0.71–2.63)	1.31 (0.73–2.36)
Ischemic heart disease	1.22 (0.62–2.36)	1.11 (0.61–2.04)
Stroke	1.71 (0.80–3.64)	1.35 (0.66–2.75)

* Adjustments were made for uric acid levels, age, gender, type of vascular surgery, renal function, heart failure, diabetes mellitus, hypertension, ischemic heart disease, stroke and the use of cardiovascular medication.

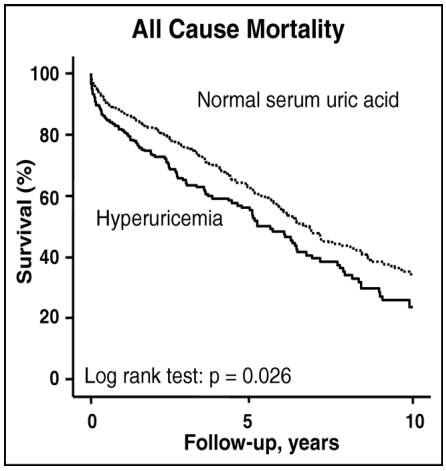

Figure 3. Long-term all-cause, mortality-free survival for serum uric acid levels.

diac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, or congestive heart failure. Sudden unexpected death in previously stable patients was considered cardiac death. MACE was defined as the composite end point of nonfatal myocardial infarction and cardiac death. Study end points were mortality and MACE during the perioperative period (30-day period after surgery) and during long-term follow-up (mean: 3.7 years). No patients were lost to follow-up.

Continuous data was expressed as mean values ± standard deviation and compared using the analysis of variance test. Categorical data were presented as percent frequencies, and differences between proportions were compared using the chi-square test with Yates' correction. Logistic regression analysis was used to identify predictors of 30-day mortality and MACE, and multivariate Cox proportional hazard regression was used to identify predictors of late mortality and MACE. The interaction term of serum uric acid level and diuretic use was tested in the Cox regression models. In multivariable analysis, adjustments were made for the variables of anemia, renal dysfunction, heart failure, age, gender, type of vascular surgery (central or peripheral open procedure), diabetes mellitus, chronic obstructive pulmonary disease, hypertension, ischemic heart disease, stroke, and the use of cardiovascular medication. The presence of interaction between serum uric acid levels and the use of diuretics were evaluated by forcing these interaction terms in the multivariable regression model. Because the interaction terms were not significant for prediction of 30-day or late mortality or major adverse cardiac events, they were not included in the final logistic regression or Cox proportional hazard regression analysis models. The probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Odds and hazard ratios are given with 95% confidence intervals. For all tests, a value of $p < 0.05$ (2-sided) was considered significant. All analysis was performed using SPSS 15.0 statistical software (SPSS, Inc., Chicago, Illinois).

Results

The mean age of the study population was 68 ± 11 years, and 76% were men. A total of 299 patients (32%) had hyperuricemia. Mean serum uric acid levels in hyperuremic patients were 0.49 ± 0.07 mmol/L for men and 0.48 ± 0.21 mmol/L for women. In patients without hyperuricemia, the mean serum uric acid levels were 0.32 ± 0.06 mmol/L for men and 0.27 ± 0.06 mmol/L for women. Patients with hyperuricemia more frequently had a history of heart failure and chronic kidney disease and more frequently used diuretics compared with patients without hyperuricemia (Table 1). No differences in age, gender, further cardiac risk factors, or medication use were observed between the 2 groups, with the exception of the use of diuretics (Table 1).

At 30 days after surgery, 46 patients (4.9%) had died and 61 patients (6.5%) experienced a MACE. The distributions of 30-day mortality and MACE, according to serum uric acid levels, are listed in Table 2. The Kaplan-Meier curves for 30-day mortality and MACE-free survival are illustrated in Figures 1 and 2, showing the difference in mortality and MACE in patients with hyperuricemia compared with those normal serum uric acid levels (log-rank tests; $p = 0.05$ and $p = 0.006$, respectively). After multivariate logistic regression analysis, adjusting for age, gender, and clinical characteristics, the presence of hyperuricemia was no longer independently associated with an increased risk of 30-day mortality or an increased risk of 30-day MACE (Table 3).

During long-term follow-up, a total of 282 patients (30.2%) died and a total of 170 (18.2%) experienced a MACE. Mean follow-up was 3.7 years with a range of 0

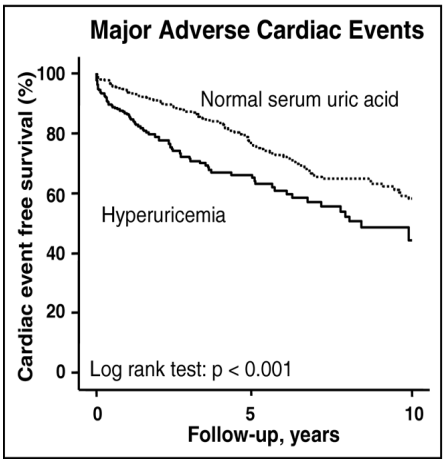

Figure 4. Long-term MACE-free survival for serum uric acid levels.

Table 4
Multivariable associations between hyperuricemia and risks of late mortality and major adverse cardiac events

Variable	Late Outcome	
	All Cause Mortality	MACE
	Hazard Ratio* (95% Confidence Interval)	Hazard Ratio* (95% Confidence Interval)
Abnormal uric acid	1.38 (1.11–1.72)	1.71 (1.25–2.30)
Age	1.04 (1.03–1.06)	1.03 (1.02–1.05)
Male gender	0.85 (0.65–1.10)	1.03 (0.72–1.49)
Central arterial surgery	0.89 (0.70–1.10)	0.79 (0.59–1.05)
Chronic kidney disease	1.61 (1.16–2.25)	1.70 (1.12–2.55)
Heart failure	1.65 (1.25–2.18)	1.94 (1.37–2.75)
Diabetes Mellitus	1.05 (0.81–1.37)	1.25 (0.89–1.76)
Hypertension	1.05 (0.86–1.36)	1.18 (0.89–1.53)
Ischemic heart disease	1.22 (0.98–1.53)	1.27 (1.01–1.59)
Stroke	1.04 (0.78–1.40)	1.13 (0.78–1.66)

* Adjustments were made for uric acid levels, age, gender, type of vascular surgery, renal function, heart failure, diabetes mellitus, hypertension, ischemic heart disease, stroke and the use of cardiovascular medication.

MACE = major adverse cardiac event.

to 17 years. The distributions of late mortality and MACE according to serum uric acid levels are listed in Table 2. The Kaplan-Meier curves for late mortality and MACE-free survival are illustrated in Figures 3 and 4, showing the increased risk of late mortality and MACE in patients with hyperuricemia compared with those normal serum uric acid levels (log-rank tests; $p = 0.026$ and $p < 0.001$, respectively).

After multivariate Cox proportional hazard regression analysis, adjusting for age, gender and clinical characteristics, the presence of hyperuricemia was associated with increased risk of late mortality compared with patients with normal serum uric acid levels, with a hazard ratio of 1.38 and 95% confidence interval of 1.10 to 1.73, as listed in Table 4. Additionally, older age, a history of heart failure, and chronic kidney disease were also associated with a significantly increased risk of late mortality (Table 4). Furthermore, after multivariate Cox proportional hazard regression analysis, the presence of hyperuricemia was associated with an increased risk of late MACE compared with patients with normal serum uric acid levels, with a hazard ratio of 1.72 and 95% confidence interval of 1.28 to 2.31 (Table 4). Additionally, older age, a history of heart failure, chronic kidney disease, and ischemic heart disease were also associated with a significantly increased risk of late MACE.

Discussion

Preoperative cardiac risk evaluation is assessed by using clinical risk factors. Commonly used is the revised cardiac risk index, described by Lee et al,[9] which includes congestive heart failure and renal disease as risk factors. These co-morbidities are also known to influence the uric acid concentrations,[10–12] which may therefore be an objective prognostic marker for perioperative events. However, this study shows that hyperuricemia is an independent predictor of long-term mortality and MACE in patients after open vascular surgery.

To our knowledge, no other studies have been published evaluating hyperuricemia before elective vascular surgery. However, the relationship of serum uric acid and risk of fatal coronary heart disease has been researched in multiple cohort studies during the past decades.[2–5,13,14] Although hyperuricemia was associated with an increased risk of fatal coronary heart disease in these investigations, the univariate associations appeared to be largely explained by the relation of serum uric acid with other CHD risk factors and mostly disappeared after additional adjustment for confounding factors. However, Fang et al[15] reported in a follow-up study from the First National Health and Nutrition Examination Survey (NHANES 1), in which 5,926 subjects (mean age 48.1 years) were followed for a mean of 16.4 years, that in addition to cardiovascular mortality, hyperuricemia was also independently associated with an increased risk of ischemic heart disease mortality.

Recently, Strasak et al[16] studied the predictive role of serum uric acid for the risk of all major forms of cardiovascular death in a prospective population-based cohort study of 286,613 elderly women who were followed for a median of 15.2 years. The mean age was 62.3 (±8.8) years, comparable to the population in our study. The end points of this study were death from congestive heart failure, stroke, and coronary heart disease as well as from total cardiovascular disease. The highest quartile of serum uric acid levels (≥0.32 mmol/L) was associated with mortality from total cardiovascular disease, with adjusted hazard ratios for the highest versus lowest quartile of 1.35 (1.20 to 1.52). Serum uric acid levels were further significantly related to all other end points, including coronary heart disease with an adjusted hazard ratio of 1.37 (1.15 to 1.63).

Additionally, in a cohort study performed by Niskanen et al,[6] in which 1,423 middle-aged, healthy Finnish men without cardiovascular disease, cancer, or diabetes were pro-

spectively followed, hyperuricemia (highest tertile) was independently associated with an increased risk of cardiovascular death with a relative risk of 2.5.

In regard to underlying pathophysiological mechanisms explaining the association of serum uric acid levels and increased risk of cardiovascular events, atherosclerotic plaques have been shown to contain uric acid, and hyperuricemia may promote thrombus formation via purine metabolism[17,18] in addition to increasing the production of oxygen-free radicals and facilitating lipid peroxidation.[19] Furthermore, recent in vitro and in vivo studies suggest that serum uric acid contributes to endothelial dysfunction by inducing antiproliferative effects and impairing nitric oxide production.[20] Although it is not possible to conclude that hyperuricemia is a causal risk factor because of the observational nature of this study, these results indicate a clinical importance of monitoring hyperuricemia in patients scheduled for vascular surgery because these patients are at increased risk for coronary heart disease.

This study has some potential limitations. The study population consisted of patients referred to a tertiary care center and may not fully represent a general population scheduled for elective vascular surgery. Also, because of the observational nature of the study, a causal relationship could not be determined between hyperuricemia and 30-day and long-term mortality and major adverse cardiac events. Additionally, the influence of metabolic syndrome was not incorporated in the multivariate analysis. Furthermore, the etiology of the measured hyperuricemia, which could be an important determinant of outcome, remains unknown.

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Chapter 8

Anemia as an Independent Predictor of Perioperative and Long-term Cardiovascular Outcome in Patients scheduled for Elective Vascular Surgery

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Anemia is common in patients scheduled for vascular surgery and is a risk factor for adverse cardiac outcome. However, it is unclear whether this is an independent risk factor or an expression of underlying co-morbidities. In total, 1,211 patients (77% men, 68 ± 11 years of age) were enrolled. Anemia was defined as serum hemoglobin levels <13 g/dl for men and <12 g/dl for women and was divided into tertiles to compare mild (men 12.2 to 13.0, women 11.2 to 12.0), moderate (men 11.0 to 12.1, women 10.2 to 11.1), and severe (men 7.2 to 11.0, women 7.5 to 10.1) anemia with nonanemia. Outcome measurements were 30-day and 5-year major adverse cardiac events (MACEs; cardiac death or myocardial infarction). All risk factors were noted. Multivariable logistic and Cox regression analyses were used, adjusting for all cardiac risk factors, including heart failure and renal disease. Data are presented as hazard ratios with 95% confidence intervals. In total, 74 patients (6%) had 30-day MACEs and 199 (17%) had 5-year MACEs. Anemia was present in 399 patients (33%), 133 of whom had mild anemia, 133 had moderate anemia, and 133 had severe anemia. Presence of anemia was associated with renal dysfunction, diabetes, and heart failure. After adjustment for all clinical risk factors, 30-day hazard ratios for a MACE per anemia group were 1.8 for mild (0.8 to 4.1), 2.3 for moderate (1.1 to 5.4), and 4.7 for severe (2.6 to 10.9) anemia, and 5-year hazard ratios for MACE per anemia group were 2.4 for mild (1.5 to 4.2), 3.6 for moderate (2.4 to 5.6), and 6.1 for severe (4.1 to 9.1) anemia. In conclusion, the presence and severity of preoperative anemia in vascular patients are significant predictors of 30-day and 5-year cardiac events, regardless of underlying heart failure or renal disease. **(Am J Cardiol 2008;101: 1196–1200)**

Anemia is not included as a factor for cardiac risk assessment in preoperative screening because it is unknown whether anemia is a primary risk factor for poor cardiac outcome, caused by decreased physiologic reserve, or whether it is secondary to other underlying co-morbidities. Currently, available data do not describe in detail the exact relation between degree of preoperative anemia and perioperative and long-term risk of cardiac morbidity and mortality in vascular surgery patients. Also, it remains unclear whether preoperative anemia predicts adverse cardiac outcomes independently from other prognostic factors, such as heart failure and renal dysfunction, and other confounders. The main goal of the present study was to assess the independent contribution of anemia to the risk of perioperative and long-term cardiac mortality and morbidity in vascular surgery patients. Furthermore, this study assessed the rate of risk increase due to extent of anemia in relation to other risk factors, including extent of renal dysfunction and presence of heart failure. Our hypothesis is that the rate of risk increase due to extent of anemia is independent of renal dysfunction and heart failure, as a predictor of perioperative and long-term cardiac outcome.

Methods

In a retrospective study, a series of 1,363 patients scheduled for elective noncardiac open vascular surgery with known or suspected coronary artery disease who were referred for preoperative testing from February 1990 to August 2006 to the Erasmus Medical Centre, Rotterdam, The Netherlands, were analyzed. Preoperative testing included laboratory

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measurement, echocardiography, and assessment of baseline characteristics. A total of 152 patients were treated at another hospital and were excluded from this study. The final study population consisted of 1,211 patients. The protocol was approved by the hospital ethics committee and all patients gave informed consent.

Preoperative hemoglobin value was defined as the hemoglobin measured during a patient's last preoperative outpatient screening before surgery. Preoperative anemia was defined by the definition put forward by the World Health Organization, which is a serum hemoglobin level <13 g/dl for men and a level <12 g/dl for women.[1] Patients with preoperative anemia were divided into tertiles to compare mild, moderate, and severe anemia, using nonanemic patients as reference. Tertiles were calculated for men and women separately, after which the 2 gender groups of mild, moderate, and severe anemic patients were joined together for analysis. This method was used instead of using continuous hemoglobin levels to decrease confounding by differences in normal hemoglobin levels in men and women.

Preoperative serum creatinine levels were used to estimate glomerular filtration rate (GFR) according to the equation from the Modification of Diet in Renal Disease (MDRD) study. Estimated GFR (milliliters per minute per 1.73 m^2) was categorized into 4 groups, namely ≥90, 60 to 89, 30 to 59, and <30. GFR ≥90 was considered normal and was used as reference for the other groups. Chronic kidney disease was defined as a GFR <60. Patients underwent a 2-dimensional echocardiographic examination at rest. Left ventricular end-diastolic and end-systolic volumes were obtained from apical 4- and 2-chamber views by using the Simpson rule formula, from which the ejection fraction was calculated. Presence of heart failure was defined as a left ventricular ejection fraction <35%.

All clinical risk factors were noted. Diabetes mellitus was defined as a fasting glucose level ≥7.0 mmol/L (126 mg/dl) or the use of insulin or oral glucose-lowering agents, and hypertension as a blood pressure ≥140/90 mm Hg or medical treatment for hypertension. Coronary heart disease was defined as a history of angina and/or myocardial infarction, stroke was defined as a previous cerebral vascular accident or transient ischemic attack, chronic obstructive pulmonary disease was defined as a forced expiratory volume in 1 second <70% of age- and gender-predicted value or medication use, and smoking was noted in patients who currently smoked or had a history of smoking.

Follow-up data collection was performed by review of hospital records, contacting patients' general practitioners, and obtaining patients' vital status from the office of civil registry. Clinical information was obtained by outpatient visits and reviewing hospital records. Nonfatal myocardial infarction was diagnosed when ≥2 of the following were present: increased cardiac enzyme levels (creatine kinase level >190 U/L and creatine kinase-MB level >14 U/L, or creatine kinase-MB fraction >10% of total creatine kinase, or cardiac troponin T >0.1 ng/ml), development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms), and typical symptoms of angina pectoris. Death certificates and autopsy reports were reviewed, and general practitioners were approached to ascertain cause of death. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, or congestive heart failure. Sudden unexpected death in previously stable patients was considered cardiac death. The composite of nonfatal myocardial infarction and cardiac death was defined as a major adverse cardiac event (MACE). Outcome measurements were 30-day and 5-year MACEs. Follow-up was successful in all 1,211 patients (100%).

Continuous data were expressed as mean ± SD and compared using analysis of variance. Categorical data were presented as percent frequencies, and differences between proportions were compared using chi-square test. Logistic regression analysis (SPSS 14.0, SPSS, Inc., Chicago, Illinois) was used to identify predictors of 30-day MACEs, and multivariate Cox proportional hazard regression was used to identify predictors of 5-year MACEs. Adjustments were made for the variables anemia, renal dysfunction, heart failure, age, gender, type of vascular surgery (central or peripheral open procedure), diabetes mellitus, chronic obstructive pulmonary disease, hypertension, ischemic heart disease, and stroke.

Interactions between anemia and renal dysfunction and between anemia and heart failure were evaluated by forcing these interaction terms in the multivariable regression model. Because the interaction terms were not significant for prediction of 30-day or 5-year MACEs, it was not included in the final logistic regression or Cox proportional hazard regression analysis models. Probability of survival was calculated using the Kaplan-Meier method, and survival curves were compared using log-rank test. A p value <0.05 was considered statistically significant.

Results

Of the 1,211 patients included in the study, 877 were men (77%) and mean age was 68 ± 11 years. At baseline, anemia was present in 399 patients (33%), of which tertiles were calculated, resulting in 133 patients with mild anemia, 133 with moderate anemia, and 133 with severe anemia. Mean hemoglobin levels were 14.5 ± 1.1 g/dl in nonanemic patients, 12.4 ± 0.5 g/dl in patients with mild anemia, 11.3 ± 0.5 g/dl in patients with moderate anemia, and 9.8 ± 0.8 g/dl in patients with severe anemia. In total, 239 patients (21%) were diagnosed with heart failure and 381 patients (33%) had renal dysfunction. Estimated GFR ≥90 was present in 202 patients (17%), GFR 60 to 89 in 547 patients (45%), GFR 30 to 59 in 389 patients (32%), and GFR <30 in 73 patients (6%).

Clinical characteristics of patients are presented in Table 1. Statistically significant independent clinical predictors of anemia were diabetes mellitus ($p = 0.001$), heart failure ($p = 0.02$), and GFR <60 ($p < 0.001$). A clear yet nonsignificant trend for increased anemia was seen in patients with a history of stroke ($p = 0.06$) and patients with older age ($p = 0.06$). When comparing the increasing severity of anemia, a statistically significant increase in percentage was seen in the number of patients with diabetes mellitus and renal dysfunction. Notably, no correlation was seen between medication use (most importantly the use of aspirin, angiotensin-converting enzyme inhibitors, or β blockers) and incidence of anemia.

At 30 days postoperatively, 59 patients (5.2%) had a

Table 1
Baseline characteristics according to presence or absence of anemia

Variable	Total (n = 1,211)	Normal (n = 812)	Anemia (n = 399)	*p* Value
Age (yrs), mean ± SD	68.3 ± 10.7	67.9 ± 10.4	69.1 ± 11.2	0.06
Male gender	77.1%	76.1%	78.6%	0.27
Diabetes mellitus	23.3%	20.3%	28.8%	0.001
Coronary heart disease	54.2%	52.7%	56.9%	0.18
Heart failure	21.1%	18.8%	24.9%	0.02
Previous coronary revascularization	13.4%	14.1%	12.1%	0.41
Hypertension	53.0%	52.2%	54.6%	0.43
Stroke	18.0%	16.4%	20.9%	0.06
Chronic kidney disease	16.8%	24.7%	38.6%	<0.001
Chronic obstructive pulmonary disease	39.3%	37.8%	42.1%	0.17
Hypercholesterolemia	42.2%	42.4%	41.9%	0.85
Central arterial surgery	57.4%	59.1%	54.4%	0.13
β Blocker	58.4%	57.6%	59.9%	0.45
Aspirin	39.1%	39.7%	37.8%	0.53
ACE inhibitor	39.7%	38.8%	41.4%	0.40
Calcium antagonist	38.0%	36.6%	40.6%	0.19
Warfarin	29.9%	28.9%	31.6%	0.35
Diuretics	27.6%	26.4%	29.8%	0.21

ACE = angiotensin-converting enzyme.

myocardial infarction and 31 patients (2.7%) died due to cardiovascular death. In total, the incidence of 30-day MACEs was 74 patients (6%). At 5-year follow-up, a total of 80 patients (7.0%) had a myocardial infarction and 146 patients (12.8%) died due to cardiovascular death. In total, the incidence of 5-year MACEs was 199 patients (16.4%). Mean follow-up was 3.4 years (range 0.0 to 16.3). Distributions of 30-day and 5-year MACEs according to preoperative hemoglobin level are listed in Table 2. Kaplan-Meier curves for 30-day and 5-year MACE-free survivals are displayed in Figures 1 and 2, respectively, illustrating the increased risk of MACEs in patients with increasing severity of preoperative anemia compared with those without anemia (log-rank tests, $p < 0.001$).

After multivariate logistic regression analysis, adjusting for age, gender, and clinical characteristics, the presence of moderate and severe preoperative anemias was associated with increased risk of 30-day MACEs, with odds ratios of 2.3 and 4.7, respectively (Table 3). Compared with nonanemic patients, mild preoperative anemia showed only a nonsignificant trend toward a worse outcome (Table 3). Additionally, heart failure and a decreasing GFR were associated with a significantly increased risk of 30-day MACEs (Table 3).

