NOVEL INSIGHTS IN PERIOPERATIVE CARE

Tabita M. Valentijn

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Introduction

INTRODUCTION

Patients undergoing non-cardiac surgery are at risk of developing postoperative cardiovascular complications, particularly due to arterial thrombosis.[1] The height of this risk does not only depend on the condition and the comorbidity of the patient prior to surgery, but also on the extent and duration of the surgical procedure. It is important to estimate a patient's individual risk of cardiovascular complications and for this purpose several preoperative risk-scoring systems exist.[2] The clinical variables most commonly used for preoperative risk stratification include the presence of coronary heart disease, congestive heart failure, prior cerebrovascular disease, insulin-dependent diabetes mellitus, renal insufficiency and surgical risk.[3] Patients undergoing low-risk surgery like breast surgery, are expected to suffer an adverse cardiovascular event in less than 1%, and this risk increases gradually to 1-5% in intermediate risk surgery including endovascular aortic aneurysm repair, and to >5% in patients undergoing high-risk surgery, including open aortic or peripheral vascular surgery.[4]

Several of the risk factors used for preoperative risk stratification are related to atherosclerosis. Atherosclerosis is a systemic disease that often affects more than one vascular bed and that eventually leads to atherothrombosis, a collective term that includes coronary artery disease, cerebrovascular disease, and peripheral arterial disease.[5] The guidelines that have been developed to optimize perioperative cardiovascular management in patients undergoing non-cardiac surgery mainly focus on the presence and adequate treatment of underlying atherothrombosis.[6]

Besides aforementioned risk factors, other risk factors might contribute to an increased risk of postoperative cardiovascular events as well. The purpose of this thesis was to evaluate the value of non-traditional risk factors on postoperative and long-term outcome in patients undergoing non-cardiac surgery.

The atherothrombotic patient populations

In **chapter 1** we present the various atherothrombotic patient populations by giving an overview of the results from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. The REACH Registry characterized the atherothrombotic risk factor profile, and evaluated treatment intensity and cardiovascular events among different atherothrombotic patient populations worldwide.[5]

Aortic valve calcification

In patients with atherothrombosis the prevalence of polyvascular disease, defined as the symptomatic involvement of more than one vascular bed, is high[5] and its' presence is associated with an increased rate of cardiovascular events.[7] Atherothrombotic disease markers, like ankle-brachial index and carotid intima-media thickness, offer simple, non-invasive methods to screen patients for the presence of asymptomatic polyvascular disease. Moreover, these markers act as risk markers for cardiovascular events and long-term mortality in vascular surgery patients.[8,9]

We were interested whether the presence of aortic valve calcification, recorded with transthoracic echocardiography, would be another risk marker in vascular surgery patients, like in the general population.[10] In **chapter 2** we evaluate the prognostic implications of aortic valve calcification on postoperative and long-term outcome in patients undergoing vascular surgery. The study sample was derived from an observational cohort of 1484 vascular surgery patients at the Erasmus Medical Center in Rotterdam, during the period between 2002 and 2011. All patients underwent elective open or endovascular surgery, including lower extremity arterial repair, abdominal aortic repair (stenotic or aneurysmatic) and carotid surgery. In **chapter 3** we focus on the relationship between aortic valve calcification and chronic kidney disease in the same cohort of vascular surgery patients. It is well known that in patients with end-stage renal disease, defined as chronic kidney disease requiring renal replacement therapy, the presence of aortic valve calcification is a strong predictor for adverse cardiovascular events and long-term mortality.[11] In patients with chronic kidney disease not requiring dialysis the association with cardiac calcifications and its prognostic value as a risk factor for all-cause mortality is less clear. In vascular surgery patients, both chronic kidney disease and aortic valve calcification is common.[12] Therefore, we examine the association between different stages of chronic kidney disease and aortic valve calcification. Moreover, we also examine the prognostic impact of chronic kidney disease and aortic valve calcification on long-term survival.

Blood type, hemoglobin and blood transfusions

As mentioned previously, arterial thrombosis is responsible for the majority of postoperative and long-term cardiovascular events in patients undergoing non-cardiac surgery. ABO blood type is known to be a major determinant of the risk of atherothrombotic events in the general population.[13] It is unclear whether ABO blood type influences outcome after vascular surgery. In **chapter 4** we evaluate the effect of ABO blood type on both postoperative cardiovascular complications and long-term survival after vascular surgery.

In addition to blood type, hemoglobin levels might also influence postoperative outcome in vascular surgery patients. Although it is well known that preoperative anemia is associated with postoperative cardiovascular events and mortality in patients undergoing non-cardiac surgery,[14] the hemoglobin level is not taken into consideration in guidelines for preoperative risk stratification in non-cardiac surgery. Moreover, anemia may be less well tolerated in vascular surgery patients, due to underlying coronary heart disease.[15] The aim of the study in **chapter 5** was to evaluate the prognostic impact of both pre- and postoperative hemoglobin levels as well as hemoglobin decrease on postoperative cardiovascular events in vascular surgery patients. The study sample was derived from the observational cohort described previously.

Low hemoglobin levels can be corrected by the administration of red blood cell transfusions, which aim to reduce tissue ischemia by increasing oxygen delivery. However, the evidence that transfusions are beneficial is contradictory.[16] In **chapter 6** the cohort of vascular surgery patients was used to examine the impact of perioperative red blood cell transfusion (transfusion within 3 days of surgery) on postoperative cardiovascular events and mortality.

Obesity

Obesity, defined by a body mass index > 30.0 kg/m^2, is related to a high prevalence of cardiovascular risk factors.[17] Despite the medical hazards of obesity, recent reports examining body mass index show an inverse relationship with all-cause mortality. This phenomenon is known as the 'obesity paradox' and has been observed both in the general population as well as in several disease specific populations.[18,19]

In **chapter 7** we present a review of the obesity paradox in the surgical population. The aim of the review is to summarize both the literature concerned with the obesity paradox in the surgical setting, as well as the theories explaining its causation. In addition, we study the presence of the obesity paradox in a general surgery population in **chapter 8** and we report both postoperative and long-term outcome, including cause-specific mortality.

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PART I

THE ATHEROTHROMBOTIC PATIENT POPULATIONS

CHAPTER 1

Lessons from the REACH registry in Europe

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ABSTRACT

Among patients with atherothrombosis, including coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral arterial disease (PAD), patients with PAD generally have the worse prognosis. The Reduction of Atherothrombosis for Continued Health (REACH) Registry characterized the atherothrombotic risk factor profile, and evaluated treatment intensity and cardiovascular events among different atherothrombotic patient populations worldwide. Two thirds of PAD patients had polyvascular disease, defined as symptomatic involvement of more than one vascular bed. The risk factor profile in patients with CAD, CVD and PAD was very much similar. However, optimal risk factor control by medical treatment and lifestyle interventions was least accomplished in PAD patients. Furthermore, PAD patients and patients with polyvascular disease showed the highest cardiovascular event rates. Of note, therapeutic strategies are similar for all atherothrombotic disease categories, irrespective of the presence of polyvascular disease. Therefore, it is of the utmost importance to achieve optimal risk factor control, particularly for PAD patients and for those with polyvascular disease, in order to prevent future cardiovascular events.

Atherothrombosis is a collective term including coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral arterial disease (PAD). It is a leading cause of mortality, and is projected to remain the principal cause of death worldwide by 2020[1]. Atherothrombosis is generally due to a combination of several risk factors for which aggressive risk reduction using lifestyle and medical therapy has proven beneficial[2-4]. However, there are important differences in (adherence to) guideline recommended therapy between these three atherothrombotic patient populations[5, 6]. Consequently, long-term survival also varies and is generally worse for PAD patients[6].

The Reduction of Atherothrombosis for Continued Health (REACH) Registry was initiated to evaluate stable outpatients with a history of, or at high risk of developing, atherothrombotic disease. The purpose was to characterize the atherothrombotic risk factor profile, and to evaluate treatment intensity and cardiovascular event rates in different atherothrombotic patient populations worldwide[7, 8]. In addition, the impact of adherence to guidelines for the control of atherothrombotic risk factors was examined[9].