After multivariate Cox proportional hazard regression analysis, adjusting for age, gender, and clinical characteristics, all 3 severity groups of preoperative anemia were associated with increased risk of 5-year MACEs compared with nonanemic patients (odds ratios 2.4 mild anemia, 3.6 moderate anemia, and 6.1 severe anemia), as presented in Table 3. Additionally, heart failure and a decreasing GFR were associated with a significantly increased risk of 5-year MACEs (Table 3).

Discussion

This study showed that extent of preoperative anemia and worsening renal function were strong predictors of perioperative and long-term MACEs, even after adjusting for known confounders. The association was graded, with increasing severity of anemia and renal dysfunction correlating with an increasing risk for MACEs. At 30 days postoperatively, only moderate and severe anemias were significantly associated with increased risk of MACEs. However, this could be due to the power of the study because a clear trend was seen for mild preoperative anemia at 30 days. At 5 years postoperatively, anemia and worsening renal function were increasingly and significantly associated with a worse outcome. Additionally, heart failure was significantly associated with worse 30-day and 5-year outcomes.

Anemia is a common and inter-related finding in chronic heart failure and kidney disease. Lower hemoglobin levels can be caused by hemodilution (pseudoanemia) in heart failure[2] or can be caused and/or worsened by various different mechanisms, including renal dysfunction,[3] malnutrition,[4] iron or vitamin deficiencies,[4] bone marrow depression due to increased levels or proinflammatory cytokines,[5] and certain medications.[1,4–9] Low hemoglobin levels have been associated with lower exercise tolerance[10,11] and increased risk of cardiac events.[2,3,7,12,13] Several mechanisms may contribute to anemia as a risk factor for cardiac events. Subclinical coronary disease may decrease the tolerance for anemia because coronary vasodilatation is not possible in the presence of significant stenosis and the cardiac oxygen extraction ratio may be limited.[14,15] Also, in patients with decreased cardiac reserve, anemia may further decrease regular physiologic compensatory capacity.[16]

However, it is not entirely clear whether this is caused by anemia or whether anemia is secondary to the risk of confounding co-morbidities. Go et al[17] studied the effects of hemoglobin levels and extent of chronic kidney disease in patients with chronic heart failure with regard to risk of hospitalization and death. They demonstrated that extent of anemia was increasingly associated with risk of hospitalization and death, independent of underlying renal dysfunction and other co-morbidities. Furthermore, Kulier et al[18] demonstrated preoperative anemia to be an independent predictor of adverse outcome in patients undergoing coronary artery bypass surgery. In 4,804 patients undergoing elective coronary artery bypass surgery, they found that preoperative anemia was associated with an increased risk in postoperative events, starting at hemoglobin levels <11 g/dl in a dose-dependent fashion. Moreover, preoperative anemia has been shown to be an independent predictor of adverse outcome in patients undergoing other vascular or extensive surgery.[6,19] In a recent study, Wu et al[20] examined the effect of preoperative hematocrit levels and postoperative outcomes in elderly patients undergoing noncardiac surgery. In this large retrospective study, 310,311 patients were included and main outcomes were 30-day mortality and the composite of 30-day mortality and cardiac events. Mortality

Table 2
Thirty-day and five-year major adverse cardiac events according to severity of anemia

Variable	Degree of Anemia (hemoglobin g/dl)				*p* Value
	None (men >13.0, women >12.0)	Mild (men 12.2–13.0, women 11.2–12.0)	Moderate (men 11.0–12.1, women 10.2–11.1)	Severe (men 7.2–11.0, women 7.5–10.1)	
30-day MACEs	3.4%	6.8%	9.1%	20.0%	<0.001
5-yr MACEs	9.1%	21.4%	29.8%	42.2%	<0.001

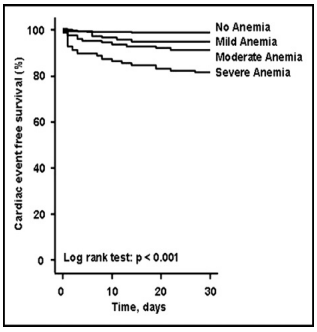

Figure 1. Thirty-day MACE-free survival for severity of preoperative anemia.

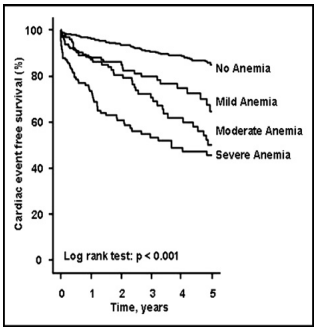

Figure 2. Five-year MACE-free survival for severity of preoperative anemia.

and cardiac event rates increased with positive or negative deviations from the reference hematocrit levels. After multivariate analysis, every percentage point deviation of hematocrit from the normal range was associated with a 1.6% increase in mortality. They concluded that even mild degrees of preoperative anemia or polycythemia were associated with an increased risk of mortality and cardiac events in elderly patients undergoing major noncardiac surgery. The main limitation if this study was that all data were gathered using the National Surgical Quality Improvement Program and not by using hospital records. Furthermore, renal dysfunction was expressed only in creatinine levels and known history of kidney disease, not as GFR, and no adjustments were made for differences in normal hematocrit levels in men and women. However, because the sample was so large, even mild preoperative anemia was significantly associated with 30-day mortality and cardiac events, supporting the trend found in this study. Furthermore, Diehm et al[21] reported anemia to be an independent risk factor for decreased long-term survival in patients with an abdominal aortic aneurysm undergoing endovascular repair.

Table 3
Multivariable associations among extent of anemia, level of estimated glomerular filtration rate, heart failure, and risks of 30-day and five-year major adverse cardiac events

Variable	30-day MACEs*†	5-yr MACEs*‡
Severity of anemia		
None	Reference	Reference
Mild	1.8 (0.8–4.1)	2.4 (1.5–4.2)
Moderate	2.3 (1.1–5.4)	3.6 (2.4–5.6)
Severe	4.7 (2.6–10.9)	6.1 (4.1–9.1)
GFR (ml/min/1.73 m^2)		
≥90	Reference	Reference
60–89	1.3 (0.7–2.8)	1.5 (1.0–2.5)
30–59	3.0 (1.4–4.9)	2.2 (1.2–4.0)
<30	4.7 (2.2–7.1)	2.6 (1.5–4.9)
Heart failure		
Left ventricular ejection fraction <35%	2.5 (1.5–4.6)	2.4 (1.5–3.6)

* Adjustments were made for anemia, GFR, heart failure, age, gender, type of vascular surgery, diabetes mellitus, hypertension, coronary heart disease, stroke, and chronic obstructive pulmonary disease.
† Values are odds ratios (95% confidence intervals).
‡ Values are hazards ratios (95% confidence intervals).

Anemia could therefore not just be a marker of other co-morbidities that increase the risk of perioperative cardiac events, but could be an independent and modifiable clinical marker. Although the clinical evidence is limited for whether treatment of anemia can improve clinical outcome, multiple studies have shown promising results.[11,22,23] In a prospective, randomized, placebo-controlled trial, Corwin et al[24] studied the effects and safety of epoetin-α treatment in 1,460 critically ill patients. They found a lower mortality in patients using epoetin-α compared with those who did not, which could have clinical implications. However, treatment with epoetin-α was also associated with an increase in thrombotic events. If this is converted to the perioperative setting, serious care should be taken because peripheral bypass surgery is associated with a high rate of thrombotic complications. With respect to long-term treatment, van Veldhuisen et al[25] conducted a prospective, randomized, placebo-controlled trial in which they found that, in patients with chronic heart failure and anemia, the use of darbepoetin-α was successful in increasing hemoglobin levels and improving certain quality-of-life indexes. Furthermore, in a randomized, open-label trial, Provenzano et al[26] showed

that treatment with epoetin-α was safe and effective in increasing hemoglobin in patients with anemia and chronic kidney disease. However, Drueke et al[27] recently showed that patients with severe renal disease (GFR <35 ml/min/$1.73m^2$) and mild anemia did not benefit from epoetin-β therapy.

Limitations of this study include those inherent to a retrospective analysis. The study population consisted of patients referred to a tertiary care center and may not fully represent a general population scheduled for elective vascular surgery. Also, due to the observational nature of the study, a causal relation could not be determined between preoperative anemia and perioperative MACEs. Furthermore, the cause of the measured anemia remains unknown, which could be important in determining possible preoperative treatments.

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Part 3

Pharmacological therapy

Chapter 9

Beta-Blockers improve Outcomes in Kidney Disease Patients Having Noncardiac Vascular Surgery

Kidney Int 2007;72:1527-34

Chapter 10

Impact of Cardioselective Beta-Blockers on Mortality in Patients with Chronic Obstructive Pulmonary Disease and Atherosclerosis

Am J Respir Crit Care Med 2008;178:695-700

Chapter 11

Statin Therapy is associated with Improved Outcomes in Vascular Surgery Patients with Renal Impairment

Am Heart J 2007;154:954-61

Chapter 12

Statin Use is associated with Early Recovery of Kidney Injury after Major Vascular Surgery and Improved Long-term Outcome

Nephrol Dial Transplant 2008, Jul 15. [Epub ahead of print]

Chapter 13

Effect of Statin Withdrawal on Frequency of Cardiac Events After Vascular Surgery

Am J Cardiol 2007;100:316-20

Chapter 14

Secondary Medical Prevention in Patients with Peripheral Arterial Disease

Eur J Vasc Endovasc Surg 2008;35:59-60

Chapter 9

Beta-Blockers improve Outcomes in Kidney Disease Patients Having Noncardiac Vascular Surgery

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β-Blockers improve outcomes in kidney disease patients having noncardiac vascular surgery

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β-Blockers are known to improve postoperative outcome after major vascular surgery. We studied the effects of β-blockers in 2126 vascular surgery patients with and without kidney disease followed for 14 years. Creatinine clearance was calculated using the Cockcroft-Gault equation, and kidney function was categorized as Stage 1 for a reference group of 550 patients, Stage 2 with 808 patients, Stage 3 with 627 patients, and combined Stages 4 and 5 with 141 patients. Outcome measures were 30-day and long-term all-cause mortality with a mean follow-up of 6 years. Cox proportional hazards models were used to control cardiovascular risk factors, including propensity for β-blocker use. In all, 129 (6%) and 1190 (56%) patients died respectively. Mortality rates were three- and two-fold higher, respectively, for patients at Stages 3–5 compared to the reference group for the two outcomes. β-Blocker use was significantly associated with a lower risk of mortality after surgery. The overall adjusted hazard ratio was 0.35 and 0.62, respectively, for individuals at Stages 3–5 compared to the reference group for 30-day and long-term mortality. This study shows that kidney function is a predictor of all-cause mortality and β-blocker use is associated with a lower risk of death in kidney disease patients undergoing elective vascular surgery.

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KEYWORDS: β-blockers; kidney disease; vascular surgery; creatinine clearance; cardiovascular disease; survival

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Recent estimates suggest that more than 20 million people have chronic kidney disease (CKD) in the US alone.[1] Furthermore, the CKD and dialysis populations are growing rapidly and are expected to exceed 30 million and 650 000, respectively, in the US by 2010.[2] In fact, progression of CKD exposes patients to an increased risk of development of vascular disease and cardiovascular morbidity and mortality.[3,4] In addition, it has recently been established that individuals with CKD are at moderately increased risk for developing abdominal aortic aneurysm (AAA) and peripheral arterial disease.[5,6]

Perioperative and long-term outcomes after vascular surgery are mainly dependent on the presence and extent of traditional cardiovascular risk factors, including hypertension, diabetes, dyslipidemia, and smoking, which are commonly present in patients with CKD.[7–10] Numerous studies have shown that CKD may be associated with higher rates of morbidity and mortality when these patients undergo open infrarenal AAA repair.[11,12] In addition, even moderate CKD seems to be a risk factor for postoperative death and complications after lower extremity revascularization procedures.[13]

To improve perioperative myocardial ischemia and long-term cardiovascular complications after noncardiac surgery, guidelines recommend β-blocker therapy in all patients at high risk for coronary artery disease.[14,15] Given the proven benefit of β-blockers in patients with normal kidney function with cardiac co-morbidities, β-blockers would seem to be attractive agents to reduce cardiovascular morbidity and mortality associated with noncardiac surgery in the CKD population. Hence, the purpose of this observational study was to describe the association of β-blocker therapy on short- and long-term outcomes of patients undergoing major noncardiac vascular surgery, for different stages of kidney dysfunction.

RESULTS

Patient characteristics

The mean age of all 2126 patients was 66±11 years, 76% were male and half of patients underwent AAA surgery

(51%). The mean follow-up was 5.98 ± 3.68 years (median, 6.21 years).

A total of 757 (36%) patients received β-blockers before surgery. β-Blocker users had a higher prevalence of cardiovascular risk factors (hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypercholesterolemia, and current history of smoking; $P<0.001$ for all), a higher proportion of patients with a history of cardiovascular disease (myocardial infarction (MI), coronary revascularization, heart failure, angina, and cerebrovascular disease; $P<0.01$ for all), and additional medication use (including statins, angiotensin-converting enzyme inhibitors (ACE) inhibitors, anti-coagulants, and calcium antagonists; $P<0.001$ for all). Importantly, no difference in baseline kidney function, assessed by serum creatinine or creatinine clearance (CrCl), was observed ($P=0.3$ and 0.9, respectively). Of note, patients using β-blockers underwent more AAA surgeries and less limb arterial revascularization procedures ($P<0.001$ for all).

The mean serum creatinine concentration and CrCl in this population was $1.27 \pm 1.1\ \mathrm{mg\,dl^{-1}}$ and $74.0 \pm 34\ \mathrm{ml\,min^{-1}}$, respectively, and 768 (36%) patients had a CrCl $<60\ \mathrm{ml\,min^{-1}}$ (mean CrCl $42.7 \pm 14\ \mathrm{ml\,min^{-1}}$; Table 1). A total of 550 (26%) patients had a CrCl of $\geqslant 90\ \mathrm{ml\,min^{-1}}$; 38% ($n=808$) had a CrCl of 60–89 $\mathrm{ml\,min^{-1}}$; 30% ($n=627$) had a CrCl of 30–59 $\mathrm{ml\,min^{-1}}$; and 7% (141) had a CrCl of $<30\ \mathrm{ml\,min^{-1}}$.

Patients with lower CrCl levels had significantly higher proportions of hypertension, hypercholesterolemia, COPD, history of MI, heart failure, angina, and cerebrovascular disease and they received more diuretics, ACE inhibitors, calcium antagonists, and nitrates. Importantly, no difference in β-blocker use was found between the different kidney function groups ($P=0.1$).

Of the subjects with a CrCl $<60\ \mathrm{ml\,min^{-1}}$, 268 (35%) patients were receiving β-blockers. Baseline characteristics are summarized in Table 2. Patients with a CrCl $<60\ \mathrm{ml\,min^{-1}}$ and receiving β-blockers were younger, had a higher proportion of traditional cardiovascular risk factors—including a history of hypertension, diabetes, and elevated cholesterol level—higher prevalence of cardiovascular disease, and usage of other cardioprotective medications including ACE inhibitors and statins. No differences were observed in the mean serum creatinine and CrCl.

Propensity score analysis

Within the propensity score analysis, the following baseline variables significantly predicted β-blocker therapy: hypertension (odds ratio (OR) 1.48, 95% confidence interval (CI): 1.16–1.88), history of MI (OR 1.78, 95% CI: 1.39–2.27), coronary revascularization (OR 1.65, 95% CI: 1.30–2.10), AAA surgery (OR 1.84, 95% CI: 1.49–2.29), and year of operation per 2 years of increase (OR 1.25, 95% CI: 1.61–1.34). According to medical therapy, usage of statins (OR 2.06, 95% CI: 1.56–2.72), diuretics (OR 1.39, 95% CI: 1.07–1.82), calcium antagonist (OR 1.78, 95% CI: 1.41–2.25), nitrates (OR 2.61, 95% CI: 2.00–3.41), and ACE inhibitors (OR 1.27, 95% CI: 1.01–1.62) were significant predictors of β-blocker prescription. The graphical method of examination by box plots showed a balance of the estimated propensity score between β-blocker users and β-blocker non-users within each decile of the propensity score.

Short-term outcome

In total, 129 (6.1%) patients died within 30 days after surgery. A clear relationship between the levels of kidney function and short-term mortality was observed. For patients with a baseline CrCl $\geqslant$ 90, 60–89, 30–59, and $<30\ \mathrm{ml\,min^{-1}}$, the mortality within 30 days was 2.7, 4.5, 9.3, and 14.2%, respectively ($P=<0.001$; Table 3). Patients with mild impairment of kidney function, that is CrCl 60–89 $\mathrm{ml\,min^{-1}}$, were not associated with adverse short-term outcome (OR 1.21, 95% CI: 0.62–2.36) when compared with the reference group. When CrCl was evaluated as a continuous variable, the adjusted OR for short-term mortality was 1.02 (95% CI: 1.01–1.04) per $1\ \mathrm{ml\,min^{-1}}$ decrease in CrCl ($P<0.001$). In addition, β-blocker therapy was associated with improved short-term outcome for the whole cohort (adjusted OR 0.39, 95% CI: 0.24–0.64). In addition, β-blocker use was associated with a lesser risk of all-cause mortality for patients with a CrCl $\geqslant 60\ \mathrm{ml\,min^{-1}}$ (adjusted OR 0.39, 95% CI: 0.19–0.83) and for patients with a CrCl $<60\ \mathrm{ml\,min^{-1}}$ (adjusted OR 0.35, 95% CI: 0.19–0.72; Table 4).

Long-term outcome

During 5.98 ± 3.68 years of follow-up, 1190 (56%) patients died. All-cause mortality rates according to baseline kidney function were 36.2, 53.7, 70.2, and 83.0% for patients with a baseline CrCl $\geqslant$ 90, 60–89, 30–59, and $<30\ \mathrm{ml\,min^{-1}}$, respectively ($P<0.001$; Figure 1). Importantly, even patients with mild kidney dysfunction, that is CrCl 60–89 $\mathrm{ml\,min^{-1}}$, were at significant higher risk (adjusted hazard ratio (HR) 1.20, 95% CI: 1.01–1.44; Table 3), compared to patients with normal kidney function. When CrCl was evaluated as a continuous variable, the adjusted HR for long-term mortality was 1.01 (95% CI: 1.01–1.02) per $1\ \mathrm{ml\,min^{-1}}$ decrease in CrCl ($P<0.001$). During this observation period, β-blocker use remained an independent predictor for long-term survival in all patients (adjusted HR 0.82, 95% CI: 0.71–0.93; Table 4). As shown in Figure 2, the association of β-blocker therapy was more pronounced in patients with a baseline CrCl of $<60\ \mathrm{ml\,min^{-1}}$ (adjusted HR 0.62, 95% CI: 0.50–0.76), compared to patients with a CrCl of $\geqslant 60\ \mathrm{ml\,min^{-1}}$ (adjusted HR 1.01, 95% CI: 0.84–1.22).

DISCUSSION

In this cohort of men and women who underwent elective vascular surgery, the level of kidney function is an independent predictor of short- and long-term mortality. We also found that the risk of all-cause mortality increased progressively with decreasing kidney function. In particular,

Table 1 | Baseline characteristics of all patients, according to the level of baseline kidney function

	All patients *N*=2126 (100%)	⩾90 ml min^{-1} *N*=550 (26%)	60–89 ml min^{-1} *N*=808 (38%)	30–59 ml min^{-1} *N*=627 (30%)	<30 ml min^{-1} *N*=141 (7%)	*P*-value
Demographics						
Mean age (±s.d.)	66.4 (±11)	56.9 (±11)	67.6 (±9)	72.7 (±8)	67.8 (±13)	<0.001
Male (%)	76	79	78	73	63	<0.001
Abdominal aorta surgery	51	46	54	54	45	0.003
Lower limb arterial revascularization surgery	49	55	46	46	55	0.003
Cardiovascular risk factor (%)						
Hypertension	49	41	50	51	64	<0.001
Diabetes mellitus	16	15	16	17	21	0.5
Current smoker	27	27	30	26	24	0.3
Hypercholesterolemia	20	22	23	14	16	<0.001
COPD	21	18	24	23	15	0.008
Body mass index (±s.d.)	24.8 (±5)	26.2 (±4)	24.7 (±4)	24.1 (±6)	22.2 (±4)	<0.001
Serum creatinine (±s.d.)	1.27 (±1.1)	0.79 (±0.2)	0.99 (±0.2)	1.3 (±0.4)	3.61 (±2.8)	<0.001
Creatinine clearance (±s.d.)	74.0 (±34)	117.6 (±28)	74.0 (±8)	48 (±8)	18.3 (±8)	<0.001
Disease history (%)						
Myocardial infarction	29	21	30	33	36	<0.001
Coronary revascularization	26	25	28	26	22	0.5
Heart failure	7	4	6	8	14	<0.001
Angina	17	13	18	20	16	0.01
Cerebrovascular disease	7	4	7	9	15	<0.001
Medication use (%)						
β-Blockers	36	33	38	34	40	0.1
Statins	26	29	29	21	19	<0.001
Diuretics	20	13	19	27	31	<0.001
ACE inhibitors	34	27	34	38	45	<0.001
Calcium antagonists	36	29	37	37	51	<0.001
Nitrates	20	16	19	23	31	<0.001
Aspirin	32	31	32	33	29	0.7
Anti-coagulation	24	26	25	22	19	0.2

ACE inhibitors, angiotensin-converting enzyme inhibitors; COPD, chronic obstructive pulmonary disease; s.d., standard deviation.

patients with a CrCl < 60 ml min^{-1} were more likely to have a significant risk of death in the first 30 days or in the first 10 years after surgery when compared with patients without kidney impairment after controlling for demographic and clinical variables. In addition, perioperative β-blocker use was associated with a 65 and 38% reduction in the short- and long-term all-cause mortality in patients with a CrCl < 60 ml min^{-1}, respectively. To our knowledge, there are a few observational studies of the relationship between kidney dysfunction, noncardiac surgery outcomes, and β-blocker use.