A total of 67 888 patients with either established atherothrombotic disease (CAD, n=40 258; CVD, n=18 843; PAD, n=8273) or risk factors only (n=12 389) were enrolled in the REACH Registry. The risk factors included were men older than 65 years or women older than 70 years, systolic hypertension despite therapy, treated hypercholesterolemia, treated diabetes mellitus, diabetic nephropathy, current smoking, ankle-brachial index (ABI) < 0.9, asymptomatic carotid stenosis of ≥ 70% or carotid intima media (IMT) thickness of 2 times or more adjacent sites[7].

In patients with established atherothrombosis, the prevalence of polyvascular disease, defined as symptomatic involvement of more than 1 vascular bed, was high: in 16% of patients 1 or 2 other vascular beds were affected[7]. The prevalence of polyvascular disease among the different subgroups increased from nearly 25% in CAD patients to 40% in CVD patients and to 61% in PAD patients[10].

The atherothrombotic risk factor profile was remarkably consistent across vascular beds and throughout the world. Hypertension was present in 80% of patients with established atherothrombotic disease, hypercholesterolemia in 70%, and overweight and obesity in 41% and 44%, respectively. However, the prevalence of diabetes (38%) and current smoking (14%) was significantly higher in PAD patients: 44% had diabetes and 24% were currently smoking[7].

Despite the high prevalence of atherothrombotic risk factors, the REACH registry demonstrated that there is important underutilization of established medical therapy and lifestyle interventions. The use of guideline recommended ACE-inhibitors was only 50%. About 80% of patients used anti-platelet therapy, and 70% were receiving statins. Optimal risk factor control, defined as being at the target goal of the international guideline recommendations[11, 12] (including systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg, blood glucose < 6 mmol/L, LDL cholesterol < 2.5 mmol/L, and smoking cessation for more than 12 months), was therefore achieved in only a minority of patients[7], and was least accomplished in PAD patients (Table 1)[10].

Table 1 I Atherothrombotic risk factors controlled and at target in patients with or without PAD in the REACH Registry[a]

	Patients with PAD [n=8322]	Patients without PAD [n=47492]	P-value
Poor risk factor control[b]			
0-2 risk factors controlled	4026 (48%)	19225 (41%)	
Good risk factor control[b]			
3-5 risk factors controlled	4296 (52%)	28227 (59%)	
Risk factors at target			
SBP < 140 mmHg	44%	55%	<0.0001
DBP < 90 mmHg	79%	81%	<0.0001
Glucose < 6.0 mmol/L	53%	59%	<0.0001
Total cholesterol < 5.0 mmol/L	53%	61%	<0.0001
Current smoking	22%	10%	<0.0001
No smoking for > 12 months	75%	87%	<0.0001

PAD peripheral arterial disease. [a] [10]. [b] Atherothrombotic risk factors are considered controlled when at the following target: systolic blood pressure (SBP) < 140 mmHg, diastolic blood pressure (DBP) < 90 mmHg, glucose < 6.0 mmol/L, total cholesterol < 5.0 mmol/L, stop smoking > 12 months

Cardiovascular (CV) events at 1-year follow-up were available for 95% of patients. The triple ischemic end point of CV death, myocardial infarction (MI) or stroke was 2.2% for patients with risk factors only and 4.7% for patients with established atherothrombotic disease[8], and was essentially constant during 4-year follow-up[13]. Patients with PAD had the highest event rates for the end point of CV death, MI, stroke or hospitalization for an atherothrombotic event. In an analysis of event rates as a function of the number of symptomatic vascular beds involved, CV event rates increased in a stepwise fashion: the end point of CV death, MI, stroke or hospitalization for an atherothrombotic event ranged from 5.3% in patients with risk factors only, to 12.6% with 1, 21.1% with 2, and 26.3% with 3 vascular beds involved[8]. In addition, the triple ischemic end point of CV death, myocardial infarction or stroke was significantly higher in patients with poor risk factor control (i.e. less than 2 risk factors being at target), than in patients with good risk factor control (i.e. 3 to 5 risk factors being at target), and increased gradually during the 3-year follow-up[9]. Independent predictors of poor risk factor control were the presence of PAD or polyvascular disease[9].