Cardiovascular disease is the major cause of morbidity and mortality in the Western world.[16] Acute and long-term therapy with β-blockers has become a standard of care of patients with acute myocardial infarction and congestive heart failure.[17] In nonrenal patients, β-blocker therapy has been shown to reduce infarct size and mortality among MI patients.[16] In addition, in a recent meta-analysis, β-blockers were shown to have a large beneficial effect on hospitalizations and all-cause mortality in stable patients with New York Heart Association class II or III heart failure and normal kidney function.[18] The main proposed mechanisms underlying the efficacy of β-blockers include decreasing cardiac energy requirements and modification of arrhythmias risk by antagonizing the deleterious effects of the sympathetic nervous system.[19]

Although the increased risk of cardiovascular events among persons with kidney disease not requiring dialysis is well established, the mechanism explaining the increased risk of cardiovascular death in patients with kidney dysfunction is the focus of the ongoing investigation.[20] Multiple possible explanations have been proposed to explain the association between kidney dysfunction and increased risks of death and cardiovascular disease, including left ventricular hypertrophy,[21] endothelial dysfunction,[22] arterial stiffness,[23] and increased levels of inflammatory factors.[24]

In addition to the above factors, sympathetic nervous system activation likely plays a significant role in the increased cardiovascular risk of patients with kidney disease. Increased sympathetic activity is now recognized as an important mechanism involved in cardiovascular complications in subjects with end-stage renal disease.[25,26] A recent review by Bakris *et al.*[27] assessed an abundance of experimental and human data linking kidney disease to the activation of the sympathetic nervous system. Using different models of kidney injury, such as renal artery ligation and 5/6 nephrectomy, it has been shown that kidney damage is associated with increased afferent sympathetic activity.[28–30]

Table 2 | Baseline characteristics of patients with a creatinine clearance $<60\ ml\ min^{-1}$, according to β-blocker use

	All patients N=768 (100%)	β-Blocker use N=268 (35%)	No β-blocker use N=500 (65%)	P-value
Demographics				
Mean age (±s.d.)	71.7 (±9)	70.7 (±8)	72.4 (±10)	0.02
Male (%)	71	70	72	0.6
Abdominal aortic surgery	52	59	49	<0.001
Lower limb arterial revascularization surgery	48	41	51	<0.001
Cardiovascular risk factor (%)				
Hypertension	53	71	43	<0.001
Diabetes mellitus	17	21	15	0.041
Current smoker	26	29	24	0.1
Hypercholesterolemia	15	22	11	<0.001
COPD	21	24	19	0.1
Body mass index (±s.d.)	23.7 (±6)	23.5 (±4)	23.9 (±7)	0.5
Disease history (%)				
Myocardial infarction	33	46	27	<0.001
Coronary revascularization	25	35	20	<0.001
Heart failure	9	12	8	0.1
Angina	19	28	14	<0.001
Cerebrovascular disease	10	16	7	<0.001
Medication use (%)				
Statins	20	35	13	<0.001
Diuretics	27	36	23	<0.001
ACE inhibitors	39	52	32	<0.001
Calcium antagonists	40	58	29	<0.001
Nitrates	24	36	18	<0.001
Aspirin	32	41	28	<0.001
Anti-coagulation	22	25	20	0.06
Baseline kidney function (%)				
Serum creatinine (±s.d.)	1.90 (±1.7)	1.99 (±1.8)	1.85 (±1.7)	0.3
Creatinine clearance (±s.d.)	42.7 (±14)	42.3 (±15)	42.9 (±14)	0.6

ACE inhibitors, angiotensin-converting enzyme inhibitors; COPD, chronic obstructive pulmonary disease; s.d., standard deviation.

Table 3 | Multivariate associations of the level of baseline kidney function and short- and long-term mortality

	Short-term all-cause mortality			Long-term all-cause mortality		
	Unadjusted OR (95% CI)	Adjusted for confounders[a] OR (95% CI)	Adjusted for confounders and propensity score[b] OR (95% CI)	Unadjusted HR (95% CI)	Adjusted for confounders[a] HR (95% CI)	Adjusted for confounders and propensity score[b] HR (95% CI)
All patients (n=2126)						
CrCl $\geqslant 90\ ml\ min^{-1}$ (ref.)	1.0	1.0	1.0	1.0	1.0	1.0
CrCl 60–89 $ml\ min^{-1}$	1.66 (0.90–3.07)	1.16 (0.60–2.24)	1.21 (0.62–2.36)	1.68 (1.42–1.99)	1.19 (1.02–1.43)	1.20 (1.01–1.44)
CrCl 30–59 $ml\ min^{-1}$	3.64 (2.04–6.50)	2.29 (1.16–4.53)	2.30 (1.16–4.54)	2.64 (2.23–3.12)	1.64 (1.35–2.00)	1.63 (1.33–1.97)
CrCl $<30\ ml\ min^{-1}$	5.90 (2.93–11.85)	4.96 (2.27–10.83)	5.32 (2.42–11.69)	5.32 (4.23–6.70)	3.89 (3.02–5.01)	4.00 (3.10–5.16)

ACE inhibitors, angiotensin-converting enzyme inhibitors; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HR, hazard ratio; OR, odds ratio.

[a]Adjusted for age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, and year of operation.

[b]Adjusted for age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, year of operation, statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anti-coagulations.

Furthermore, Klein *et al.*[31] recently reported that sympathetic activity was inappropriately high in a group of 57 patients with renal parenchymal disease. The authors hypothesized that renal structural changes lead to stimulation of the sympathetic nervous system by causing local or diffuse renal ischemia, which has been reported to stimulate renal afferents in animal experiments. In addition to renal afferent sympathetic discharge, there are other plausible mechanisms connecting kidney disease to sympathetic overactivity,[32] including elevated angiotensin II,[33] and suppressed brain nitric oxide. Hence, the factors responsible for sympathetic activation in patients with CKD appear to be multifactorial.

Table 4 | Multivariate associations of the level of baseline kidney function, β-blocker therapy, and short- and long-term mortality

	Short-term all-cause mortality			Long-term all-cause mortality		
	Unadjusted OR (95% CI)	Adjusted for confounders[a] OR (95% CI)	Adjusted for confounders and propensity score[b] OR (95% CI)	Unadjusted HR (95% CI)	Adjusted for confounders[a] HR (95% CI)	Adjusted for confounders and propensity score[b] HR (95% CI)
All patients (n=2126)						
β-Blocker therapy	0.48 (0.31–0.74)	0.34 (0.21–0.55)	0.39 (0.24–0.64)	0.91 (0.81–1.03)	0.79 (0.69–0.90)	0.82 (0.71–0.93)
Patients with CrCl ⩾ 60 ml min^{-1} (n=1358)						
β-Blocker therapy	0.54 (0.28–1.03)	0.36 (0.17–0.74)	0.39 (0.19–0.83)	1.06 (0.90–1.24)	0.92 (0.77–1.11)	1.01 (0.84–1.22)
Patients with CrCl < 60 ml min^{-1} (n=768)						
β-Blocker therapy	0.45 (0.25–0.79)	0.32 (0.17–0.61)	0.35 (0.19–0.72)	0.74 (0.61–0.88)	0.62 (0.51–0.76)	0.62 (0.50–0.76)

ACE inhibitors, angiotensin-converting enzyme inhibitors; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HR, hazard ratio; OR, odds ratio.

[a]Adjusted for age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, and year of operation.

[b]Adjusted for age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, year of operation, statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anti-coagulations.

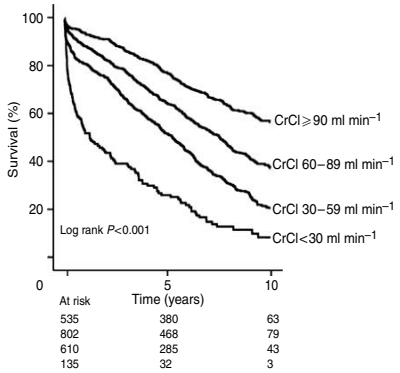

Figure 1 | Kaplan–Meier estimate of overall survival by level of kidney function (CrCl) during 5.98±3.68 years of follow-up.

The sympathetic nervous system, by acting through β_1 and β_2 receptors, in addition to its effect on myocardial repolarization, can increase heart rate, which not only adversely affects the relation between myocardial demand and supply, but can also alter the structure and function of the heart, in particular by causing hypertrophy and fibrosis.[19] Therefore, the use of adrenergic inhibitors is a logical strategy to examine whether interference with the sympathetic system reduces the high cardiovascular morbidity and mortality of patients with kidney dysfunction. Although several observational studies and a small randomized trial[34–36] suggest definite survival benefits derived from the use of β-blockers in hemodialysis patients, there are a few data on the use of β-blockers in treating patients with different stages of kidney dysfunction and its relationship with short- and long-term outcomes after major noncardiac surgery. Of note, β-blockers have been associated with a reduction in mortality in 419 patients with renal insufficiency and heart failure in a Canadian prospective study.[37]

Estimates of β-blocker use in patients with kidney disease vary, but all studies show that β-blockers are used by only a minority of patients. The US Renal Data System Waves 3 and 4 studies observe that only 8.5% of the chronic dialysis patient population was using a β-blocker.[34] In addition, available data indicate that the actual use of β-blockers in patients with kidney dysfunction actually decreases as the kidney function declines.[38] McAlister *et al.*[37] and Gibney *et al.*[39] have reported that only 18 and 32% of CKD patients with heart failure and post-coronary artery bypass graft were receiving β-blockers, respectively. These observations are consistent with our findings as only 35% of patients of our cohort with a CrCl < 60 ml min^{-1} were receiving some type of β-blocker. The juxtaposition of these results suggests that the underutilization of β-blockers appears to be present in all stages of kidney disease including in the chronic dialysis patients. The four major reasons cited for this low utilization are as follows: (1) therapeutic nihilism for these chronically ill patients; (2) the unconventional epidemiology of CVD in this population; (3) the paucity of efficacy data in patients with serum creatinine > 2.0 mg dl^{-1}; and (4) the potential for higher rates of adverse effects, including hypotension, hyperkalemia, and glycemic abnormalities.[40]

Limitations of this study should be noted. First, the analysis of cardioprotective medication, like β-blockers, in a retrospective cohort analysis is prone to potential bias, as the use of β-blockers was not randomized. Despite using propensity to adjust as much as possible for the bias inherent in the decision about β-blocker therapy,[41] we cannot exclude the possibility of residual confounding. Second, the analysis was performed on the basis that if patients were or not receiving β-blocker therapy on the day of hospital admission, we could not assess changes in the type or dosage of β-blockers after the initiation of the study. Third, the study

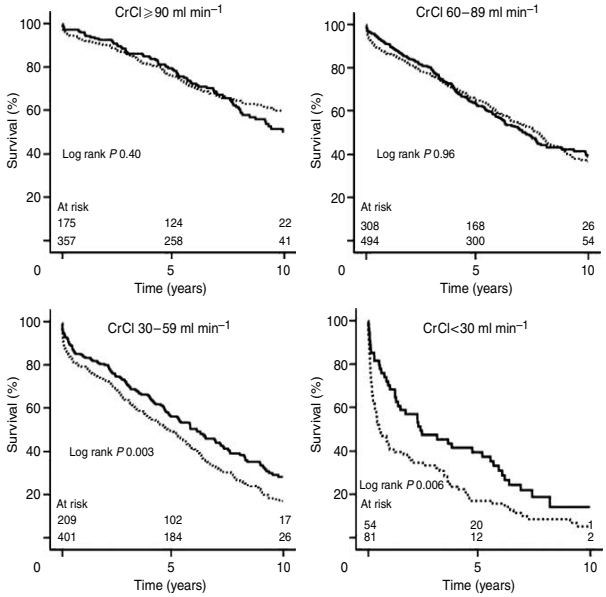

Figure 2 | Kaplan–Meier estimate of overall survival by level of kidney function (CrCl) and β-blocker therapy during 5.98 ± 3.68 years of follow-up. —β-Blocker use; ..... No β-blocker use.

population included in this analysis is almost entirely Caucasian, making these results not generalizable to other populations or places. Finally, our definition of kidney function was based on a CrCl derived from a single serum creatinine on the day of the procedure, rather than on a direct measurement of kidney function like iothalamate clearance. Additionally, the creatinine value we did use could have been influenced by cardioprotective medications or clinical status. It is possible that within-person variation in serum creatinine resulted in misclassification of kidney function. Furthermore, we did not collect data regarding the duration or cause of kidney dysfunction or other signs of kidney disease such as microalbuminuria or overt proteinuria, which is a well-established risk factor for cardiovascular mortality.[42]

In this large observational study, the perioperative administration of β-blockers was associated with clear and clinically significant reductions in short- and long-term mortality in patients with moderate and advanced kidney dysfunction who underwent high-risk elective vascular surgery. This study also demonstrates an underuse of β-blocker therapy in patients with kidney dysfunction undergoing major vascular surgery, which is comparable to other epidemiologic studies. Although the data reported in this cohort suggest a beneficial association of β-blockers with survival in a high-risk patient population, large long-term clinical trials are desperately needed to evaluate the safety and efficacy of β-blockers in patients with kidney disease not requiring dialysis.

MATERIALS AND METHODS

Study design and patient selection

Between January 1993 and June 2006, a cohort of 2126 patients older than 18 years of age underwent open noncardiac vascular surgery at Erasmus MC, Rotterdam, the Netherlands, and were entered into a computerized database. All patients had undergone elective open infrarenal AAA or lower limb arterial revascularization procedures. Patients scheduled for lower extremity amputations were excluded. The analysis was made according to whether or not patients were taking β-blockers on the day of hospital admission, and does not incorporate changes in medical treatment during the follow-up period. All patients agreed on participation in the study, and the study was conducted according to the Declaration of the Helsinki Principle.

Baseline characteristics

On all patients the information on cardiovascular risk factors was recorded and included age, gender, hypertension (defined as systolic blood pressure $\geqslant$140 mm Hg, diastolic blood pressure $\geqslant$90 mm Hg, or use of anti-hypertensive medication), diabetes mellitus (the presence of a fasting blood glucose $\geqslant$140 mg dl^{-1} ($\geqslant$7.8 mmol l^{-1}) or requirement for insulin or oral hypoglycemic agents), smoking status, hypercholesterolemia (total cholesterol of $>$200 mg dl^{-1} ($>$5.2 mmol l^{-1})), COPD according to symptoms and pulmonary function tests (i.e. forced expiratory volume in 1 s $<$70% of maximal age and gender predictive value), body mass index, serum

creatinine, the presence of ischemic heart disease (prior MI, prior coronary revascularization and angina pectoris), heart failure (defined according to the New York Heart Association classification), cerebrovascular disease (history of cerebrovascular accident or transient ischemic attack), and preoperative medication use (β-blockers, statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anti-coagulants). All prescription and over-the-counter medications were noted on the day of admission and were ascertained if medication was documented at least 1–3 months before hospital admission for surgery.

Kidney function assessment

Fasting serum creatinine was measured preoperatively in all patients, either at the outpatient preoperative screening visit or on the day of hospital admission. Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method.[43] Because a number of factors such as age and gender can influence serum creatinine concentrations,[44,45] the level of kidney function was defined by CrCl using the Cockcroft and Gault formula, which includes measures of age, weight, and sex:

$\mathrm{CrCl}\ (\mathrm{ml\,min^{-1}}) = (140 - \mathrm{age}) * (\mathrm{body\ weight})/72 * \mathrm{serum\ creatinine}$ (multiplied by 0.85 in women),[46] where serum creatinine is in $\mathrm{mg\,dl^{-1}}$, age is in years, and weight is in kilograms.

Classification of kidney function

Patients were divided into four categories, based on the baseline CrCl value: $\geqslant 90$, (reference); 60-89; 30–59, and $<30\,\mathrm{ml\,min^{-1}}$. These cutoffs were chosen on the basis of the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines as they correspond to the different stages of CKD.[47,48]

Clinical follow-up and end points

Postoperative clinical information was retrieved from an electronic database of patients maintained in our hospital. From the municipal civil registries, we obtained the survival status. Follow-up was complete in 97.9%. The primary end point of this analysis was the composite of short- and long-term all-cause mortality. Short-term mortality was defined as all deaths occurring during postoperative in-hospital stay or after hospital discharge but within the first 30 days after surgery. Long-term mortality was defined as death occurring in the first 10 years after surgery. For both the short- and long-term mortality survival time was calculated from the date of surgery to the date of censoring for the occurrence of death.

Data analysis

Continuous data are described as mean values and their standard deviations (SDs), and dichotomous data are described as percentage frequencies. The χ^2-test was used for categorical variables, and the analysis of variances test was used for continuous variable to evaluate differences in baseline characteristics between β-blocker users and between the four kidney function categories.

We developed a propensity score for the likelihood of receiving β-blocker therapy, and applied a multivariable logistic regression analysis to calculate the propensity score. The variables included in the model were age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of MI and coronary revascularization, heart failure, angina, cerebrovascular disease, year of operation, and use of statins, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anti-coagulation.

Kaplan–Meier survival analysis was used to describe the incidence of death over time. The log-rank test was applied to study differences in survival between the four categories of kidney function ($\geqslant 90$, 60-89, 30-59, and $<30\,\mathrm{ml\,min^{-1}}$) and the association with β-blocker use within different categories of kidney function. For further evaluation, the multivariate logistic regression analysis and the Cox proportional hazard regression analysis, with adjustment for confounders and propensity, were performed for the short- and long-term analysis, respectively. All potential confounders (age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of MI, coronary revascularization, heart failure, angina, cerebrovascular disease, and year of operation) were entered in the multivariable model to ensure an unbiased estimate for the relation between β-blocker use and short- and long-term all-cause mortality for all patients and for the different stages of kidney dysfunction.

Unadjusted and adjusted ORs and HRs were reported with corresponding 95% CIs. $P<0.05$ was considered to be significant. All computations were performed with SPSS software version 12.0.1 (SPSS Inc., Chicago, IL, USA), running under Windows 2000 Professional.

CONFLICT OF INTEREST

There are no conflicts of interest, including specific financial interest and relationships and affiliations relevant to the subject matter or materials discussed in this study.

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Chapter 10

Impact of Cardioselective Beta-Blockers on Mortality in Patients with Chronic Obstructive Pulmonary Disease and Atherosclerosis

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Impact of Cardioselective β-Blockers on Mortality in Patients with Chronic Obstructive Pulmonary Disease and Atherosclerosis

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Rationale: **β-Blocker use is associated with improved health outcomes in patients with cardiovascular disease. There is a general reluctance to prescribe β-blockers in patients with chronic obstructive pulmonary disease (COPD) because they may worsen symptoms.**
Objectives: **We investigated the relationship between cardioselective β-blockers and mortality in patients with COPD undergoing major vascular surgery.**
Methods: **We evaluated 3,371 consecutive patients who underwent major vascular surgery at one academic institution between 1990 and 2006. The patients were divided into those with and without COPD on the basis of symptoms and spirometry. The major endpoints were 30-day and long-term mortality after vascular surgery. Patients were defined as receiving low-dose therapy if the dosage was less than 25% of the maximum recommended therapeutic dose; dosages higher than this were defined as intensified dose.**
Measurements and Main Results: **There were 1,205 (39%) patients with COPD of whom 462 (37%) received cardioselective β-blocking agents. β-Blocker use was associated independently with lower 30-day (odds ratio, 0.37; 95% confidence interval, 0.19–0.72) and long-term mortality in patients with COPD (hazards ratio, 0.73; 95% confidence interval, 0.60–0.88). Intensified dose was associated with both reduced 30-day and long-term mortality in patients with COPD, whereas low dose was not.**
Conclusions: **Cardioselective β-blockers were associated with reduced mortality in patients with COPD undergoing vascular surgery. In carefully selected patients with COPD, the use of cardioselective β-blockers appears to be safe and associated with reduced mortality.**

Keywords: chronic obstructive pulmonary disease; β-adrenergic blocking agents; peripheral arterial disease; vascular surgery

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

β-Blockers are often withheld from patients with chronic obstructive pulmonary disease (COPD) because of fear of pulmonary worsening. However, cardioselective β-blockers are demonstrated to be safe and beneficial in patients with COPD.

What This Study Adds to the Field

Cardioselective β-blockers are beneficial in the reduction of mortality in patients with COPD undergoing vascular surgery, with an intensified dosage being most effective.

During the last decade, β-blocker therapy has become an increasingly important treatment in patients undergoing noncardiac surgery. Several studies have shown that perioperative β-blocker therapy can reduce the incidence of peri- and postoperative cardiac complications, including sudden death, angina, and myocardial infarction in patients undergoing noncardiac vascular surgery (1–5). Accordingly, the American College of Cardiology and the American Heart Association recommend the use of β-blockers in patients undergoing major vascular surgery (6). Many patients with cardiovascular disease (CVD) have coexisting chronic obstructive pulmonary disease (COPD) and vice versa possibly because they share the same risk factor, cigarette smoking (7). In patients with COPD, approximately 30% of all deaths are from CVD (8). β-Blockers are, however, frequently withheld from patients with COPD with coexisting CVD because of the concern that they may induce bronchoconstriction from blockade of β_2-adrenoreceptors. Although nonselective β-blockers act on the β_2-adrenoreceptors to inhibit bronchodilation (9), there is substantial evidence that cardioselective β-blockade is likely safe and beneficial in patients with COPD and CVD (10–18). Additional concern regarding use of β-blockers in COPD is the potential for insensitivity. COPD is associated with systemic inflammation, which may accelerate metabolism of β-blockers, leading to reduced efficacy. Patients are particularly vulnerable to cardiac events during and after major vascular surgery (19). The primary aim of the present study was to investigate the association between cardioselective β-blockers and 30-day and long-term mortality in patients with COPD who undergo major vascular surgery. The secondary objective was to determine the relationship between low and intensified dosage and mortality. Some of the results of this study have been previously reported in the form of an abstract (20).

METHODS

Study Population

This observational retrospective study included 3,371 consecutive patients undergoing elective vascular surgery between 1990 and 2006 at the Erasmus Medical Center, Rotterdam, The Netherlands. The surgical procedures included abdominal aortic surgery (comprising

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aortic-to-aortic or aortic-bifurcation prostheses procedures, removal of infected prostheses, and other operations of the abdominal aorta), carotid endarterectomy (including reconstruction or desobstruction of the carotid artery), and lower limb arterial reconstruction procedures (including iliac-femoral, femoral-popliteal, femoral-tibila artery bypass procedures, removal of infected prostheses, peripheral desobstruction and other elective peripheral arterial surgical reconstructions). Vascular reconstructions due to trauma and ruptured abdominal aortic aneurysms were excluded.

Abstracted variables included patient demographics (age and sex) and cardiac risk factors, including the following: hypertension (defined as a blood pressure ⩾ 140/90 mm Hg), hypercholesterolemia (total cholesterol of >5.2 mmol/L), diabetes mellitus (presence of fasting blood glucose of ⩾140 mg/dl or treatment with insulin or oral hypoglycemic agents), serum creatinine renal dysfunction (baseline serum creatinine > 1.5 mg/dl), current smoking status, and body mass index (BMI) calculated as weight divided by height squared (kg/m^2). The patient's cardiovascular history was assessed and included the following: previous myocardial infarction, coronary revascularization (coronary artery bypass graft and/or percutaneous coronary intervention), heart failure (defined according to the New York Heart Association classification), angina pectoris, stroke, and/or transient ischemic attack. The use of bronchodilators and corticosteroids at baseline was captured. Cardiac medications at baseline were also evaluated. These included β-blockers, statins, angiotensin-converting enzyme inhibitors, diuretics, aspirin, anticoagulants, nitrates, and calcium channel blockers. Almost all (97%) of the prescribed β-blockers were cardioselective β-blocking agents: metoprolol, bisoprolol, and atenolol. To evaluate the association of low and intensified β-blocker dose with mortality, we converted the β-blocker dosage at initial hospitalization. Low dose was defined as patients using less than 25% of the maximum recommended therapeutic dose, whereas intensified dose was defined as an average dose exceeding or equal to 25% of the maximum recommended therapeutic dose. For metoprolol, a maximum recommended therapeutic dose of 400 mg was used, for bisoprolol 10 mg was used, and for atenolol 100 mg was used.

Pulmonary Function Testing

A diagnosis of COPD was based on post-bronchodilator spirometric values in conjunction with a history of cough, sputum production, and/or dyspnea. COPD was defined according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (FEV_1 to FVC ratio less than 70% [21]). Disease severity was classified into three groups: I = mild COPD ($FEV_1/FVC < 0.70$ and $FEV_1 \geqslant 80\%$ of the predicted FEV_1), II = moderate COPD ($FEV_1/FVC < 0.70$ and FEV_1 $50\% \leqslant FEV_1 < 80\%$ of the predicted FEV_1), and III = severe COPD ($FEV_1/FVC < 0.70$ and FEV_1 $30\% \leqslant FEV_1 < 50\%$ of the predicted FEV_1) (21). We used the equation of Quanjer and colleagues (22), adjusted for age, sex, and height, to calculate the predicted FEV_1 value, which has been demonstrated to make an accurate prediction (23). The equation for males is $4.30 \times \text{height (m)} - \text{age} \times 0.029 - 2.49$ and for women is $3.95 \times \text{height (m)} - \text{age} \times 0.025 - 2.60$ (22). In 82% of the patients with COPD, a preoperative spirometry was performed. The patients without a preoperative pulmonary function test were classified as having no COPD if they were free of pulmonary complaints (cough and dyspnea), and not currently receiving pulmonary medications (i.e., bronchodilators and corticosteroids) and demonstrated normal arterial blood gases on room air ($Pco_2 < 6.4$ kPa and $Po_2 > 10.0$ kPa).

Follow-up and Endpoints

Follow-up was completed in 96% of the study patients, with a median follow-up of 5 years. Survival status was obtained from the municipal civil registries. Clinical baseline characteristics were retrieved from the hospital medical records. Endpoints of the study were 30-day and long-term (10-yr) mortality regardless of the cause.

Statistical Analysis

Continuous data are presented as means ± SD and compared using the Student's t test. Categorical variables among the patient groups are expressed as percentages and compared using χ^2 tests. Univariate and multivariate logistic regression analyses were used to determine the relationship of cardioselective β-blockers and their dose with 30-day mortality. Cox proportional hazards models were used to analyze the impact of these drugs on long-term mortality, adjusted for salient covariates, including age, sex, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, BMI, type of surgery, year of surgery, and cardiovascular history. In addition, a composite variable of statins, aspirin, and angiotensin-converting enzyme inhibitors was included. Patients who received nonselective β-blockers (n = 112; 3%) were excluded from the analysis. In addition, using a multivariate logistic regression model, we developed a propensity score to adjust for the likelihood of receiving β-blockers in subjects with COPD and non-COPD subjects. The variables in this model included age, sex, COPD hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, BMI, type of surgery, year of surgery, all variables on cardiovascular history, and all cardiac and pulmonary medications (Table 1). The fit of the propensity score model was assessed using c-statistics and the Hosmer-Lemeshow goodness-of-fit test. In all comparative analysis of β-blockers, patients who were not on β-blocker therapy were used as the reference group. Odds ratios (ORs) and hazard ratios (HRs) were calculated from these models together with their 95% confidence intervals (CIs). For all tests, a two-sided P value of less than 0.05 was considered significant. All statistical analyses were performed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Baseline Characteristics

Of the 3,371 patients (mean age, 66 ± 12 yr; 73% male), 1,029 (31%) received cardioselective β-blockers at their initial hospitalization (Table 1). The commonly used β-blockers were bisoprolol at 50% (n = 514), atenolol at 15% (n = 151), and metoprolol at 32% (n = 325). Patients with β-blockers were more likely to have underlying history of cardiac disease, hypertension, and hypercholesterolemia (all $P < 0.001$). The percentage of β-blocker use was not significantly different among the COPD severity groups (mild COPD, 39%; moderate COPD, 35%; and severe COPD, 33%; $P = 0.20$).

Association between Cardioselective β-Blockers and Mortality

Overall, there were 1,265 (39%) patients with COPD. Of these patients, 462 (37%) used cardioselective β-blocking agents. In comparison, 567 (28%) of the patients who did not have COPD used β-blockers. Within 30 days of surgery, 16 (4%) patients with COPD who were receiving β-blockers died. In contrast, 66 (8%) patients who did not use β-blockers died during the same period of time ($P = 0.001$). Over the entire follow-up period, 184 (40%) patients with COPD who were and 532 (67%) who were not on β-blocker therapy died ($P < 0.001$). Cardioselective β-blockers were independently associated with reduced 30-day mortality in patients with (OR, 0.37; 95% CI, 0.19–0.72) and without COPD (OR, 0.34; 95% CI, 0.17–0.66) (Table 2). Over the entire follow-up period, cardioselective β-blocking agents reduced long-term mortality in patients with COPD (HR, 0.73; 95% CI, 0.60–0.88). In the long term, a trend was observed in patients without COPD, although it did not achieve statistical significance (HR, 0.84; 95% CI, 0.69–1.02).

A sensitivity analysis was performed using propensity score measurements for adjustment of various factors, including severity of disease to address the issue of confounding by indication. In this analysis, the relationship of cardioselective β-blockade with mortality in patients with COPD was similar to the main analysis (OR, 0.41; 95% CI, 0.20–0.81; and HR, 0.75; 95% CI, 0.61–0.91). In patients without COPD, a significant association was found between β-blocker use and 30-day mortality (OR, 0.36; 95% CI, 0.18–0.72). Similar to the main analysis, a trend was observed with long-term mortality, although the relationship was not significant (HR, 0.88; 95% CI, 0.72–1.07).

TABLE 1. BASELINE CHARACTERISTICS ACCORDING TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND β-BLOCKER USE

	COPD (*n = 1,265*)			No COPD (*n = 1,994*)		
	β-Blocker (*n = 462*)	No β-Blocker (*n = 803*)	*P* Value	β-Blocker (*n = 567*)	No β-Blocker (*n = 1,427*)	*P* Value
Demographics						
Mean age, yr (SD)	69 (9)	69 (10)	0.61	65 (11)	63 (13)	0.01
Male sex, %	82	78	0.07	70	68	0.30
Type of surgery, %			<0.001			<0.001
AAA	54	43		37	24	
CEA	15	13		31	31	
LLR	31	44		32	46	
Cardiovascular history, %						
Myocardial infarction	33	21	<0.001	31	14	<0.001
Coronary revascularization*	25	14	<0.001	22	11	<0.001
Heart failure	7	5	0.22	5	4	0.29
Angina pectoris	26	11	<0.001	23	9	<0.001
Stroke or TIA	24	20	0.14	35	35	0.76
Clinical characteristics, %						
Hypertension	49	36	<0.001	54	28	<0.05
Diabetes mellitus	17	12	<0.05	18	14	0.08
Hypercholesterolemia	26	11	<0.001	28	14	<0.001
Renal dysfunction	9	8	0.43	10	4	<0.001
Body mass index (SD)	26 (4)	25 (4)	<0.05	26 (4)	25 (4)	<0.05
Current smoking status	35	33	0.41	27	24	0.21
Cardiac medication, %						
Statins	49	11	<0.001	46	14	<0.001
ACE inhibitors	31	19	<0.001	34	18	<0.001
Calcium antagonists	28	22	<0.05	33	16	<0.001
Diuretics	28	19	<0.05	23	11	<0.001
Aspirin	47	30	<0.001	58	37	<0.001
Anticoagulants	32	38	<0.05	41	42	0.84
Nitrates	17	11	<0.05	18	7	<0.001
Pulmonary medication, %						
Bronchodilators	13	18	<0.05	0	0	0.85
Corticosteroids	23	11	<0.001	1	1	0.88

Definition of abbreviations: AAA = abdominal aortic surgery; ACE = angiotensin-converting enzyme; CEA = carotid endarterectomy; COPD = chronic obstructive pulmonary disease; LLR = lower limb arterial reconstruction; TIA = transient ischemic attack.

* Coronary artery bypass graft or percutaneous coronary intervention.

The relationship between β-blockers and mortality across different COPD severity groups is also summarized in Table 2. Even in moderate to severe group, β-blocker therapy was associated with reduced mortality in the short and long term.

Cardioselective β-Blocker Dose and Mortality

Of the patients using cardioselective β-blockers, 41% received low-dose β-blocker therapy at the time of surgery and 59% received an intensified dose. These percentages were similar among patients with COPD, with 42% of the patients on a low-dose and 58% on an intensified dose. In patients with COPD, an intensified but not low dose was associated with reduced 30-day mortality (OR, 0.26; 95% CI, 0.10–0.66) (Figure 1). However, in the long term, both dosing regimens were associated with reduced mortality (low dose: HR, 0.70; 95% CI, 0.54–0.91; and intensified dose: HR, 0.76; 95% CI, 0.59–0.98). In patients without COPD, both low and intensified dosing regimens were associated with reduced 30-day mortality (OR, 0.30; 95% CI, 0.12–0.77, and OR, 0.36; 95% CI, 0.15–0.86, respectively). The relationships became insignificant for low-dose β-blockers when long-term mortality was considered, although a trend for reduced mortality was still observed in non-COPD patients who were treated with an intensified dose (HR, 0.80; 95% CI, 0.62–1.03).

TABLE 2. THE ASSOCIATION BETWEEN CARDIOSELECTIVE β-BLOCKERS AND MORTALITY

	30-Day Mortality		Long-Term Mortality	
β-Blocker	Univariate OR (*95% CI*)	Multivariate OR (*95% CI*)	Univariate HR (*95% CI*)	Multivariate HR (*95% CI*)
Total	0.45 (0.30–0.66)	0.35 (0.22–0.57)	0.84 (0.74–0.95)	0.78 (0.68–0.89)
No COPD	0.46 (0.26–0.81)	0.34 (0.17–0.66)	0.86 (0.73–1.02)	0.84 (0.69–1.02)
COPD	0.40 (0.23–0.70)	0.37 (0.19–0.72)	0.74 (0.63–0.88)	0.73 (0.60–0.88)
Mild COPD	0.45 (0.21–0.98)	0.46 (0.18–1.16)	0.70 (0.54–0.92)	0.68 (0.50–0.93)
Moderate/severe	0.34 (0.15–0.78)	0.32 (0.12–0.85)	0.79 (0.64–0.98)	0.82 (0.64–1.05)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; HR = hazard ratio; OR = odds ratio.

DISCUSSION

The present study demonstrated that cardioselective β-blockers were associated with reduced 30-day and long-term mortality in patients with COPD who underwent major vascular surgery. We also found that an intensified dosing regimen appeared to be superior to low-dose therapy in terms of its impact on 30-day mortality.

These findings are consistent with other studies that demonstrated the beneficial effects of β-blockers in patients with COPD who had recently experienced myocardial infarction (13, 15, 18). A major limitation of the previous studies was that there was no or little information on lung function and, as such,

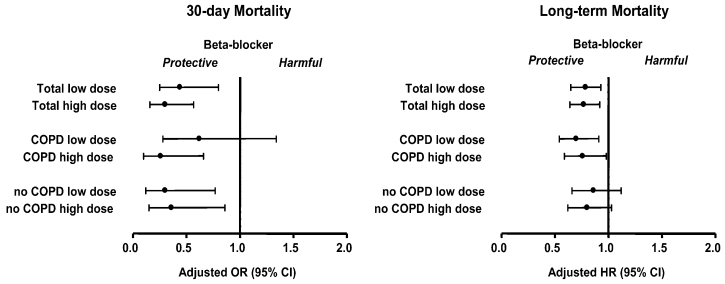

Figure 1. The association between low and intensified cardioselective β-blocker dose and mortality. Adjusted for age, sex, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, body mass index, type of surgery, year of surgery, and cardiovascular history. CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; OR = odds ratio.

the diagnosis of COPD could not be confirmed. We extend these findings by demonstrating among a large group of well-characterized patients with COPD, defined both clinically and spirometrically, that β-blockers were safe and beneficial in prolonging survival after major vascular surgery. There is evolving evidence showing that cardioselective β-blockade probably does not induce bronchospasm in patients with COPD (11, 12, 14, 16, 17). In addition, a meta-analysis of Salpeter and colleagues that evaluated the relationship between cardioselective β-blockers and COPD found no significant differences in FEV_1 or respiratory symptoms between those who were treated with cardioselective β-blockers or those treated with placebo, even in patients with severe COPD (24). In a study of patients with congestive heart failure, patients with and without COPD had similar rates of withdrawal from β-blockers because of intolerance (25). These data suggest that COPD does not increase the rate of adverse reactions to cardioselective β-blockers (leading to withdrawal). In view of the observed beneficial effect of cardioselective β-blockers in our study, we believe that cardioselective β-blocking agents may be used cautiously in patients with COPD with underlying ischemic vascular disease. Because cardioselective β-blocking agents may have some (although minor) effects on β_2-adreneroreceptors, such patients should be monitored very closely for any adverse effects. Moreover, although we found that intensified dose was superior to low-dose therapy with regard to 30-day mortality, we believe that it may be prudent to initiate therapy at the lowest dose feasible and to gradually increase the dose to the target range over several weeks to ensure safety.

Why β-blockers would be effective in COPD is largely unknown; however, it is well established that CVD is an important comorbidity in COPD. In the Lung Health Study, for instance, which studied 5,887 smokers, aged 35 to 60 years, with GOLD stage 1 and 2 disease ($FEV_1 \geq 50\%$ predicted), CVDs were primarily responsible for 22% of all deaths (26) and cardiovascular events accounted for 42% of the first hospitalizations and 48% of the second hospitalizations (27). The increased CVD risk in COPD may, in part, be related to excess adrenergic activity. Using microneurography of the peroneal nerve, Heindl and colleagues showed that patients with COPD have a marked increase in peripheral sympathetic discharge compared with control subjects (28), which was inversely related to the patients' oxyhemoglobin saturation ($r = 0.54$) (29). Patients with COPD also demonstrate reduced cardiac accumulation of meta-iodobenzylguanidine, an analog of guanetidine, a higher washout rate from the heart, and increased plasma norepinephrine levels than control subjects, indicating excess activity of the sympathetic nervous system with increased norepinephrine turnover than do control subjects (30). In patients who demonstrate excess sympathetic nervous activity, such as those with chronic heart failure or previous myocardial infarction, the use of β-adrenoceptor blockers, which attenuate sympathetic nervous activity, improves cardiac function and reduces CVD morbidity and mortality (31). In addition, β-blockers may reduce peri- and postoperative cardiac complications by attenuating cardiac workload and myocardial ischemia through β_1-blockade. β_1-Blockade may also inhibit catecholamine-induced necrosis and apoptosis of the myocardium, which may confer additional benefits to the stressed heart (32).

Our finding that an intensified dosing regimen was superior to a low-dose regimen in reducing 30-day mortality is consistent with those from a previous study that examined the effect of low- and intensive-dose therapy in vascular surgery patients (19). It is also consistent from the findings of the MOCHA (Multicenter Oral Carvedilol Heart Failure Assessment), SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure), and the COMET (Carvedilol or Metoprolol European Trial) trials, which also demonstrated a dose-related reduction in mortality (33–35). Conversely, the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure) trial and the CIBIS (Cardiac Insufficiency Bisoprolol Study) II trial failed to demonstrate this dose-dependent effect (36, 37). However, all these trials were conducted in patients with heart failure and should therefore be carefully compared with our study. Unfortunately, in most of these trials, patients with COPD were excluded because of concerns about bronchoconstriction, which makes cross-comparisons difficult. To our knowledge, the present study is the first of its kind to investigate the dose-dependent association between β-blockers and mortality in vascular surgery patients with COPD.

There were limitations to the study. First, we could not fully rule out the possibility that some individuals with COPD also had asthma. However, although bronchial hyperresponsiveness is more common (and more severe) in asthma than in COPD, over 70% of patients with COPD also demonstrate bronchial hyperresponsiveness. Thus, in reality, a clear separation is not always possible in clinical practice (38). Second, this was an observational study and not a clinical trial, which raises the possibility of confounding. To mitigate this possibility, we carefully collected salient clinical and demographic information and used sophisticated statistical modeling and inclusion of lung function measurements. We calculated a propensity score for β-blocker use and included this propensity score in the multivariable analysis to correct for the conditional probability of receiving the medication. We found that this made no material difference to the overall results. Although we cannot entirely rule out confounding by reverse indication, the adjustments of these factors including spirometric data suggest that these findings are not spurious and unlikely due to treatment selection. Nevertheless, additional prospective studies are needed to validate these early findings. Third, the prescription of β-blockers increased during 10 years of follow-up. To minimize

the effect of this potential bias, we adjusted for the year of surgery in the analysis. Moreover, although we found that β-blocker therapy was associated with both short- and long-term survival, our measure of β-blocker exposure occurred at one time point. We did not have follow-up data on β-blocker use, which may have led to exposure misclassification. However, it is likely that patients who were prescribed β-blockers at baseline were more likely to have received similar therapy in subsequent periods of follow-up (39). Thus, the long-term benefits of β-blocker therapy are likely on the basis of ongoing use of these medications as an outpatient.

In summary, our results suggest that cardioselective β-blockers are beneficial in patients with COPD undergoing vascular surgery, with an intensive dose being most effective in the reduction of 30-day mortality. Therefore, cardioselective β-blocking agents should not be withheld from patients with COPD undergoing vascular surgery.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Chapter 11

Statin Therapy is associated with Improved Outcomes in Vascular Surgery Patients with Renal Impairment

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Statin therapy is associated with improved outcomes in vascular surgery patients with renal impairment

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Background Little is known about the association between baseline kidney function, statin therapy, and outcome after vascular surgery in patients with and without chronic kidney disease.

Methods A total of 2126 patients underwent elective major vascular surgery and were divided into 2 categories based on baseline creatinine clearance (CrCl), calculated using the Cockcroft-Gault equation: CrCl ≥60 mL/min (n = 1358, reference) and CrCl <60 mL/min (n = 768). Outcome measures were 30-day and long-term all-cause, cardiac, and cerebrocardiovascular mortality. Mean follow-up was 6.0 ± 3.7 years. Multivariate Cox regression analysis, including potential confounders and propensity score for statin use, was applied. Data are presented as hazard ratios (HRs) with 95% CI.

Results Thirty-day all-cause, cardiac, and cerebrocardiovascular mortality rates were 3.8% versus 10.2%, 1.3% versus 4.2%, and 2.7% versus 7.8%, respectively, according to the 2 categories of kidney function. In addition, long-term all-cause, cardiac, and cerebrocardiovascular mortality rates were 46.6% versus 72.5%, 14.6% versus 26.4%, and 23.0% versus 40.6%, respectively. Statin therapy was associated with an overall significant improved 30-day and long-term all-cause mortality, independent of other important confounders. However, in patients with a CrCl ≥60 mL/min, the long-term cardiac and cerebrocardiovascular beneficial effects did not reach statistical significance (HR 0.93, 95% CI 0.61-1.41 and HR 0.89, 95% CI 0.63-1.24, respectively) when compared with patients with a CrCl of <60 mL/min (HR 0.63, 95% CI 0.41-0.96 and HR 0.67, 95% CI 0.48-0.94, respectively).

Conclusions The level of kidney function is an independent predictor of short- and long-term outcome after major noncardiac surgery. In addition, perioperative statin use in patients with kidney disease is associated with a reduction in the short- and long-term all-cause, cardiac, and cerebrocardiovascular mortality. (Am Heart J 2007;154:954-61.)

Chronic kidney disease (CKD) is becoming an increasingly important health issue worldwide, affecting more than 20 million people in the United States.[1] Patients with CKD are at higher risk of cardiovascular morbidity and mortality because of higher prevalence of traditional cardiovascular risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and ischemic heart disease.[2] The spectrum of dyslipidemia in patients with CKD is distinct from that of the general population and shows considerable variations depending on the stage of CKD.[3] There seems to be a gradual shift to the uremic lipid profile as kidney function deteriorates, which is characterized by increasing levels of low-density lipoprotein cholesterol and triglycerides and decreasing levels of high-density lipoprotein cholesterol.[4,5]

Dyslipidemia is an established cardiovascular risk factor in the general population, and drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) (statins) are highly effective for reducing low-density lipoprotein cholesterol and cardiovascular outcome in patients with coronary artery disease in the general population.[6-8] Although the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) has established guidelines for dyslipidemia therapy in CKD,[9] epidemiologic studies[3,10] and clinical trials[11-14] have raised uncertainties regarding the impact of dyslipidemia on clinical outcomes and, consequently, the optimal lipid profile. Therefore, we

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conducted the present study with the aim of describing the association of statin therapy with 30-day and long-term all-cause, cardiac, and cerebrocardiovascular outcome of patients with and without CKD undergoing major elective vascular surgery.