There are several possible explanations for the poor control of risk factors in PAD patients. The perception of risk associated with PAD is lower compared to the risk associated with CAD or CVD. This may be caused by a lack of physician knowledge and insufficient awareness of risk of CV events by PAD patients themselves. Another important patient factor is the fact that PAD is often not diagnosed until symptoms are severe and therefore preventive pharmacotherapeutic interventions are not, or at a late stage, prescribed[10].

The REACH Registry demonstrated that in PAD patients polyvascular disease is common and risk factors are less intensively controlled. Furthermore, CV event rates are highest for

these patients and for those with symptomatic polyvascular disease. It is well established that atherothrombosis is a systemic disease, which often affects more than one vascular bed. Atherothrombotic disease markers, like ABI and carotid IMT, offer simple, non-invasive methods to screen patients with established atherothrombosis for the presence of asymptomatic involvement of other vascular beds. In vascular surgery patients, referred for carotid artery or abdominal aortic aneurysm repair, an asymptomatic low ABI (<0.9) was associated with increased perioperative CV events and long-term mortality[14] and a similar association was also seen for an increased IMT of the common carotid artery (≥ 1.25 mm) in patients referred for lower extremity artery or abdominal aortic repair[15]. Although these studies showed that the presence of asymptomatic polyvascular disease was associated with decreased survival, up to now, specific therapeutic strategies are not different from atherothrombotic patients with involvement of 1 vascular bed. Therefore, patients with established atherothrombotic disease in 1 vascular bed should not be routinely referred for screening of asymptomatic involvement of other vascular beds.

Instead, optimal risk factor control with medical therapy and lifestyle interventions according to guideline recommendations should be the primary goal especially for PAD patients and for those with symptomatic polyvascular disease, in order to prevent CV events.

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PART II

AORTIC VALVE CALCIFICATION

CHAPTER 2

Influence of aortic valve calcium on outcome in patients having peripheral vascular surgery

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ABSTRACT

Vascular surgery patients are at increased risk of adverse cardiovascular events because of silent coronary artery disease and an increased propensity for left ventricular dysfunction. The Revised Cardiac Risk Index is commonly used for preoperative risk stratification. Aortic valve calcium is associated with cardiovascular mortality in the general population. The present study evaluated the prognostic implications of aortic valve calcium on 30-day postoperative and long-term outcomes in vascular surgery patients. Echocardiographic aortic valve evaluation was completed in 1,172 vascular surgery patients. Aortic valve sclerosis was defined by the presence of thickening and/or calcium of ≥ 1 cusps of a tricuspid aortic valve not inducing stenosis (i.e. with a maximal velocity at continuous Doppler < 2.5 m/s). Stenosis was defined as a maximal velocity > 2.5 m/s. Troponin-T measurements and electrocardiograms were performed routinely after surgery. The study end points were the composite of postoperative cardiovascular events and long-term mortality. Aortic valve sclerosis was present in 416 patients (36%) and aortic valve stenosis in 30 patients (3%). After multivariate regression analyses adjusted for age, gender, Revised Cardiac Risk Index, hypertension, hypercholesterolemia and medication use, aortic valve sclerosis was not associated with either the postoperative or long-term outcomes. In contrast, aortic valve stenosis was associated with a greater postoperative and long-term event rate (odds ratio 3.9, 95% confidence interval 1.7 to 8.7 and hazard ratio 2.1, 95% confidence interval 1.2 to 3.7, respectively). In conclusion, this study has shown that aortic valve calcium is common in vascular surgery patients. Its presence is associated with negative postoperative and long-term outcomes.

INTRODUCTION

Patients with peripheral arterial disease undergoing vascular surgery are known to be at increased risk for perioperative and late cardiovascular (CV) events because of silent coronary artery disease[1,2] and greater propensity for left ventricular dysfunction[3]. The Revised Cardiac Risk Index (RCRI) is commonly used for preoperative risk stratification in this patient population[4,5]. Aortic valve calcium is associated with CV mortality in the general population[6]. It is unknown whether the presence of aortic valve calcium increases the risk of CV events in patients with peripheral arterial disease.
The aim of the present study was to evaluate the prognostic implications of aortic valve calcium on the 30-day postoperative and long-term outcomes in patients with peripheral arterial disease requiring vascular surgery.