Methods

Study design and patient selection

The study population was composed of 2126 patients who were referred for elective open infrarenal abdominal aortic surgery (AAA) or lower limb arterial revascularization procedures between January 1993 and June 2006 in the Erasmus Medical Center, Rotterdam, the Netherlands, and whose data were entered into a computerized database. Hence, this is a retrospective study of prospectively collected data. The Medical Ethics Committee of the Erasmus Medical Center was informed about the study protocol, and per institutional practice, no official approval was requested.

Baseline characteristics

For all patients we recorded data on age, sex, hypertension, diabetes, smoking status, hypercholesterolemia (total cholesterol >200 mg/dL (>5.2 mmol/L) or the requirement of lipid-lowering medication), chronic obstructive pulmonary disease (COPD), body mass index, serum creatinine level, presence of ischemic heart disease (prior myocardial infarction [MI], prior coronary revascularization, and angina pectoris), heart failure, cerebrovascular disease, and preoperative medication use (β-blockers, statins, diuretics, angiotensin-converting enzyme [ACE] inhibitors, calcium antagonists, nitrates, aspirin, and anticoagulants). All prescription and over-the-counter medications were noted on the day of admission, and it was ascertained whether medication was documented at least 1 to 3 months before hospital admission for surgery.

Classification of kidney function

Fasting serum creatinine level was measured preoperatively in all patients, either at the outpatient preoperative screening visit or on the day of hospital admission. Serum creatinine level was assessed by a nonkinetic alkaline picrate (Jaffe) method.[15] The level of kidney function was defined by creatinine clearance (CrCl) calculated with the Cockcroft-Gault formula from serum creatinine concentration, age, sex, and body weight. The following equation was used: CrCl (mL/min) = [140 − age (years)] × [body weight (kg)]/72 × serum creatinine (mg/dL), multiplied by 0.85 for women.[16]

Patients were divided into 2 categories based on CrCl values at baseline: patients with a baseline kidney function of ≥60 mL/min (reference group) and patients with a baseline kidney function of <60 mL/min. We prespecified CrCl <60 mL/min as our primary definition of CKD according to the NKF K/DOQI guidelines.[1]

Clinical follow-up and end points

Postoperative clinical information was retrieved from an electronic database of patients maintained in our hospital. Survival status was obtained from the municipal civil registries. Follow-up was complete in 97.9%. The primary end point of this study was the composite short-term (within 30 days after surgery) and long-term (defined as death occurring in the first 10 years after surgery) all-cause, cardiac, and cerebrocardiovascular mortality. Cardiac death was defined as death secondary to MI, heart failure, or arrhythmias; cerebrocardiovascular death included MI, heart failure, arrhythmias, and stroke. Sudden unexpected death was classified as cardiac death. The cause of death was ascertained by reviewing medical records, the computerized hospital database, and autopsy reports or by contacting the referring physician or general practitioner.

Table I. Baseline characteristics of all patients according to statin use

No. of patients	All patients (n = 2126) (100%)	Statin use (n = 553) (26%)	No statin use (n = 1573) (74%)	P
Demographics				
Age (mean ± SD) (y)	66.4 ± 11	64.9 ± 10	66.9 ± 12	<.001
Male (%)	76	76	76	.9
Abdominal aortic surgery (%)	51	57	49	.002
Lower limb arterial revascularization surgery (%)	49	43	51	.002
Cardiovascular risk factor (%)				
Hypertension	49	66	43	<.001
Diabetes mellitus	16	21	14	<.001
Current smoker	27	36	25	<.001
Hypercholesterolemia	20	59	6	<.001
COPD	21	26	20	.001
Body mass index (mean ± SD) (kg/m^2)	24.8 ± 5	24.9 ± 4	24.9 ± 5	.8
Myocardial infarction	29	39	25	<.001
Coronary revascularization	26	36	23	<.001
Heart failure	7	10	5	<.001
Angina	17	25	14	<.001
Cerebrovascular disease	7	11	6	<.001
Baseline kidney function (%)				
Serum creatinine (mean ± SD) (mg/dL)	1.27 ± 1.1	1.20 ± 1.03	1.29 ±1.19	.1
Creatinine clearance (mean ± SD) (mL/min)	74.0 ± 34	78.1 ± 32	72.5 ± 34	.001
Creatinine clearance ≥60 mL/min	64	72	61	<.001
Creatinine clearance <60 mL/min	36	28	39	<.001
Medication use (%)				
β-Blockers	36	56	28	<.001
Diuretics	20	25	19	.002
ACE inhibitors	34	49	29	<.001
Calcium antagonists	36	50	31	<.001
Nitrates	20	25	18	.001
Aspirin	32	50	25	<.001
Anticoagulants	24	28	23	.007

Table II. Baseline characteristics of all patients according to level of kidney function

No. of patients	All patients (n = 2126) (100%)	≥60 mL/min (n = 1358) (64%)	<60 mL/min (n = 768) (36%)	P
Demographics				
Age (mean ± SD) (y)	66.4 ± 11	63.3 ± 11	71.8 ± 9	<.001
Male (%)	76	79	71	<.001
Abdominal aorta surgery (%)	51	53	50	.4
Lower limb arterial revascularization surgery (%)	49	50	46	.4
Cardiovascular risk factor (%)				
Hypertension	49	46	53	.002
Diabetes mellitus	16	16	17	.2
Current smoker	27	29	26	.1
Hypercholesterolemia	20	22	15	<.001
COPD	21	21	21	.8
Body mass index (mean ± SD) (kg/m^2)	24.8 ± 5	25.4 ± 4	23.8 ± 6	<.001
Myocardial infarction	29	26	33	.001
Coronary revascularization	26	27	25	.4
Heart failure	7	5	9	<.001
Angina	17	16	19	.1
Cerebrovascular disease	7	6	10	<.001
Baseline kidney function (%)				
Serum creatinine (mean ± SD) (mg/dL)	1.27 ± 1.1	0.91 ± 0.2	1.90 ± 1.7	<.001
Creatinine clearance (mean ± SD) (mL/min)	74.0 ± 34	91.7 ± 29	42.7 ± 14	<.001
Medication use (%)				
β-Blockers	36	36	35	.6
Statins	26	29	20	<.001
Diuretics	20	16	27	<.001
ACE inhibitors	34	31	39	<.001
Calcium antagonists	36	34	40	.007
Nitrates	20	18	24	.001
Aspirin	32	31	32	.6
Anticoagulants	24	25	22	.05

Data analysis

Continuous data are described as mean values and their SDs, and dichotomous data are described as percentage frequencies. The χ^2 test was used for categorical variables and analysis of variance was used for continuous variables to evaluate differences in baseline characteristics between statin users and between CrCl groups.

We developed a propensity score for the likelihood of receiving statin therapy and applied multivariable logistic regression analysis to calculate the propensity score. The variables included in the model were age, sex, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of MI, coronary revascularization, heart failure, angina, cerebrovascular disease, year of operation, and use of β-blockers, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anticoagulants.

Kaplan-Meier survival analysis was used to describe the incidence of all-cause death over time. The log-rank test was applied to study differences in survival between the 2 categories of kidney function (CrCl ≥60 mL/min vs CrCl <60 mL/min) and the effect of statin use within different categories of kidney function. For further evaluation, multivariate Cox proportional hazards regression analysis, with adjustment for confounders and propensity score, was performed. All potential confounders (age, sex, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of MI, coronary revascularization, heart failure, angina, cerebrovascular disease, and year of operation) were entered into the multivariable model to ensure an unbiased estimate is given for the relation between statin use and short- and long-term mortality for all patients.

Unadjusted and adjusted odds ratios (ORs) and hazard ratios (HRs) were reported with corresponding 95% CIs. A P value <.05 was considered significant. All computations were performed with SPSS software version 12.0.1 (SPSS Inc, Chicago, IL) running under Windows 2000 Professional.

Results

Baseline characteristics

The study population consisted of 2126 patients (mean age 66 ± 11 years); 76% were male and 51% of patients underwent AAA surgery. In total, 553 (26%) patients were statin users at baseline. Baseline patient characteristics are shown in Table I. All cardiovascular risk factors and medication use differed between the statin and non-statin users, except sex, body mass index, and serum creatinine level. The mean serum creatinine concentration and CrCl in this cohort was 1.27 ± 1.1 mg/dL and

Table III. Multivariate associations of baseline kidney function with short and long-term all-cause, cardiac and cerebrocardiovascular mortality

	Short term			Long term		
	Unadjusted, OR (95% CI)	**Adjusted for confounders,* OR (95% CI)**	**Adjusted for confounders and propensity score,† OR (95% CI)**	**Unadjusted, HR (95% CI)**	**Adjusted for confounders,* HR (95% CI)**	**Adjusted for confounders and propensity score,† HR (95% CI)**
All-cause mortality						
CrCl ≥60 mL/min (reference)	1.0	1.0	1.0	1.0	1.0	1.0
CrCl <60 mL/min	2.90 (2.01-4.17)	2.36 (1.56-3.56)	1.87 (1.22-2.87)	2.12 (1.89-2.38)	1.60 (1.40-1.82)	1.52 (1.34-1.74)
Cardiac mortality						
CrCl ≥60 mL/min (reference)	1.0	1.0	1.0	1.0	1.0	1.0
CrCl <60 mL/min	3.43 (1.89-6.22)	2.60 (1.35-5.00)	1.94 (1.01-3.83)	2.44 (2.01-2.97)	1.79 (1.43-2.23)	1.68 (1.34-2.10)
Cerebrocardiovascular mortality						
CrCl ≥60 mL/min (reference)	1.0	1.0	1.0	1.0	1.0	1.0
CrCl <60 mL/min	3.11 (2.04-4.75)	2.48 (1.55-3.99)	1.97 (1.20-3.21)	2.37 (2.03-2.78)	1.83 (1.53-2.18)	1.73 (1.44-2.07)

*Adjusted for age, sex, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, and year of operation.
†Adjusted for age, sex, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, year of operation, and use of β-blockers, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anticoagulants.

Table IV. Multivariate associations of statin use with short- and long-term all-cause, cardiac, and cerebrocardiovascular mortality

	Short term			Long term		
Statin therapy	**Unadjusted, OR (95% CI)**	**Adjusted for confounders,* OR (95% CI)**	**Adjusted for confounders and propensity score† OR (95% CI)**	**Unadjusted HR (95% CI)**	**Adjusted for confounders* HR (95% CI)**	**Adjusted for confounders and propensity score† HR (95% CI)**
All-cause mortality						
All patients	0.30 (0.17-0.54)	0.23 (0.11-0.47)	0.27 (0.13-0.54)	0.65 (0.56-0.75)	0.54 (0.45-0.65)	0.58 (0.48-0.69)
CrCl ≥60 mL/min	0.26 (0.10-0.65)	0.13 (0.04-0.39)	0.15 (0.05-0.46)	0.71 (0.59-0.85)	0.54 (0.42-0.69)	0.57 (0.44-0.73)
CrCl <60 mL/min	0.42 (0.20-0.88)	0.33 (0.14-0.79)	0.40 (0.16-0.96)	0.67 (0.53-0.83)	0.52 (0.40-0.68)	0.56 (0.43-0.73)
Cardiac mortality						
All patients	0.39 (0.17-0.92)	0.28 (0.10-0.79)	0.35 (0.12-0.98)	0.87 (0.69-1.08)	0.69 (0.52-0.92)	0.75 (0.56-0.99)
CrCl ≥60 mL/min	0.52 (0.15-1.81)	0.23 (0.06-1.20)	0.29 (0.06-1.50)	1.09 (0.81-1.46)	0.86 (0.57-1.29)	0.93 (0.61-1.40)
CrCl <60 mL/min	0.39 (0.12-1.30)	0.27 (0.07-1.14)	0.36 (0.09-1.48)	0.78 (0.54-1.11)	0.58 (0.38-0.88)	0.63 (0.41-0.96)
Cerebrocardiovascular mortality						
All patients	0.36 (0.19-0.67)	0.28 (0.13-0.60)	0.33 (0.15-0.71)	0.88 (0.73-1.05)	0.71 (0.57-0.89)	0.76 (0.61-0.96)
CrCl ≥60 mL/min	0.22 (0.07-0.71)	0.09 (0.02-0.37)	0.10 (0.03-0.43)	1.02 (0.81-1.30)	0.82 (0.59-1.14)	0.89 (0.63-1.24)
CrCl <60 mL/min	0.36 (0.27-1.24)	0.50 (0.20-1.23)	0.61 (0.25-1.50)	0.86 (0.65-1.13)	0.62 (0.45-0.86)	0.67 (0.48-0.94)

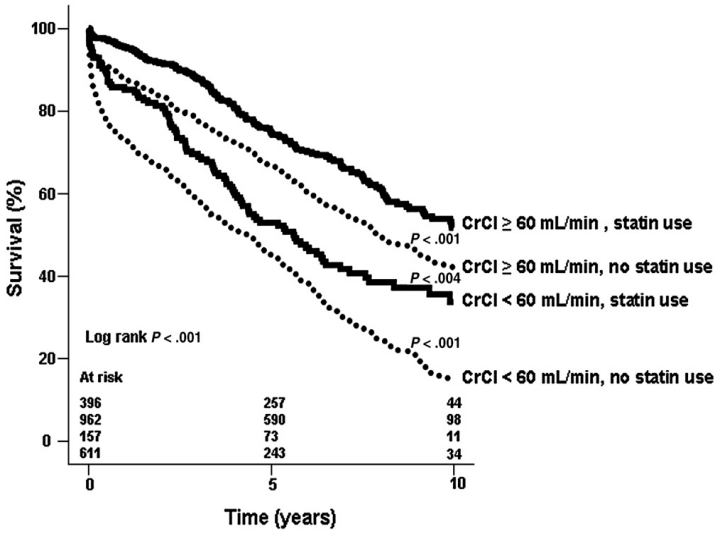
*Adjusted for age, sex, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, and year of operation.
†Adjusted for age, sex, hypertension, diabetes mellitus, smoking, hypercholesterolemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, year of operation, and use of β-blockers, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin, and anticoagulations.

74.0 ± 34 mL/min, respectively, and 768 (36%) patients had a CrCl of <60 mL/min (mean CrCl 42.7 ± 14 mL/min) (Table II). Patients with a CrCl of <60 mL/min were older, were more likely to be women, and had more cardiovascular risk factors (hypertension, MI, heart failure, and cerebrovascular diseases). Patients with kidney disease were less likely to receive statin therapy and were more likely to be treated with diuretics, ACE inhibitors, calcium antagonists, and nitrates, when compared with patients with a CrCl of ≥60 mL/min.

Propensity score analysis

Within the propensity score analysis, the following baseline variables significantly predicted statin therapy: hypertension (OR 1.45, 95% CI 1.07-1.97), hypercholesterolemia (OR 21.17, 95% CI 15.57-28.76), AAA surgery (OR 1.40, 95% CI 1.07-1.83), and year of operation per 2 years of increase (OR 2.06, 95% CI 1.20-1.43). Patients with a CrCl of <60 mL/min had a trend of receiving less statins compared with patients with a CrCl of ≥60 mL/min (OR 0.75, 95% CI 0.56-1.01, $P = .054$).

Figure 1



Kaplan-Meier estimate of overall survival by level of kidney function (CrCl) and statin use during 5.98 ± 3.68 years of follow-up.

According to medical therapy, β-blocker therapy (OR 2.07, 95% CI 1.56-2.57), aspirin therapy (OR 1.61, 95% CI 1.23-2.12), and ACE inhibitors therapy (OR 1.60, 95% CI 1.19-2.16) were significant predictors of statin prescription. The graphical method of examination by box plots showed a balance of the estimated propensity score between statin users and nonusers of statin within each decile of the propensity score.

Short-term outcome

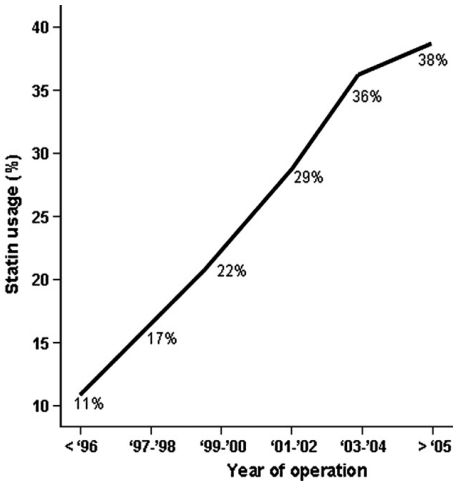
In total, 129 (6.1%) patients died within 30 days after surgery. A clear relationship between baseline kidney function and short-term all-cause, cardiac, and cerebrocardiovascular mortality was observed: 3.8% vs 10.2%, 1.3% versus 4.2%, and 2.7% versus 7.8%, respectively, for patients with a CrCl of ≥60 mL/min when compared with subjects with a CrCl of <60 mL/min ($P \leq .001$ for all) (Table III). A significant relationship was observed between statin therapy and all-cause mortality in patients with a CrCl <60 mL/min, although no significant association was observed between statin administration and cardiac and cardiocerebrovascular mortality in patients with a CrCl <60 mL/min. Statin therapy was associated with improved short-term all-cause (adjusted OR 0.27, 95% CI 0.13-0.54), cardiac (adjusted OR 0.35, 95% CI 0.12-0.98), and cerebrocardiovascular (adjusted OR 0.33, 95% CI 0.15-0.71) mortality in the overall cohort (Table IV).

Long-term outcome

During 5.98 ± 3.69 years of follow-up, 1190 (56%) patients died. All-cause mortality rates according to baseline kidney function were 46.6% for a CrCl of ≥60 mL/min and 72.5% for a CrCl <60 mL/min ($P \leq .001$); cardiac mortality rates were 14.6% for a CrCl of ≥60 mL/min and 26.4% for a CrCl of <60 mL/min ($P \leq .001$); and cerebrocardiovascular mortality rates were 23.0% for a CrCl of ≥60 mL/min and 40.6% for a CrCl of <60 mL/min ($P \leq .001$) (Table III). Statin use remained an independent predictor for long-term survival in all patients (adjusted HR 0.58, 95% CI 0.48-0.69) (Table IV). When CrCl was evaluated as a continuous variable, the adjusted HR for all-cause mortality was 1.01 (95% CI 1.008-1.013) per 1 mL/min decrease in CrCl. Similar results were observed for cardiac and cerebrocardiovascular outcomes.

As shown in Table IV and Figure 1, the association of statin therapy with all-cause mortality was similar for patients with a baseline CrCl of <60 mL/min (adjusted HR 0.56, 95% CI 0.43-0.73) when compared with patients with a CrCl of ≥60 mL/min (adjusted HR 0.57, 95% CI 0.44-0.73). Statin administration was also an independent predictor for long-term cardiac and cerebrocardiovascular survival in patients with a CrCl <60 mL/min. However, a relationship between statin usage and cardiac and cerebrocardiovascular survival was not observed in patients with a baseline CrCl of

Figure 2



Prescription of statins according to different years of surgery.

≥60 mL/min (adjusted HR 0.93, 95% CI 0.61-1.40 and adjusted HR 0.89, 95% CI 0.63-1.24, respectively), compared with patients with a baseline CrCl of <60 mL/min (adjusted HR 0.63, 95% CI 0.41-0.96 and adjusted HR 0.67, 95% CI 0.48-0.94, respectively). More important, during our follow-up period, we observed a more than a 3-fold increase of statin use in the period 1995-2006 (Figure 2).

Discussion

The main finding of our study is that administration of statin therapy is associated with an improved 30-day and long-term survival after elective vascular surgery, irrespective of baseline kidney function. Statin therapy was also associated with a reduced rate of long-term cardiac and cerebrocardiovascular events; however, in patients with preserved renal function this effect did not reach statistical significance. Furthermore, in this large cohort of patients who underwent elective vascular surgery, we observed that the level of kidney function is an independent predictor of short- and long-term all-cause, cardiac, and cerebrocardiovascular mortality.

Recently published clinical guidelines by the NKF K/DOQI define a CrCl of <60 mL/min for 3 months or more as the presence of CKD.[1] The treatment of these patients is challenging because of the complexity and severity of underlying cardiovascular condition, accompanied by a high prevalence of peripheral arterial disease.[17,18] In addition, untreated CKD can progress to end-stage renal disease requiring kidney transplantation or hemodialysis, exposing this patient population to an increased risk of worsening vascular disease.[18] Lipid-lowering agents have been shown to reduce cholesterol synthesis, lower peripheral vascular resistance, improve endothelial function, and even reduce inflammation, all cardiovascular risk factors present in patients with kidney disease.[19-21] In fact, post hoc analyses of 2 classic secondary prevention trials with statins have shown that administration of lipid-lowering drugs appears to be effective in lowering cardiovascular morbidity and mortality in patients with CKD.[12,22]

In 2004, Tonelli et al[12] investigated whether the use of pravastatin (an HMG-CoA inhibitor) was effective for secondary prevention of cardiovascular events in persons with CKD (defined by an estimated glomerular filtration rate of 30 to 59 mL/min per 1.73 m^2) in the pravastatin pooling project. In this analysis, among the 4491 subjects with moderate CKD, pravastatin significantly reduced the incidence of the primary outcome, defined as time to MI, coronary death, or percutaneous/surgical coronary revascularization (HR 0.77, 95% CI 0.68-0.86), although only a marginal significant reduction in total mortality was noticed in those subjects with CKD (adjusted HR 0.86, 95% CI 0.74-1.00, $P = .045$). In our study, long-term all-cause, cardiac, and cerebrovascular mortality was reduced by 44%, 37%, and 33%, respectively. The combination of these results suggests that statin therapy appears to be effective for the secondary prevention of all-cause mortality and major cardiovascular events in patients with CKD. In addition, as the randomized trials included in the pravastatin pooling project, treatment did not start until at least 3 months after the index event short-term outcomes were not evaluated. In this analysis, the short-term all-cause mortality was decreased by 58% in patients with a CrCl <60 mL/min. These findings extend previous observations about the earlier effect of statins[23] on cardiovascular outcomes to patients with CKD in the initial 30 days after undergoing elective vascular surgery.

In our study, we observed that only 20% of patients with a CrCl <60 mL/min received statins at baseline. This underutilization of statin therapy is consistent with statin usage in other CKD cohorts.[24] Furthermore, our propensity analysis showed a tendency for fewer prescriptions of statin therapy to patients with CKD when compared with patients with a baseline CrCl of ≥60 mL/min. Although statin therapy is thought to be safe, irrespective of kidney function,[13,25] other classes of lipid-lowering medication, such as fibrates, increase levels of creatinine[26] and adverse event rates in patients with kidney dysfunction.[27] The potential for side effects and the therapeutic nihilism for these patients and the lack of large controlled

studies evaluating statin use in the CKD population remain the major reasons for the underutilization of statins in patients with kidney disease.

As with all observational studies, this analysis has some limitations. We used CrCl, with its well-known shortcomings, rather than more definite measurements of kidney function such as iothalamate clearance. In addition, we did not have information regarding microalbuminuria or overt proteinuria to detect kidney damage. Therefore, we were unable to control for urine protein excretion, known to be an important independent predictor of adverse cardiovascular outcome.[28] The association of time of statin exposure with short- and long-term outcome was also not investigated because data on duration of therapy were not available. Although we observed a beneficial effect of statin on long-term outcome in patients with CKD, we did not investigate whether statin use reduced progression of CKD because we did not have a long-term follow-up of creatinine measurements. Another important limitation of this study is that the use of statins was not randomized and therefore subject to confounding by indication. However, propensity analysis was performed to adjust as much as possible for the bias inherent in the decision about statin therapy.[29]

In conclusion, the use of HMG-CoA reductase inhibitors is associated with reduced mortality among a cohort of patients with CKD and peripheral vascular disease. This reduction in short- and long-term risk of death was independent of other known cardiovascular risk factors. These results suggest that statin therapy may be effective in improving survival in patients with CKD undergoing elective major noncardiac surgery.

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Chapter 12

Statin Use is associated with Early Recovery of Kidney Injury after Major Vascular Surgery and Improved Long-term Outcome

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

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Abstract

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

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

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

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

Keywords: acute kidney injury; recovery; renal injury; statin therapy; vascular surgery

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Introduction

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

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

In the present study, we hypothesized that statin usage would be associated with a shorter course of kidney dysfunction after controlling for other important risk factors.

We examined the association of preoperative statin usage on the onset of AKI, the recovery of AKI in the postoperative period and the influence on long-term survival of patients undergoing major vascular surgery.

Subjects and methods

Study design and patient selection

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

Patients on chronic haemodialysis, with a baseline creatinine clearance (CrCl) <30 mL/min, and those who required renal revascularization and died within 3 days after surgery were excluded.

The analysis was made according to whether or not patients were taking statins on the day of hospital admission, and does not incorporate changes in medical treatment during the follow-up period.

Baseline characteristics

On all patients the information on cardiovascular risk factors was recorded and included age, gender, hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or use of anti-hypertensive medication), diabetes mellitus (the presence of a fasting blood glucose ≥140 mg/dL or requirement for insulin or oral hypoglycaemic agents), smoking status, hypercholesterolaemia (total cholesterol of >200 mg/dL), chronic obstructive pulmonary disease (COPD) according to symptoms and pulmonary function tests [i.e. forced expiratory volume in one second (FEV1) <70% of maximal age and gender predictive value], body mass index (BMI), serum creatinine, the presence of ischaemic heart disease [prior myocardial infarction (MI), prior coronary revascularization and angina pectoris], heart failure [defined according to the New York Heart Association classification (NYHA)], cerebrovascular disease (history of cerebrovascular accident or transient ischaemic attack), the occurrence of suprarenal cross-clamping during surgery and preoperative medication use [statins, β-blockers, diuretics, angiotensin-converting-enzyme inhibitors (ACE inhibitors), calcium antagonists, nitrates, aspirin and anti-coagulants]. Of note, baseline body weight was used to calculate BMI. All prescription and over-the-counter medications were noted on the day of admission and ascertained if medication was documented at least 1–3 months prior to hospital admission for surgery.

Kidney function assessment

Fasting serum creatinine was measured preoperatively at baseline in all patients, either at the outpatient preoperative screening visit or on the day of hospital admission, and on Days 1, 2 and 3 after surgery. Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method. Kidney function was estimated with the Cockcroft and Gault equation from age, gender, serum creatinine and body weight [17]. The following equation was used:

$$\text{Creatinine clearance (CrCl, mL/min)} = (140 - \text{age/years}) * (\text{body weight/kg})/72 * \text{serum creatinine (mg/dL)}, \text{multiplied by } 0.85 \text{ in women.}$$

Clinical follow-up and end-points

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

The primary end-point of this study was postoperative AKI with and without complete recovery. AKI was defined as >10% decrease in CrCl on Day 1 or 2, compared to the baseline value. Complete recovery of kidney function was defined as a CrCl >90% of the baseline value at Day 3 after surgery. Additional analyses were performed using the above definitions of AKI measured by the Modification of Diet in Renal Disease (MDRD) prediction equation [18].

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

Statistical analysis

Continuous data are described as mean values and standard deviation (±SD) or median values and range, and dichotomous data are described as percentage frequencies. The chi-square test was used for categorical variables and the analysis of variance (ANOVA) was used for continuous variables.

Multivariable logistic regression analysis was used to evaluate whether statin use prevented kidney injury within 2 days after surgery. If kidney injury was present, multivariable logistic regression analysis was used to evaluate if statin use was associated with an increased chance of complete recovery of kidney function at Day 3 after surgery. Multivariable analysis included the following covariates: a propensity score for statin use, age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolaemia, COPD, BMI, type of surgery, history of MI, coronary revascularization, heart failure, angina, cerebrovascular disease, baseline kidney function, suprarenal aortic cross-clamping, year of surgery and statin, β-blockers, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin and anti-coagulation usage at baseline. Year of surgery was included as a categorical variable (January 1995 through December 1999 and January 2000 through June 2006). We included the time period of surgery to adjust for possible confounding

(i.e. change in perioperative management) due to the long follow-up period of the analysis.

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

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

Finally, the probability of long-term all-cause mortality, according to the presence of kidney injury and statin use, was calculated by the Kaplan–Meier method and the resulting curves were compared by the log-rank test.

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

Results

Patient characteristics

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

The mean age of the study population was 66.6 ± 11 years and 78% were male (Table 1). In total, 1031 patients (53%) underwent AAA surgery and 913 patients (47%) underwent LLR surgery. The mean serum creatinine at baseline was 1.17 ± 0.8 mg/dL, and the mean CrCl was 74.9 ± 33 mL/min.

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

Primary end-point

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

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

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

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

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

In multivariable analysis, statin use and diabetes mellitus were independently associated with complete recovery of kidney function. Statin use was associated with increased odds of complete recovery of kidney function [adjusted OR

Table 1. Baseline characteristics of all patients, according to the presence of kidney injury within 2 days after major vascular surgery

Number of patients	All patients 1944 (100%)	No kidney injury[a] 1280 (66%)	Kidney injury 664 (34%)	*P*-value
Demographics *n* (%)				
Mean age (±SD)	66.6 (±11)	66.1 (±11)	67.6 (±11)	0.04
Male	1492 (77)	977 (76)	515 (78)	0.5
Non-Caucasian	73 (4)	49 (4)	24 (4)	0.8
Abdominal aortic surgery	1031 (53)	581 (45)	450 (68)	<0.001
Lower limb arterial reconstruction	913 (47)	699 (55)	214 (32)	<0.001
Suprarenal aortic cross-clamping	185 (10)	56 (4)	129 (19)	<0.001
Cardiovascular risk factor *n* (%)				
Hypertension	937 (48)	575 (45)	515 (55)	<0.001
Diabetes mellitus	310 (16)	207 (16)	103 (16)	0.7
Current smoker	543 (28)	355 (28)	188 (28)	0.8
Hypercholesterolaemia	379 (20)	246 (19)	133 (20)	0.7
COPD	418 (22)	257 (20)	161 (24)	0.04
Body mass index (±SD)	24.8 (±5)	24.5 (±4)	25.5 (±6)	0.005
Myocardial infarction	563 (29)	364 (28)	199 (30)	0.5
Coronary revascularization	513 (26)	344 (27)	169 (26)	0.5
Heart failure	129 (7)	82 (6)	47 (7)	0.6
Angina	333 (17)	214 (17)	119 (18)	0.5
Cerebrovascular disease	147 (8)	94 (7)	53 (8)	0.6
Baseline kidney function				
Serum creatinine (mg/dL ± SD)	1.17 (±0.8)	1.17 (±0.85)	1.17 (±0.80)	0.8
CrCl (mL/min ± SD)	74.9 (±33)	74.0 (±30)	76.5 (±38)	0.2
Estimated GFR (MDRD) (mL/min/1.73 m^2 ± SD)	78.0 (±26)	77.3 (±24)	79.4 (±29)	0.1
Surgery parameters				
Total blood loss (mL)	2356	1856	3272	<0.001
Suprarenal clamping time (min)	58.2	47.2	63.6	0.01
Medication use *n* (%)				
Statins	515 (27)	322 (25)	193 (29)	0.1
β-blockers	707 (36)	443 (35)	264 (40)	0.03
Diuretics	398 (21)	266 (21)	132 (20)	0.6
ACE inhibitors	669 (34)	439 (34)	230 (35)	0.9
Calcium antagonists	694 (36)	430 (34)	264 (41)	0.004
Nitrates	399 (21)	265 (21)	134 (20)	0.8
Aspirin	613 (32)	403 (32)	210 (32)	0.9
Anti-coagulation	457 (24)	330 (26)	127 (19)	0.001

ACE-inhibitors, angiotensin-converting-enzyme inhibitors; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; CrCl, creatinine clearance; MDRD, Modification of Diet in Renal Disease.
[a]Kidney injury >10% decrease in kidney function on Day 1 or 2, compared to the baseline value.

Table 2. Independent predictors for developing kidney injury after major vascular surgery

	Univariate odds ratio, 95% confidence interval	*P*-value	Multivariate odds ratio[a], 95% confidence interval	*P*-value
Age (per 1 year increase)	1.013 (1.004–1.022)	0.005	1.027 (1.015–1.040)	<0.001
Hypertension	1.47 (1.22–1.77)	<0.001	1.48 (1.15–1.89)	0.002
Suprarenal aortic cross-clamping	5.27 (3.79–7.33)	<0.001	4.07 (2.76–6.00)	<0.001
AAA surgery versus LLR procedures	2.53 (2.08–3.08)	<0.001	2.08 (1.63–2.65)	<0.001
Baseline kidney function				
CrCl (per 1 mL/min increase)	1.002 (0.999–1.005)	0.11	1.010 (1.006–1.014)	<0.001
Estimated GFR (MDRD; per 1 mL/min/1.73 m^2 increase)	1.003 (0.999–1.007)	0.10	1.008 (1.004–1.013)	<0.001
Statin use	1.22 (0.99–1.50)	0.06	1.15 (0.86–1.54)	0.35

AAA surgery, elective abdominal aortic surgery; LLR procedures, lower limb arterial reconstruction procedures; MDRD, Modification of Diet in Renal Disease.
[a]Adjusted for the propensity score for statin use, age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolaemia, chronic obstructive pulmonary disease, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, baseline creatinine clearance, suprarenal aortic cross-clamping, year of surgery, β-blockers, diuretics, angiotensin-converting-enzyme inhibitors, calcium antagonists, nitrates, aspirin and anti-coagulation.

Table 3. Independent predictors for all-cause mortality during 6.24 ± 4.2 years' follow-up

	Univariate hazard ratio, 95% confidence interval	*P*-value	Multivariate hazard ratio[b], 95% confidence interval	*P*-value
Age (per 1 year increase)	1.051 (1.044–1.058)	<0.001	1.038 (1.029–1.048)	<0.001
Diabetes mellitus	1.22 (1.04–1.42)	0.013	1.18 (1.00–1.43)	0.048
COPD	1.65 (1.45–1.88)	<0.001	1.53 (1.29–1.81)	<0.001
Smoking	1.17 (1.03–1.32)	0.017	1.32 (1.13–1.53)	<0.001
Postoperative dialysis (temporary or persistent)	3.55 (2.56–4.94)	<0.001	3.45 (1.99–5.96)	<0.001
Baseline kidney function				
CrCl (per 1 mL/min increase)	0.986 (0.984–0.988)	<0.001	0.993 (0.990–0.996)	<0.001
Estimated GFR (MDRD; per 1 mL/min/1.73 m^2 increase)	0.990 (0.987–0.992)	<0.001	0.994 (0.991–0.998)	<0.001
Kidney injury[a]	1.38 (1.22–1.55)	<0.001	1.24 (1.06–1.45)	0.007
Statin use	0.71 (0.62–0.82)	<0.001	0.60 (0.48–0.75)	<0.001

COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

[a]Kidney injury >10% decrease in creatinine clearance on Day 1 or 2, compared to the baseline value.

[b]Adjusted for the propensity score for statin use, age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolaemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, the presence of kidney injury, suprarenal aortic cross-clamping, year of surgery, baseline kidney function, postoperative dialysis, β-blockers, diuretics, angiotensin-converting-enzyme inhibitors, calcium antagonists, nitrates, aspirin and anti-coagulation.

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

Of note, results were similar when the MDRD prediction equation was used to define kidney function (Tables 2 and 3).

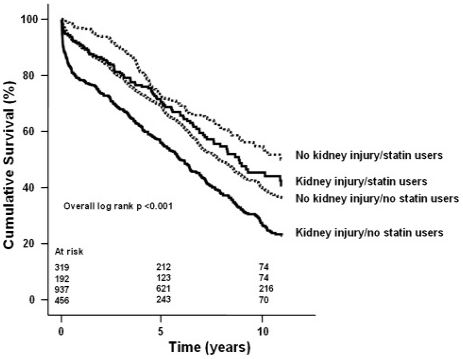

Fig. 1. All-cause long-term mortality in vascular surgery patients, according to the presence of kidney injury and statin use. Kidney injury >10% decrease in creatinine clearance on Day 1 or 2, compared to the baseline value. Mean follow-up is 6.24 ± 4.2 years.

Secondary end-point

In total, 1062 patients (55%) died during 6.2 ± 3.6 years of follow-up. Statin use was associated with long-term all-cause mortality, irrespective of the presence of kidney injury after surgery (Figure 1). The adjusted HR for statin use was 0.60, 95% CI 0.48–0.75. Importantly, statin use was associated with an improved outcome for patients who develop kidney injury (adjusted HR 0.53, 95% CI 0.37–0.77), compared to patients without AKI (adjusted HR 0.65, 95% CI 0.49–0.86).

Other independent predictors for long-term all-cause mortality are listed in Table 3. Importantly, the presence of AKI after surgery was associated with an adverse outcome (adjusted HR 1.24, 95% CI 1.06–1.45). Baseline CrCl (per 1 mL/min increase) was also independently associated with all-cause mortality, with an adjusted HR of 0.993, 95% CI 0.990–0.996.

In a sub-analysis among the 48 patients who died within 3 days after surgery, statin therapy was associated with a decreased chance of immediate postoperative death (unadjusted OR 0.40, 95% CI 0.17–0.94, *P*-value = 0.035). We were unable to perform multivariate analysis, because of decreased statistical power to detect differences in outcomes in this subgroup.

Discussion

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

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

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

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

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

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

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

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Chapter 13

Effect of Statin Withdrawal on Frequency of Cardiac Events After Vascular Surgery

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Effect of Statin Withdrawal on Frequency of Cardiac Events After Vascular Surgery

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The discontinuation of statin therapy in patients with acute coronary syndromes has been associated with an increase of adverse coronary events. Patients who undergo major surgery frequently are not able to take oral medication shortly after surgery. Because there is no intravenous formula for statins, the interruption of statins in the postoperative period is a serious concern. The objective of this study was to assess the effect of perioperative statin withdrawal on postoperative cardiac outcome. Also, the association between outcome and type of statin was studied. In 298 consecutive statin users who underwent major vascular surgery, detailed cardiac histories were obtained, and medication use was noted. Postoperatively, troponin levels were measured on days 1, 3, 7, and 30 and whenever clinically indicated by electrocardiographic changes. End points were postoperative troponin release, myocardial infarction, and a combination of nonfatal myocardial infarction and cardiovascular death. Multivariate analyses and propensity score analyses were performed to assess the influence of type of statin and the discontinuation of statins for these end points. Statin discontinuation was associated with an increased risk for postoperative troponin release (hazard ratio 4.6, 95% confidence interval 2.2 to 9.6) and the combination of myocardial infarction and cardiovascular death (hazard ratio 7.5, 95% confidence interval 2.8 to 20.1). Extended-release fluvastatin was associated with fewer perioperative cardiac events compared with atorvastatin, simvastatin, and pravastatin. In conclusion, the present study showed that statin withdrawal in the perioperative period is associated with an increased risk for perioperative adverse cardiac events. Furthermore, there seemed to be better outcomes in patients who received statins with extended-release formulas. **(Am J Cardiol 2007;100:316–320)**

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

Methods

The study population consisted of 294 consecutive patients receiving long-term statin therapy who underwent elective major vascular surgery at Erasmus Medical College in Rotterdam, The Netherlands, from July 2000 to August 2006. Long-term statin therapy was defined as the use of statins at the first preoperative vascular outpatient clinic visit. These patients were identified in a prospectively maintained database of all patients who underwent vascular surgery at this institution. The study was approved by the Medical Ethics Committee of Erasmus Medical College.

Before surgery, detailed cardiac histories were obtained, and patients were screened for hypertension (blood pressure ≥140/90 mm Hg or medical therapy to control hypertension), diabetes mellitus (fasting glucose level ≥7.0 mmol/L or medication to control diabetes), and renal failure (serum creatinine level ≥2.0 mg/dl). The presence of coronary artery disease was indicated by a previous myocardial infarction, previous coronary intervention, present stable angina pectoris, and positive cardiac stress test results. Other cardiovascular risk factors scored in all patients included a

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Table 1
Patient characteristics

Variable	Total (n = 298)	Continuation (n = 228)	Withdrawal (n = 70)	p Value
Men	233 (75%)	168 (74%)	55 (79%)	0.44
Mean age (yrs)	64.9 ± 10.5	64.2 ± 10.5	67.0 ± 10.3	0.02
Myocardial infarction	98 (33%)	70 (31%)	28 (40%)	0.15
Angina pectoris	92 (31%)	57 (25%)	35 (50%)	0.001
Heart failure	12 (4%)	7 (3%)	5 (7%)	0.16
Cerebrovascular accident or transient ischemic attack	53 (18%)	36 (16%)	17 (24%)	0.15
Coronary artery bypass graft or percutaneous coronary intervention	77 (26%)	50 (22%)	27 (39%)	0.008
Renal failure	11 (4%)	7 (3%)	4 (6%)	0.30
Diabetes mellitus	82 (28%)	64 (28%)	18 (26%)	0.76
Hypertension	133 (45%)	97 (43%)	36 (51%)	0.27
Chronic obstructive pulmonary disease	108 (36%)	75 (33%)	33 (47%)	0.05
Low cardiac risk*	67 (23%)	58 (25%)	9 (13%)	0.002
Intermediate cardiac risk*	169 (57%)	131 (58%)	38 (54%)	
High cardiac risk*	62 (21%)	39 (17%)	23 (33%)	
Type of surgery				0.001
Aortic	154 (52%)	91 (40%)	63 (90%)	
Lower extremity revascularization	144 (48%)	137 (60%)	7 (10%)	
Type of statin				0.48
Extended-release fluvastatin	100 (34%)	78 (34%)	22 (31%)	
Simvastatin	86 (29%)	65 (29%)	21 (30%)	
Pravastatin	35 (12%)	30 (13%)	5 (7%)	
Atorvastatin	77 (26%)	55 (24%)	22 (31%)	

* According to the Erasmus index.

history of a cerebrovascular accident or transient ischemic attack, age >70 years, chronic heart failure, and chronic obstructive pulmonary disease (defined as forced expiratory volume in 1 second <70% of age- and gender-predicted value or medication use). The type and dosage of long-term statin therapy were noted in all patients.

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

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

End points were postoperative troponin release (myocardial damage), nonfatal myocardial infarction, cardiovascular death <30 days after surgery, and a combination of nonfatal myocardial infarction and cardiovascular death <30 days after surgery.

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

The cardiac risk score for each patient in our data set was calculated according to the score of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE) I and II studies,[4,5] and 1 point was assigned to each of the following characteristics: history of myocardial infarction, history of angina pectoris, history of congestive heart failure, history of cerebrovascular disease, diabetes mellitus, renal failure, and age >70 years. Patients with no risk factors were considered to be at low cardiac risk, with 1 or 2 risk factors to be at intermediate cardiac risk, and with >3 risk factors to be at high cardiac risk.

Dichotomous data are described as numbers and percentages, and continuous data are presented as mean ± SD. Differences in baseline characteristics between statin users

Table 2
Characteristics of patients taking different types of statins

Variable	Fluvastatin (n = 100)	Simvastatin (n = 86)	Pravastatin (n = 35)	Atorvastatin (n = 77)
Cholesterol (mg/dl)	184 ± 42	181 ± 41	182 ± 44	182 ± 63
Low-density lipoprotein (mg/dl)	114 ± 40	106 ± 39	103 ± 41	110 ± 58
High-density lipoprotein (mg/dl)	49 ± 46	47 ± 16	47 ± 14	47 ± 19
Triglycerides (mg/dl)	184 ± 100	183 ± 111	170 ± 97	187 ± 129
Statin dose (mg)				
10	0	10 (12%)	5 (14%)	19 (25%)
20	0	50 (58%)	11 (31%)	25 (33%)
40	0	24 (28%)	19 (54%)	28 (36%)
80	100 (100%)	2 (2%)	0	5 (7%)
Aortic surgery	48 (48%)	51 (59%)	11 (31%)	44 (57%)
Cardiac risk				
Low	27 (27%)	14 (16%)	8 (23%)	18 (23%)
Intermediate	56 (56%)	48 (56%)	19 (54%)	46 (60%)
High	17 (17%)	24 (28%)	8 (23%)	13 (17%)

were evaluated by analysis of variance and chi-square tests as appropriate.

We developed a propensity score for the likelihood of receiving continuous statin therapy and used applied multivariate logistic regression analysis to calculate the propensity score. The variables included in the model were type of surgery, gender, year of surgery, hypertension, chronic obstructive pulmonary disease, cardiac risk factors, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, oral nitrates, and antiplatelet agents. The performance of the propensity score model was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish statin continuation from statin interruption; it was quantified by the c-statistic. Calibration refers to whether the predicted probability of continuous statin use agrees with the observed probability and was measured with the Hosmer-Lemeshow goodness-of-fit test.