METHODS

The present prospective cohort study included 1,484 vascular surgery patients treated at the Erasmus Medical Center (Rotterdam, The Netherlands) from 2002 to 2011. The institutional review board approved the study, and the study complied with the Declaration of Helsinki. The patients were screened before surgery at the outpatient clinic using physical examination, laboratory measurements, electrocardiograms, and lung function tests.
Before surgery, a detailed medical history was obtained from every patient. The baseline characteristics included the following: age, gender, blood pressure, coronary heart disease (angina pectoris, previous myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting), cerebrovascular disease (history of stroke or transient ischemic attack), renal dysfunction (estimated glomerular filtration rate < 60 ml/min/1.73m^2), heart failure (by history), diabetes mellitus (history or antidiabetic medication requirement), hypertension (blood pressure ≥ 140/90 mmHg in nondiabetics and ≥ 130/80 mmHg in diabetics or antihypertensive medication requirement), hypercholesterolemia (low-density lipoprotein cholesterol ≥ 135 mg/dL or lipid-lowering medication requirement), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification) and smoking status. Medication use was recorded for aspirin, oral anticoagulants, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, diuretics, nitrates and statins.
The cardiac risk score was determined for every patient using the RCRI. The RCRI assigns 1 point to each of the following characteristics: high-risk surgery, coronary heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes mellitus, and renal insufficiency (serum creatinine > 2.0 mg/dL)[7].
Aortic valve evaluation with transthoracic echocardiography was performed preoperatively or within 30-days postoperatively, using a portable Acuson Cypress Ultrasound system (Acuson, A Siemens Company, Mountain View, California) with a 7V3c transducer or a portable Vivid-I Ultrasound System (Vivid-I, GE Healthcare, Solingen, Germany) with a 3S-RS transducer. The aortic valve evaluation included assessment of cusps anatomy and valvular

calcium. Continuous wave Doppler echocardiography was used to measure aortic jet velocity. *Aortic valve sclerosis* (AVS) was defined by the presence of thickening and/or calcium of ≥ 1 cusps of a tricuspid valve not inducing stenosis (i.e. with a maximal velocity < 2.5 m/s). *Aortic valve stenosis* (AoS) was defined as a jet velocity > 2.5 m/s[6,8]. That jet velocity was chosen, because this is the strongest predictor of clinical outcomes in patients with AoS[9]. Patients with moderate AoS (jet velocity 3.0 to 4.0 m/s) or severe AoS (jet velocity > 4.0 m/s) were referred to a cardiologist for regular follow-up. Patients with unstable cardiac conditions or severe aortic stenosis requiring preoperative intervention were excluded.

Serial electrocardiograms and troponin-T measurements were routinely obtained before surgery and postoperatively on day 1, 3 and 7. The study end points were 30-day CV events and long-term mortality. The 30-day CV events were a composite of non-fatal myocardial infarction, new or worsened congestive heart failure, severe cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), stroke (including transient ischemic attack), CV mortality (any death from a cerebrovascular cause, including death after myocardial infarction, congestive heart failure, arrhythmia, stroke, and surgery-related bleeding complications or sudden unexpected death), and asymptomatic troponin-T release. Myocardial infarction was defined as the characteristic increase and decrease of (postoperative) troponin-T levels greater than the 99th percentile with either electrocardiographic or clinical signs of myocardial ischemia. The troponin-T level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany). The 30-day follow-up was completed from patients' visits to the outpatient clinic. For patients still admitted or readmitted at the Erasmus Medical Center, the follow-up data was completed using the Erasmus Medical Center medical records. Long-term mortality was ascertained from the municipal civil registries. The follow-up data were complete for all patients.