The Kaplan-Meier method was used to describe the incidence of myocardial infarction and cardiac death over time. A log-rank test was applied to study differences in survival between continuous users and stoppers. These relations were further evaluated by multivariate Cox proportional-hazard regression analysis, with adjustment for confounders and propensity score. All potential confounders were entered in the multivariate model to ensure giving as unbiased an estimate as possible for the relation between statin discontinuation and perioperative cardiac outcome. Crude and adjusted hazard ratios (HRs) are reported with corresponding 95% confidence intervals (CIs). For all tests, a p value <0.05 (2 sided) was considered significant. All statistical analyses were performed using SPSS statistical software (SPSS, Inc., Chicago, Illinois).

Results

The baseline characteristics of the 298 patients (mean age 64.9 ± 10.5 years, 75% men) are listed in Table 1. Patients were taking extended-release fluvastatin (n = 100), simvastatin (n = 86), pravastatin (n = 35), and atorvastatin (n = 77). There were no differences in total cholesterol, high-density lipoprotein, and low-density lipoprotein levels among the different statin types measured at the first outpatient clinic visit (Table 2).

Table 3
Predictors for myocardial damage

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

* Propensity score included in analysis.

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

Myocardial damage, myocardial infarction, and cardiovascular death occurred in 26.8%, 11.4%, and 3.0%, respectively, of the entire study cohort. In univariate analysis,

Table 4
Predictors for myocardial infarction

Variable	Univariate Analysis		Multivariate Analysis		Multivariate Analysis*	
	HR	95% CI	HR	95% CI	HR	95% CI
Statin interruption	7.1	3.3–15.1	7.1	2.7–18.7	7.5	2.8–20.1
Cardiac risk						
Low	1		1		1	
Intermediate	8.8	1.2–67.4	7.7	1.0–62.0	9.5	1.1–82.6
High	17.5	2.2–138.4	12.3	1.4–105.3	17.8	1.8–181.2
Type of statin						
Fluvastatin	1		1		1	
Simvastatin	4.7	1.5–14.8	4.1	1.2–14.2	3.7	1.0–13.3
Pravastatin	4.0	1.0–15.9	5.2	1.1–24.1	5.1	1.1–23.9
Atorvastatin	4.0	1.2–13.1	3.8	1.1–13.6	4.0	1.1–14.1
Surgical site						
Peripheral	1		1		1	
Aortic	2.1	1.0–4.5	0.9	0.3–2.7	1.5	0.3–7.2
Chronic obstructive pulmonary disease	0.9	0.4–2.0	0.7	0.3–1.6	0.7	0.3–1.7
Hypertension	1.6	0.8–3.4	1.3	0.6–2.9	1.3	0.6–3.1
C-index				0.82		0.83

* Propensity score included in analysis.

Table 5
Predictors for the combined end point of nonfatal myocardial infarction and cardiac death

Variable	Univariate Analysis		Multivariate Analysis		Multivariate Analysis*	
	HR	95% CI	HR	95% CI	HR	95% CI
Statin interruption	7.6	3.6–16.1	7.3	2.8–18.9	7.5	2.8–20.1
Cardiac risk						
Low	1		1		1	
Intermediate	8.9	1.2–67.4	8.0	1.0–64.6	8.8	1.0–76.5
High	19.3	2.4–151.4	14.6	1.7–123.9	17.3	1.7–174.8
Type of statin						
Fluvastatin	1		1		1	
Simvastatin	4.7	1.5–14.8	4.4	1.3–15.1	4.1	1.1–14.8
Pravastatin	4.0	1.0–15.9	5.9	1.3–27.6	5.7	1.2–26.8
Atorvastatin	4.4	1.4–14.3	4.5	1.3–16.1	4.6	1.3–16.3
Surgical						
Peripheral	1		1		1	
Aortic	2.2	1.1–4.7	1.0	0.4–2.8	1.3	0.3–6.1
Chronic obstructive pulmonary disease	1.0	0.5–2.1	0.8	0.3–1.7	0.8	0.3–1.8
Hypertension	1.5	0.7–3.1	1.2	0.5–2.6	1.2	0.5–2.8
C-index				0.83		0.84

* Propensity score included in analysis.

patients who continued statin therapy had significantly better cardiac outcomes than patients who interrupted statin therapy: myocardial ischemia 16.7% versus 60.0%, myocardial infarction 5.7% versus 30.0%, cardiovascular death 1.8% versus 7.1%, and the combination of cardiovascular death and nonfatal myocardial infarction 5.7% versus 31.4%. Other univariate predictors of adverse cardiac outcome are listed in Tables 3 to 5. Also, in multivariate analysis, statin interruption remained an independent predictor of adverse cardiac outcome (Tables 3 to 5). When the propensity score was included in the model with all the covariates to adjust for the chance of interruption of statins, the effect of continuous statin therapy and withdrawal was comparable with the analysis adjusted for only covariates (Tables 3 to 5).

In univariate analysis, patients who were receiving extended-release fluvastatin therapy had a lower risk for adverse cardiac events than those taking simvastatin, pravastatin, or atorvastatin. Troponin T release was present in 14.0%, 31.4%, 34.3%, and 35.1% of patients, respectively, for fluvastatin, simvastatin, pravastatin, and atorvastatin, and myocardial infarctions occurred in 4.0%, 16.3%, 14.3%, and 14.3%, respectively. The incidence of cardiovascular death did not differ significantly between statin types: 2.0%, 3.5%, 5.7%, and 2.6%, respectively. As listed in Tables 3 to 5, also in multivariate analysis, adjusting for covariates and propensity score, patients who were taking extended-release fluvastatin had a significantly lower rate of adverse cardiac events.

Discussion

This study showed that acute statin withdrawal in the perioperative period is associated with an increased risk for perioperative cardiac events compared with statin continuation in long-term users. The extended-release formula of fluvastatin appeared to have beneficial effects over other statins in patients who discontinued statin therapy.

The possible detrimental effects of sudden statin withdrawal have been reported previously in long-term statin users with acute coronary syndromes.[6–9] In a cohort study, the Global Registry of Acute Coronary Events (GRACE) investigators found that 428 long-term statin users in whom statin therapy was discontinued at admission for acute coronary syndromes had the same risk for the composite of death, stroke, and myocardial infarction as nonusers.[6] In contrast, 3,628 patients who continued statin therapy throughout the admission had a significant 34% relative risk reduction compared with nonusers. Another large observational study found the same effect of statin withdrawal in patients admitted for non-ST-segment elevation myocardial infarction: there was no difference in the in-hospital death rate between 4,870 patients who discontinued statin therapy and 54,635 nonusers, whereas 9,001 patients who continued statin therapy had a highly significant 45% relative risk reduction compared with nonusers.[7]

The lipid-lowering effects of statins might explain most of the beneficial effects of long-term statin use in patients at increased risk for coronary artery disease. However, this might not explain the effects of sudden statin withdrawal in the current study. All patients were long-term statin users up to the day of surgery, and significant changes in serum lipid levels may take days to weeks. Another explanation might be the effect of sudden statin withdrawal on statins' pleiotropic properties. These pleiotropic effects include the inhibition of inflammation, the modulation of endothelial function, and antithrombotic effects. The pleiotropic effects of statins are present within hours to days after statin therapy initiation. Importantly, several studies have shown that these pleiotropic effects might be lost within hours after statin withdrawal, while lipid levels remain continuously

low. Vulnerable coronary plaque rupture[10,11] leading to thrombus formation and subsequent vessel occlusion is 1 of the main causative mechanisms of perioperative cardiac complications. The pleiotropic effects of statins are thought to influence the susceptibility of vulnerable plaques for rupture. While surgical patients are at highest cardiac risk within the first 3 days after surgery, possibly also because of the detrimental effects of surgery on mechanisms leading to vulnerable plaque rupture, statin therapy is discontinued.

The present study showed that statin therapy is interrupted in about 25% of patients who undergo major noncardiac surgery. The main cause for interruption was the inability to take oral medications shortly after surgery. Because statins are not available as intravenous formulas, this leads to unintended statin withdrawal. Our study suggests that fluvastatin might be associated with better outcomes after major noncardiac surgery compared with other statins. There are several possible explanations for these observations. Fluvastatin is the only statin with an extended-release formula. Because most patients with statin withdrawal restarted statin therapy <3 to 4 days after surgery, it might be hypothesized that the extended-release fluvastatin formula is capable of extending the duration of the pleiotropic effects of statins. Furthermore, the pharmacokinetics of statins might be influenced by concomitant drug use in the perioperative period. Of special interest in this respect is the cytochrome P450 (CYP) isoenzyme system. Most drugs are metabolized in the liver by the CYP 3A4 isoenzyme. As a consequence, this might cause interaction with simvastatin and atorvastatin, which are also metabolized by this pathway.[12] Fluvastatin, in contrast, has only limited interactions with the CYP 3A4 pathway, because it is mainly metabolized by the CYP 2C9 isoenzyme. As shown in a review by Bellosta et al,[13] other differences between statins include half-life, systemic exposure, maximum plasma concentration, bioavailability, protein binding, lipophilicity, the presence of active metabolites, and excretion routes. Fluvastatin is the only statin that is a racemic compound, half of the molecule being presumably inactive at reducing plasma cholesterol. It is not excluded that some of the beneficial pleiotropic effects may be shared by the "nonactive" half, therefore potentially increasing that capacity.

The nonrandomized nature of the present study has certain limitations. It could be argued that patients with more complex, lengthy, and difficult operations in rather poorer general conditions were less likely to recover soon and resume their oral medications. However, these are the type of patients who are more likely to end up with cardiovascular complications. The propensity score indeed showed that patients with aortic aneurysms and high cardiac risk were more likely to be in the statin withdrawal group. However, in multivariate analysis, the propensity score was included to minimize the potential bias caused by this.[8,9]

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Chapter 14

Secondary Medical Prevention in Patients with Peripheral Arterial Disease

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INVITED COMMENTARY

Re: Secondary Medical Prevention in Patients with Peripheral Arterial Disease

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The 5-year event rate of patients with peripheral arterial disease (PAD) is high. The Reduction of Atherothrombosis for Continued Health (REACH) Registry, including 55 814 patients with known atherosclerotic disease (coronary artery disease, peripheral arterial disease and cerebrovascular disease) showed that patients with polyvascular disease have a significant worse outcome compared to patients with coronary artery disease only.[1] The adverse event rate increased with the number of affected vascular beds from 13% for patients with 1, 21% for patients with 2, and 26% for patients with 3 symptomatic arterial disease locations.

The cause of this high event rate in polyvascular disease is multifactorial. In the present study patients with PAD were significantly less likely to receive cardiovascular therapy; i.e. antiplatelet therapy, statins, ACE-inhibitors, and beta-blockers.[2] For all therapies there is substantial evidence that these are associated with an improved event-free survival. A limitation of the present study is the lack of follow-up data.

The consultation of PAD patients by the vascular surgeon offers an unique opportunity to implement cardiovascular medical therapy according to the current guidelines.[3] The recent guidelines include clear recommendations concerning medical treatment of patients with PAD.

Statins

Treatment target is a LDL cholesterol level of less than 100 mg/dL. Furthermore it is reasonable to aim at a target LDL cholesterol level of less than 70 mg/dL for patients with PAD at very high risk of ischemic events.

Antihypertensive Medication

Treatment target is a blood pressure of less than 140 mm Hg systolic over 90 mm Hg diastolic (non-diabetics) or less than 130 mm Hg systolic over 80 mm Hg diastolic (diabetics and individuals with chronic renal disease). Thiazides and ACE inhibitors should be considered as initial blood-pressure lowering drugs. Importantly, beta-adrenergic blocking drugs are effective antihypertensive agents and are not contraindicated in patients with PAD.

Antiplatelet Medication

Aspirin, in daily doses of 75–325 mg therapy is indicated to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic PAD. Clopidogrel (75 mg/day) is effective in reducing cardiovascular events in a subgroup of patients with symptomatic. PAD, with or without other clinical evidence of cardiovascular disease.

Conclusion

The current study by Gasse *et al.* clearly reveals the need for more awareness of routine and continued medical therapy in patients with PAD. To improve this awareness, protocols should be developed and implemented in clinical practice. Future surveys are important to assess improvement of medical therapy over time and to explore reasons for not adhering to recommended treatment strategies.

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Part 4

Summary and conlcusions

Samenvatting en conclusies

Publications and presentations

Acknowledgements

Summary and conclusions

In this thesis, the prognosis, prognostic value of preoperative cardiovascular risk factors and the effect of different pharmacological therapies are described of patients with peripheral arterial disease (PAD) undergoing major vascular surgery.

PART 1: PROGNOSIS

Chapter 1 highlights the health burden of PAD. A review of selected publications summarizes the epidemiology, diagnosis, prognosis and interventions of patients with PAD. The worldwide prevalence of PAD is suggested to be more than 30 million. However, this is probably an underestimation as PAD may be asymptomatic or present with atypical symptoms. Importantly, coronary artery disease (CAD) is a very common co-morbidity in patients with PAD as only 8% of patients undergoing vascular surgery have angiographically normal coronary arteries. Since the prognosis of patients with PAD is related to the presence and extent of underlying CAD, a careful cardiac risk assessment is of critical importance. The summarized data from published literature further shows that beta-blockers and statins reduce perioperative cardiac event rates in patients with PAD undergoing major vascular surgery. In addition, these patients benefit from long-term atherosclerotic risk factor management and optimal medical treatment to improve the long-term prognosis. Beta-blocker and statin use seem to play an important role to optimize the secondary treatment of PAD patients. However, antiplatelet therapy for secondary prevention remains the cornerstone of pharmacologic intervention in patients with PAD.

In Chapter 2, the prognosis of 2,730 patients undergoing major vascular surgery is compared to 2,730 risk factor matched patients with severe myocardial ischemia referred for coronary angioplasty, without signs or symptoms of PAD obtained from review of medical records. We conclude that patients with PAD undergoing major vascular surgery have a 2.4-fold increased risk of mortality during 13 years of follow-up compared to patients with severe CAD. PAD patients receive less cardiovascular medical therapy (i.e. beta-blockers, statins, ACE-inhibitors, calcium antagonists, nitrates and aspirin) compared to CAD patients, which might explain their worse long-term outcome. This under treatment is striking, since the secondary prevention of subjects with PAD should be similar to that of patients with CAD. Physician awareness for this problem is necessary to improve the prognosis of these patients.

In addition, we conclude that cerebro-cardiovascular death is the major cause of perioperative and long-term mortality among vascular surgical patients with PAD (76% and 46%, respectively). Myocardial infarction accounts for 18% and 19% of short- and long-term mortality respectively, illustrating the high prevalence of cardiac complications in patients undergoing major vascular surgery.

In chapter 3, the long-term effect of endovascular abdominal aortic aneurysm (AAA) repair is compared with open AAA repair in cardiac high-risk patients. Although endovascular repair is superior to open repair in terms of perioperative cardiovascular outcome, the long-term outcome of high-risk patients however remained ill-defined. During a median follow-up of 3.3 years, no significant difference is observed in overall survival in patients treated either by endovascular (n= 55) or open (n= 69) AAA repair. However, the perioperative cardiac benefit of endovascular AAA repair is sustained during long-term follow-up. Aggressive medical treatment seems to have more impact on overall and cardiac event free survival than does the choice of AAA treatment modality.

PART 2: RISK FACTORS

In chapter 4, the impact of mild renal impairment (glomerular filtration ratio (GFR) 60-90 ml/min) on long-term survival is studied in 6,447 patients with known or suspected CAD. Chronic kidney disease has been shown to be an independent risk factor for cardiovascular morbidity and mortality in patients with CAD. However, it remains unclear whether mild renal dysfunction is related to adverse cardiovascular outcome. We observe that mild renal impairment is an independent predictor of all-cause mortality and cardiac death during a mean follow-up of 7 years. Early recognition of renal dysfunction may identify patients at increased risk for long-term mortality and hard cardiac events. These patients could benefit from intensified medical therapy like antiplatelet therapy, beta-blockers, statins and ACE-inhibitors. Unfortunately, this optimal management is still not widespread standard of care in patients with renal impairment.

In chapter 5, we describe the predictive value of subtle renal function changes within three days after surgery of patients undergoing open AAA surgery. Little is known about acute changes of renal function in the postoperative period, and its impact on short and long-term outcome. Especially, there is sporadic information on the influence of temporary worsening of renal function and outcome. Patients with temporary worsening of renal function have a 3.7-fold increased risk for 30-day mortality, while patients with persistent worsening of renal function have a 7.3-fold increased risk, compared to patients with improved or unchanged renal function. However, during a mean follow-up of 6 years, the prognosis of these patients is the same as patients with persistent worsening of renal function. Therefore, we conclude that subtle postoperative renal function changes after AAA surgery are strong predictors for adverse short- and long-term outcome. These patients might need more intense medical follow-up than

suggested previously, to prevent further postoperative worsening of renal function. Moreover, since only few studies have described the prognostic value of acute renal function changes after major vascular surgery on outcome in the postoperative period, additional clinical studies are required to further explore this common complication.

In chapter 6, we evaluate the prognostic value of the Revised Cardiac Risk Index in 2,642 procedures for major adverse cardiac events (MACE) and mortality within 30 days after major vascular surgery. We further determine if the accuracy could be improved by the addition of different age categories and additional risk factors. The Revised Cardiac Risk Index assigns 1 point to each of the following 6 characteristics: high-risk surgery, ischemic heart disease, history of heart failure, cerebrovascular disease, renal insufficiency and insulin dependent diabetes mellitus. The observed incidence of MACE is 6%, 13% and 20% for 1, 2 and $\geq$3 points, respectively. However, the prognostic value of this index is reduced in elderly vascular surgery patients (aged > 75), compared to patients aged < 55 years. If additional information is added to this index (i.e. age, a more detailed classification of type of vascular surgery and history of hypertension), the accuracy of the Revised Cardiac Risk Index to predict postoperative MACE improves significantly among the entire strata of age. Since the vascular surgery population is increasing, becoming older and presenting with complex co-morbidities, risk indices should include age to improve the preoperative cardiovascular risk stratification.

In chapter 7, the independent contribution of preoperative serum uric acid levels to the risk of 30-day and late mortality and MACE is assessed in patients scheduled for open vascular surgery with suspected or proven coronary artery disease. Although the association between serum uric acid levels and the risk of cardiovascular disease is well defined, the role of preoperative hyperuricemia as a risk factor for cardiac outcome in vascular surgery patients remains unclear. Among 936 patients undergoing vascular surgery, preoperative hyperuricemia (serum uric acid >0.42 mmol/l for men and >0.36 mmol/l for women) was not associated with 30-day all-cause mortality or MACE. However, the presence of preoperative hyperuricemia is an independent predictor for late adverse outcomes during 3.7 years of follow-up. Preoperative cardiac risk evaluation for adverse late cardiovascular outcome in vascular surgery patients can be improved with the incorporation of the risk factor hyperuricemia.

In chapter 8, we evaluate the association between the extent of preoperative anemia and perioperative and long-term MACE in patients undergoing noncardiac surgery. Since it is unknown whether anemia is a primary risk factor for poor cardiac outcome, or whether it is secondary to other underlying co-morbidities, anemia has not been included as a factor for cardiac risk assessment in the preoperative screening. Also, it remains unclear whether preoperative anemia predicts adverse cardiac outcomes in patients undergoing vascular surgery. In a study population of 1,211 patients, higher incidences of risk factors such as chronic kidney disease, heart failure and diabetes mellitus are found in patients with anemia. In multivariate analysis, patients with mild (serum haemoglobin levels in men 12.2-13 g/dl, women 11.2-12 g/dl), moderate (men 11-12.1 g/dl, women 10.2-11.1 g/dl) and severe anemia (men 7.2-11 g/dl,

women 7.5-10.1 gl/dl) had an independent increased risk for 30-day and 5-year MACE. Because of these findings, the factor anemia might be used for preoperative cardiac risk assessment.

PART 3: PHARMACOLOGICAL THERAPY

In chapter 9 we observe that lower levels of renal function are associated with higher incidences of co-morbidities like hypertension, hypercholesterolemia, chronic obstructive pulmonary disease (COPD), history of MI, heart failure, angina and cerebrovascular disease, among 2,126 patients undergoing major vascular surgery. The level of renal function prior to major vascular surgery appears to be a predictor for both short- and long-term mortality, independent of other known risk factors. Given the proven benefit of beta-blockers in patients with normal renal function with cardiac co-morbidities, beta-blockers would seem to be attractive agents to reduce cardiovascular morbidity and mortality associated with noncardiac surgery in the chronic kidney disease population. This chapter shows that beta-blocker therapy is associated with improved short- and long-term outcome. Especially in patients with renal impairment (GFR <60 ml/min), beta-blockers are associated with a 65% and 38% reduction in the incidence of short- and long-term all-cause mortality. Although these results are promising, the under use of beta-blocker therapy in patients with renal impairment undergoing major vascular surgery remains a worrisome problem. Since the number of patients with chronic kidney disease is growing rapidly, optimal management of these high-risk patients is of imminent importance. Beta-blocker therapy can improve postoperative outcomes in patients with renal impairment.

In chapter 10, we investigate the relationship between cardioselective beta-blockers and mortality in COPD patients undergoing major vascular surgery. Although beta-blocker use is associated with improved outcomes in patients with cardiovascular disease, there is a general controversy whether to prescribe beta-blockers in patients with COPD, as they may worsen pulmonary symptoms (like bronchospasm). We demonstrate that the use of cardioselective beta-blockers is safe and is associated with a reduced 30-day and long-term mortality during a median follow-up of 5 years. We conclude that patients with COPD undergoing major vascular surgery should not be withheld from beta-blocker therapy, as they improve postoperative outcomes.

In chapter 11, we discuss the association of statin use and 30-day and long-term all-cause, cardiac and cerebro-cardiovascular outcome of 2,126 patients undergoing major elective vascular surgery, with and without chronic kidney disease (GFR <60 ml/min). Although the National Kidney Foundation has established guidelines for dyslipidemia therapy in patients with chronic kidney disease, epidemiologic studies and clinical trials have raised uncertainties regarding the impact of statin therapy on clinical outcomes. We conclude that, irrespective of baseline renal function, statin therapy is associated with an improved 30-day and long-term survival after elective vascular surgery (a 73% and 42% mortality reduction, respectively). Statin therapy is

also related to improved cardiac and cerebro-cardiovascular outcome during long-term follow-up. Furthermore, we observe that the preoperative level of renal function is an independent predictor of overall, cardiac and cerebro-cardiovascular outcome. We found a more than threefold increase of statin use during our follow-up period from 1995 to 2006. Despite these positive effects and increased prescription rate of statin therapy in patients undergoing major vascular surgery, patients with chronic kidney disease are less likely to receive statin therapy, when compared with patients without chronic kidney disease.

In chapter 12, the relation between statin therapy and the incidence of acute kidney injury (AKI) in the post-operative period is studied. Surgical patients experiencing AKI are at high risk of cardiovascular morbidity and mortality. Statin therapy may be effective in improving survival in patients with AKI after elective major non-cardiac surgery. However, studies evaluating the effects of statins on the course of AKI are lacking. Of all 1,944 vascular surgical patients, AKI occurred in 34% patients. Statin therapy could not prevent the development of AKI within two days after surgery. However, if AKI is present, preoperative statin therapy does increase the odds of complete recovery of renal function at day 3 after surgery (adjusted OR of 1.96, 95% CI 1.02 – 3.75). Furthermore, during long-term follow-up, patients with AKI have a 1.24-fold increased risk of all-cause mortality.

In chapter 13, the impact on perioperative cardiac events of statin withdrawal in 298 long-term statin users undergoing major vascular surgery is studied. Patients undergoing major vascular surgery are often not able to take oral medications shortly after surgery. Since there is no intravenous formula of statins, the interruption of statin therapy is a serious concern, because it is known that the risk of cardiac events is the highest within the first three days after surgery. We conclude that patients who interrupted their statin therapy (23% of all patients) have a 7.5-fold increased chance of experiencing an adverse cardiac event within 30 days after surgery. When we compare different types of statins on outcome, we further observed that fluvastatin is associated with fewer perioperative cardiac events, compared to atorvastatin, simvastatin, and pravastatin. A possible explanation for this observation is that fluvastatin is the only statin with an extended-release formula.

Finally, chapter 14 discusses the secondary medical prevention in patients with PAD based on results of a large Danish study. Recent guidelines clearly advise several treatment strategies to control cardiovascular risk factors of patients with PAD, like antihypercholesterolemia, antihypertensive and antiplatelet therapy. However, PAD patients are still less likely to receive cardiovascular therapy i.e. antiplatelet therapy, statins, ACE-inhibitors, and beta-blockers, compared to patients with a first-time hospitalization for MI. This chapter emphasizes the importance of physician awareness for optimal and routine medical treatment in patients with PAD. A more stringent use of and adherence to protocols in clinical practice could improve secondary medical interventions and more importantly outcome of patients with PAD.

IN CONCLUSION, patients with PAD undergoing major vascular surgery are at significant risk of cardiovascular morbidity and mortality. Preoperative identification of risk factors and optimization of perioperative management is of critical importance. These patients could benefit from beta-blocker and statin therapy, as these appear to be independently associated with a reduced incidence of perioperative and long-term mortality. Although secondary medical treatment has proven its benefit, patients with PAD are still less likely to receive optimal cardiovascular therapy. Physician's awareness for this problem is urgently needed, to improve the prognosis.

With the help of our research, we hope that we contributed to the understanding of peripheral arterial disease and to possible improvements in management and outcome of these patients.

Samenvatting en conclusies

In dit proefschrift wordt de prognose, de prognostische waarde van preoperatieve cardiovasculaire risicofactoren en het effect van verschillende farmacologische therapieën beschreven van patiënten met perifeer arterieel vaatlijden (PAV) die een vasculaire ingreep ondergaan.

PART 1: PROGNOSIS - PROGNOSE

Hoofdstuk 1 beschrijft het gezondheidsprobleem van PAV. Een overzicht van geselecteerde publicaties vat de epidemiologie, diagnose, prognose en behandeling van patiënten met PAV samen. Wereldwijd wordt de prevalentie van PAV geschat op meer dan 30 miljoen patiënten. Aangezien PAV asymptomatisch kan zijn of gepaard kan gaan met atypische symptomen, zal dit echter een onderschatting zijn van de daadwerkelijke populatie van patiënten met PAV. Een veel voorkomende co-morbiditeit van PAV is coronairlijden, aangezien slechts 8% van de patiënten die een vaatchirurgische ingreep ondergaan angiografisch normale coronair arteriën heeft. Omdat de prognose van patiënten met PAV gerelateerd is aan de aanwezigheid en uitgebreidheid van het onderliggend coronairlijden, is een nauwkeurige inschatting van het cardiale risicoprofiel van groot belang. De samengevatte data van wetenschappelijke publicaties toont verder aan dat bèta-blokkers en statines perioperatieve cardiale complicaties verminderen bij patiënten met PAV en een vasculaire ingreep. Daarnaast profiteren deze patiënten tevens op lange termijn van een optimale behandeling van atherosclerotische risicofactoren en medicamenteuze behandeling. Bèta-blokkers en statines lijken dus een belangrijke rol te spelen bij het optimaliseren van de secundaire behandeling van PAV. Echter, de medicamenteuze hoeksteen van de secundaire preventie blijft het gebruik van trombocytenaggregatieremmers.

In hoofdstuk 2 wordt de prognose van 2730 patiënten die een vasculaire operatie ondergaan vergeleken met 2730 door middel van risico factor gekoppelde patiënten met uitgebreide myocardischemie verwezen voor een coronaire angioplastiek. Deze patiënten hadden volgens hun medische dossiers geen PAV. We concluderen dat patiënten met PAV die een vaatchirurgische ingreep ondergaan een 2.4 keer hoger risico hebben op overlijden gedurende follow-up van 13 jaar in vergelijking met patiënten met alleen coronairlijden. Patiënten met PAV ontvangen minder cardiovasculaire medicamenteuze dekking (zoals bèta-blokkers, statines, ACE-remmers, calcium antagonisten, nitraten en aspirine) vergeleken met patiënten met coronairlijden, hetgeen de slechtere lange termijn prognose kan verklaren. Deze onderbehandeling is zorgwekkend,

aangezien de secundaire preventie van patiënten met PAV hetzelfde moet zijn als van patiënten met coronairlijden. De behandelende specialisten moeten zich bewust worden van deze onderbehandeling om uiteindelijk de prognose van deze patiënten te verbeteren.

Vervolgens concluderen we dat een cerebrale of cardiovasculaire complicatie de belangrijkste oorzaak is van perioperatieve en late mortaliteit bij chirurgische patiënten met PAV (76% en 46%, respectievelijk). Een myocardinfarct draagt respectievelijk voor 18% en 19% bij aan alle oorzaken van perioperatieve en late sterfte.

In hoofdstuk 3 wordt het lange termijn effect van endovasculaire behandeling van een aneurysma aorta abdominalis (AAA) vergeleken met een open AAA behandeling in patiënten met een verhoogd cardiaal risico profiel. Endovasculaire behandeling is superieur aan open behandeling wat betreft de perioperatieve cardiovasculaire morbiditeit en mortaliteit. Echter, de lange termijn resultaten van specifiek hoog risico patiënten in deze groep zijn nauwelijks beschreven. Gedurende de follow-up (gemiddeld 3.3 jaar) is er geen significant verschil in totale overleving tussen endovasculaire (n= 55) en open (n= 69) AAA behandeling. Echter, de geobserveerde lagere perioperatieve incidentie van cardiale complicaties door endovasculaire behandeling is ook aantoonbaar op de lange termijn. Agressieve medicamenteuze behandeling lijkt van groter belang te zijn dan de keuze van type AAA behandeling teneinde de postoperatieve prognose te verbeteren.

PART 2: RISK FACTORS – RISICOFACTOREN

In hoofdstuk 4 is de invloed van mild nierfalen (glomerulaire filtratie ratio (GFR) 60-90 ml/min) op lange termijn sterfte vergeleken met een normale nierfunctie (GFR >90 ml/min) in 6447 patiënten met bewezen of verdacht coronairlijden. Chronisch nierfalen is een bewezen onafhankelijke risicofactor voor cardiovasculaire morbiditeit en mortaliteit voor patiënten met coronairlijden. Echter, het blijft onbekend of ook mild nierfalen is geassocieerd met een slechte cardiovasculaire uitkomst. Mild nierfalen is een onafhankelijke voorspeller voor totale sterfte en cardiaal bepaalde sterfte gedurende follow-up (gemiddeld 7 jaar). Het tijdig opsporen van nierfalen zal patiënten identificeren met een verhoogd risico op late cardiovasculaire morbiditeit en mortaliteit. Deze patiënten kunnen profiteren van adequate medicamenteuze therapie zoals trombocytenaggregatieremmers, bèta-blokkers, statines en ACE-remmers. Helaas is dit beleid nog steeds niet geprotocolleerd bij patiënten met nierfalen.

In hoofdstuk 5 beschrijven we de voorspellende waarde van subtiele nierfunctie veranderingen in de eerste drie postoperatieve dagen van patiënten die een open AAA behandeling ondergingen. Weinig is bekend van deze acute nierfunctie veranderingen in de postoperatieve periode en het effect op korte en late mortaliteit. Kijken we naar de invloed van passagère nierfunctiestoornissen op het postoperatieve beloop, dan is hier nauwelijks iets over bekend. Patiënten met passagère nierfunctiestoornissen hebben een 3.7 keer verhoogd risico op

30-dagen mortaliteit, terwijl patiënten met persisterende achteruitgang in nierfunctie een 7.3 keer verhoogd risico hebben, vergeleken met patiënten met een onveranderde of verbeterde nierfunctie. Tevens is de prognose van deze patiënten gedurende een follow-up van gemiddeld 6 jaar gelijk aan patiënten met een persisterende achteruitgang in nierfunctie. Daarom concluderen wij dat subtiele postoperatieve nierfunctieveranderingen na AAA chirurgie een hoog voorspellende waarde hebben voor korte en late mortaliteit. Deze patiënten hebben een stringenter beleid nodig dan eerder is gesuggereerd, om verdere achteruitgang in nierfunctie te voorkomen. Er is weinig onderzoek naar de prognostische waarde van acute nierfunctie veranderingen na een vasculaire ingreep op de postoperatieve morbiditeit en mortaliteit verricht. Aanvullende klinische studies zijn nodig om meer inzicht in deze veelvoorkomende complicatie te verkrijgen.

In hoofdstuk 6 evalueren wij de prognostische waarde van de 'Revised Cardiac Risk Index' in 2642 vasculaire ingrepen voor ernstige cardiale complicaties (MACE; Major Adverse Cardiac Events) en sterfte binnen 30 dagen na een vaatchirurgische ingreep. Onderzocht wordt of de nauwkeurigheid van dit risicomodel verbetert kan worden door er verschillende leeftijdsgroepen en aanvullende risicofactoren aan toe te voegen. De 'Revised Cardiac Risk Index' schrijft 1 punt aan de volgende 6 factoren toe: hoog risico chirurgie, ischemisch hartlijden, hartfalen, cerebrovasculaire ziekte, nierfalen en insuline afhankelijke diabetes mellitus. De waargenomen incidentie van MACE is 6%, 13% en 20% voor 1, 2 en 3 of meer punten, respectievelijk. Echter, de prognostische waarde van dit risicomodel is verminderd in oudere vaatchirurgische patiënten (>75 jaar), vergeleken met patiënten jonger dan 55 jaar. Als extra informatie wordt toegevoegd aan dit model (zoals leeftijd, een meer gedetailleerde classificatie van type van vaatoperatie en hypertensie), verbetert de nauwkeurigheid van de 'Revised Cardiac Risk Index' om MACE te voorspellen significant, ongeacht de leeftijd van de patiënt. Omdat de vaatchirurgische populatie ouder wordt, in omvang toeneemt en meer co-morbiditeit heeft, moeten risicomodellen ook leeftijd als apart onderdeel includeren om de preoperatieve cardiovasculaire risicostratificatie te verbeteren.

In hoofdstuk 7 wordt de onafhankelijke bijdrage van de preoperatieve serum urinezuur waarde op het risico van 30-dagen en late MACE en mortaliteit beschreven in patiënten met bewezen of verdacht coronairlijden die een open vasculaire ingreep ondergaan. Hoewel de relatie van het serum urinezuur en de kans op een cardiovasculaire ziekte uitvoerig is onderzocht, blijft de betekenis van preoperatieve hyperuricemie als risicofactor voor cardiale complicaties in vaatchirurgische patiënten onbekend. In een studie populatie van 936 vaatchirurgische patiënten wordt geen relatie van preoperatieve hyperuricemie (serum urinezuur >0.42 mmol/l voor mannen en >0.36 mmol/l voor vrouwen) en 30-dagen MACE en mortaliteit gevonden. Echter, de aanwezigheid van preoperatieve hyperuricemie is een onafhankelijke voorspeller voor een slechte lange termijn prognose gedurende een follow-up van 3.7 jaar. De preoperatieve cardiale risico-inschatting voor late cardiovasculaire complicaties in vaatchirurgische patiënten zal verbeterd worden door het toevoegen van de risicofactor hyperuricemie.

In hoofdstuk 8 beschrijven we de invloed van de ernst van preoperatieve anemie op perioperatieve en late MACE in patiënten die niet-cardiale chirurgie ondergaan. Aangezien het onbekend is of anemie een primaire risicofactor is voor een slechte cardiale prognose of secundair is aan het onderliggend lijden, wordt anemie niet geïncludeerd als een risicofactor voor cardiale risicostratificatie in de preoperatieve screening. Ook blijft het onbekend of preoperatieve anemie cardiale complicaties voorspelt in patiënten die een vaatoperatie ondergaan. In een studiepopulatie van 1211 patiënten worden hogere incidenties van nierfalen, hartfalen en diabetes mellitus gevonden in patiënten met anemie. Patiënten met mild (serum hemoglobine 12.2-13 g/dl voor mannen, 11.2-12 g/dl voor vrouwen), gematigd (mannen 11-12.1 g/dl, vrouwen 10.2-11.1 g/dl) en ernstige anemie (mannen 7.2-11 g/dl, vrouwen 7.5-10.1 g/dl) hebben een verhoogde kans op het krijgen van MACE binnen 30 dagen en 5 jaren na chirurgie. Gezien deze bevindingen zou preoperatieve anemie gebruikt kunnen worden voor de inschatting van cardiaal risico.

PART 3: PHARMACOLOGICAL THERAPY – FARMACOLOGISCHE THERAPIËN

Hoofdstuk 9 laat zien dat een verminderde nierfunctie geassocieerd is met hogere incidenties van co-morbiditeiten zoals hypertensie, hypercholesterolemie, chronic obstructive pulmonary disease (COPD), doorgemaakt myocardinfarct, hartfalen, angina pectoris en cerebrovasculaire ziekte, vergeleken met patiënten met een normale nierfunctie, beschreven in 2126 vaatchirurgische patiënten. De nierfunctie voor aanvang van vasculaire chirurgie is een onafhankelijke voorspeller voor korte en late mortaliteit, onafhankelijk van bekende risicofactoren. Aangezien bèta-blokkers een beschermend effect hebben in patiënten met een normale nierfunctie met cardiale co-morbiditeiten zou bèta-blokkade een aantrekkelijke therapie zijn om de cardiovasculaire morbiditeit en mortaliteit te verminderen in een populatie met chronisch nierfalen die niet-cardiale chirurgie ondergaan. In dit hoofdstuk wordt beschreven dat behandeling met bèta-blokkers de korte en late prognose verbeteren. Met name in patiënten met nierfalen (GFR <60 ml/min) zorgt bèta-blokker therapie voor een 65% en 38% reductie in korte en late mortaliteit, respectievelijk. Ondanks deze resultaten blijft de onderbehandeling met bèta-blokkers in patiënten met nierfalen die een vaatchirurgische ingreep ondergaan zorgwekkend. Omdat de populatie van patiënten met chronisch nierfalen zich snel uitbreidt, lijkt een optimaal medicamenteus beleid in deze patiënten van groot belang. Behandeling met bèta-blokkers kan het postoperatief beloop bij patiënten met nierfalen verbeteren.

In hoofdstuk 10 wordt de relatie tussen cardioselectieve bèta-blokade en mortaliteit bij patiënten met COPD beschreven die een vasculaire ingreep ondergaan. Ondanks het feit dat bèta-blokkers zijn geassocieerd met een verbeterde prognose in patiënten met cardiovasculaire aandoeningen, heerst er een algemene terughoudendheid om bèta-blokkers voor te schrijven bij patiënten met COPD, omdat ze mogelijk pulmonale symptomen (zoals bronchospasme)

kunnen verergeren. Wij laten zien dat het gebruik van cardioselectieve bèta-blokkers veilig is en gepaard gaat met een reductie van de 30-dagen en late mortaliteit gedurende een follow-up van gemiddeld 5 jaar. We concluderen dat therapie middels bèta-blokkers niet onthouden moet worden aan patiënten met COPD die een vasculaire ingreep ondergaan aangezien ze de postoperatieve prognose verbeteren.

In hoofdstuk 11 wordt het effect beschreven van statines in relatie tot de 30-dagen en late totale, cardiaal en cerebro-cardiovasculaire bepaalde mortaliteit in 2126 patiënten die een electieve vaatoperatie ondergaan, met en zonder nierfalen (GFR <60 ml/min). Ondanks het feit dat de National Kidney Foundation richtlijnen heeft opgesteld voor cholesterol verlagende therapie in patiënten met nierfalen, hebben epidemiologische studies en klinische onderzoeken onzekerheid teweeggebracht over de impact van statines. Wij concluderen dat het gebruik van statines een betere 30-dagen en late overleving geeft na electieve vaatchirurgie (een mortaliteit reductie van 73% en 42%, respectievelijk), ongeacht de preoperatieve nierfunctie. Ook blijkt dat, op lange termijn, statines de cardiaal en cerebro-cardiovasculaire bepaalde mortaliteit verminderen. Tevens wordt beschreven dat de preoperatieve nierfunctie een onafhankelijke voorspeller is voor totale, cardiaal en cerebro-cardiovasculair bepaalde sterfte. Gedurende de follow-up periode van 1995 – 2006 neemt het gebruik van statines meer dan drievoudig toe. Ondanks deze positieve resultaten en een toenemend gebruik van statines in deze patiënten groep, blijken patiënten met chronisch nierfalen toch nog steeds minder statines te gebruiken dan patiënten zonder nierfalen.

In hoofdstuk 12 wordt de relatie beschreven van statines en de incidentie van postoperatieve acute nierfunctiestoornissen. Chirurgische patiënten die acute nierfunctiestoornissen ontwikkelen hebben een verhoogd risico op cardiovasculair bepaalde morbiditeit en mortaliteit. Het gebruik van statines zou van invloed kunnen zijn op de overleving van patiënten met acute nierfunctiestoornissen na een vasculaire ingreep. Echter, studies die het effect van statines op het beloop van acute nierfunctiestoornissen beschrijven ontbreken. In een groep van 1944 vaatchirurgische patiënten ontwikkelde 34% acute nierfunctiestoornissen. Statines kunnen acute nierfunctiestoornissen de eerste twee postoperatieve dagen niet voorkomen. Echter, als patiënten deze acute nierfunctiestoornis ontwikkelen, dan hebben zij die reeds preoperatief statines gebruikten een betere kans op een compleet herstel van nierfunctie op de derde postoperatieve dag (gecorrigeerde odds-ratio 1.96, 95% CI 1.02 – 3.75). Tenslotte hebben patiënten met acute nierfunctiestoornissen een 1.24 keer verhoogde kans op late mortaliteit.

In hoofdstuk 13 wordt de invloed van het acuut stoppen van statines in 298 patiënten met langdurig statine gebruik die een vasculaire ingreep ondergaan op postoperatieve cardiale complicaties beschreven. Patiënten die een vasculaire ingreep hebben ondergaan zijn vaak niet in staat om orale medicijnen tot zich te nemen kort na de operatie. Aangezien er geen intraveneuze toediening van statines bestaat, is de onthouding van statines een probleem, daar de kans op cardiale complicaties het hoogst is in de eerste drie postoperatieve dagen. Wij concluderen dat patiënten die tijdelijk perioperatief gestopt zijn met het gebruik van statines

(23% van alle patiënten) een 7.5 keer hogere kans hebben op het krijgen van een cardiale complicatie binnen 30 dagen na chirurgie. Vergelijken we het effect van verschillende soorten statines op het postoperatief beloop, dan blijkt dat fluvastatine geassocieerd is met minder perioperatieve cardiale complicaties, vergeleken met atorvastatine, simvastatine en pravastatine. Een mogelijke verklaring hiervoor is, is dat fluvastatine als enige statine een langdurige afgifte heeft.

Tot slot wordt in hoofdstuk 14 de secundaire medicamenteuze behandeling van patiënten met PAV, gebaseerd op resultaten van een grote Deense studie, besproken. Richtlijnen adviseren verschillende therapieën ten aanzien van het cardiovasculaire risico management van patiënten met PAV, zoals antihypercholesterolemie, antihypertensiva en trombocytenaggregatieremmers. Echter, patiënten met PAV worden nog steeds onderbehandeld (zoals trombocytenaggregatieremmers, statines, ACE-remmers en bèta-blokkers), vergeleken met patiënten met een eerste ziekenhuisbezoek vanwege een doorgemaakt myocardinfarct. Dit hoofdstuk benadrukt het belang van een optimale en routinematig medicamenteuze behandeling van patiënten met PAV. Een stringenter gebruik van en vasthouden aan protocollen aangaande de secundaire medicamenteuze behandeling zal de prognose van patiënten met PAV verbeteren.

CONCLUDEREND: patiënten met PAV die een vaatchirurgische ingreep ondergaan hebben een verhoogd risico op cardiovasculaire morbiditeit en mortaliteit. Het preoperatief identificeren van risicofactoren en een optimaal perioperatief beleid zijn van uiterst belang. Deze patiënten kunnen profiteren van bèta-blokkers en statines, aangezien ze onafhankelijk geassocieerd zijn met een lagere perioperatieve en late mortaliteit. Ondanks het feit dat de secundaire medicamenteuze behandeling zijn effect heeft bewezen, zijn patiënten met PAV nog steeds onderbehandeld ten aanzien van cardiovasculaire risicofactoren. Bewustwording van dit probleem door de behandelende specialist is dringend nodig om de prognose van deze patiënten te verbeteren.

Door middel van ons onderzoek hopen we dat we hebben bijgedragen aan het verder begrijpen van perifeer arterieel vaatlijden en mogelijke verbeteringen in het beleid en prognose van deze patiënten.

Publications and presentations

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