Continuous variables are described as the mean ± SD and dichotomous data as numbers and percentages. Continuous data were compared using analysis of variance and categorical data using chi-squared tests. Cumulative long-term survival was determined using the Kaplan-Meier method and compared using the log rank test. The prognostic value of AVS and AoS toward the 30-day and long-term end points was evaluated with logistic and Cox regression analyses, respectively. Multivariate analyses were primarily adjusted for predefined potential confounders (age, gender, RCRI, hypertension and hypercholesterolemia). A second multivariate analysis was performed to adjust for medication with known beneficial effects (aspirin, beta-blockers, statins and ACE inhibitors). For all tests, a P value <.05 (2-sided) was considered significant. All statistical analyses were performed using SPSS, version 17.0, statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

The study population consisted of 1,484 vascular surgery patients, of whom 1,172 patients had complete echocardiographic aortic valve data available. Open vascular surgery was performed in 660 (56%) patients, and 511 (44%) underwent endovascular surgery.

Table 1 | Baseline characteristics according to aortic valve calcium

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

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

Of the 1,172 patients, 338 (29%) underwent lower extremity artery repair, 569 (49%) underwent abdominal aortic repair, and 251 (21%) underwent carotid artery repair. General anesthesia was applied in 97% of the open vascular surgery cases and 45% of the endovascular surgery cases. Spinal and local (infiltration) anesthesia was used in 11% and 44% patients undergoing endovascular surgery, respectively.

The mean age of the study population was 68 ± 10 years and most (74%) were men. AVS was diagnosed in 416 patients (36%) and AoS in 30 patients (3%). Of these patients, 14 (1.2%) had mild aortic stenosis (peak velocity 2.5 to < 3.0 m/s), 9 (0.8%) had moderate aortic stenosis (peak velocity 3.0 to < 4.0 m/s) and 7 (0.6%) had severe aortic stenosis (peak velocity > 4.0 m/s).

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

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

During the long-term follow-up period 253 patients (22%) died. Of these 253 patients, 140 patients (19%) with a normal aortic valve compared to 98 (24%) with AVS and 15 (50%) with AoS ($P < 0.001$; Table 2). The cumulative survival for all patients, stratified according to aortic valve calcium, was studied using Kaplan-Meier survival analyses (log rank $P < 0.001$; Figure 1 and Table 2). Multivariate analyses demonstrated that AoS was associated

Table 2 | Association between aortic valve calcium and outcome

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

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

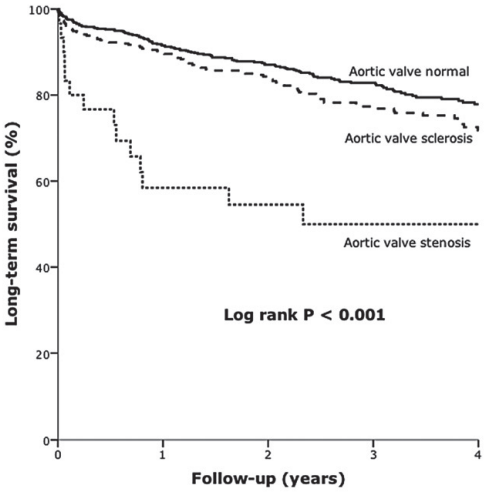

Figure 1 | Kaplan-Meier curves of long-term survival in patients with aortic valve calcium after vascular surgery

with long-term mortality with a hazard ratio [HR] of 2.1 (95% CI 1.2 to 3.7). No association was observed for AVS and long-term outcome with a HR of 1.0 (95% CI 0.7 to 1.3). An RCRI of ≥ 2 points and age were also associated with long-term mortality (RCRI 2 points, HR 1.9, 95% CI 1.4 to 2.6, RCRI ≥ 3 points, HR 3.1, 95% CI 2.3 to 4.2; age, HR 1.0, 95% CI 1.0 to 1.1). Similar HRs were obtained after additional adjustment for medication use (aspirin, beta-blockers, ACE inhibitors and statins).

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

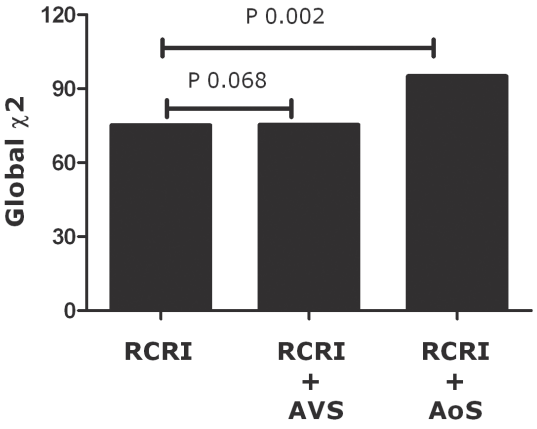

Figure 2 | Incremental value of aortic valve calcium in the prediction of long-term mortality

DISCUSSION

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

Aortic valve calcium is a disease continuum, which comprises aortic valve sclerosis and aortic valve stenosis[10]. AVS does not cause hemodynamic perturbations, and its effect on CV mortality in the general population[6] has been attributed to underlying coronary artery disease[11]. In patients with peripheral arterial disease, polyvascular atherosclerotic disease is common, and its presence is an independent CV risk factor[12]. In the present study, patients with aortic valve calcium had more coronary heart disease. They had greater cardiac risk scores, as represented by the RCRI. The RCRI is a risk stratification tool for noncardiac surgery that has been well validated in different studies[4,13,14]. Not only postoperative, but also long-term outcomes are associated with the RCRI[14]. In unadjusted analyses, the presence of AVS was not associated with 30-day postoperative CV events but it was with long-term mortality. However, after correction for co-morbidities and CV risk factors on multivariate analyses, this association was no longer present. The presence of AVS was probably attenuated in this cohort of vascular surgery patients with extensive polyvascular disease.

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

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

The standard of care for severe, symptomatic AoS is aortic valve replacement[20]. No medical therapy is able to delay the inevitability of surgery. Although atherosclerosis and aortic valve calcium share pathological features, such as lipid deposition, and the presence of ACE has been demonstrated in sclerotic aortic valves[10], statins and ACE-inhibitors have not proved to be successful in reducing AoS progression. Retrospective studies showed promising

results[17,21-24], but these were not confirmed by prospective, randomized trials[25-27]. In the present study, no difference was found in the use of ACE-inhibitors or statins in patients with aortic valve calcium. The reported HRs did not change after correction for medication use. It would be interesting to determine whether AoS progression is different in this population of vascular surgery patients compared to the patient populations in the previously cited randomized trials, because in those trials, patients with peripheral arterial disease[26,27] or patients on statin therapy[25], were excluded.

The present study had several limitations. First, the presence, but not the extent, of valvular calcium, which is a strong negative predictor of a poor outcome[19], was recorded. Second, in a number of patients echocardiography was performed postoperatively. Because aortic valve calcium is slowly progressive[10], its presence at the time of surgery was expected. Third, no follow-up echocardiography was performed to evaluate progression of aortic valve calcium. Finally, the present study was an observational study; thus, the causal relationship between aortic valvular disease and the clinical outcomes could not be established.

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

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PART II

AORTIC VALVE CALCIFICATION

CHAPTER 3

Association of chronic kidney disease with aortic valve sclerosis in vascular surgery patients: an observational cohort study

BMC Nephrology (under review)

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ABSTRACT

Background

Aortic valve sclerosis (AVS) is a predictor of cardiovascular events in patients with end-stage renal disease. Whether chronic kidney disease (CKD) not requiring dialysis is associated with AVS is less well established.

Methods

This observational cohort included 1484 vascular surgery patients at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period between 2002 and 2011. Echocardiographic aortic valve evaluation was completed in 1172 patients. Preoperatively, glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease prediction equation. Kidney function was categorized as normal (eGFR > 60 mL/min/1.73m^2), moderate 3a CKD (eGFR 45-59 ml/min/1.73m^2), moderate 3b CKD (eGFR 30-44 mL/min/1.73m^2), and severe CKD (eGFR < 30 mL/min/1.73m^2). Logistic regression analyses were used to study the association between different CKD stages and AVS. Long-term mortality risk for patients with CKD with and without AVS was evaluated with Cox regression analyses.

Results

In 286 (25%) patients CKD was present (eGFR < 60 mL/min/1.73m^2). The prevalence of AVS increased from 43% in moderate 3a CKD to 55% in moderate 3b CKD and severe CKD (P < 0.001). Moderate 3b CKD and severe CKD were associated with AVS (OR 1.9; 95% CI 1.2-3.0 and OR 2.2; 95% CI 1.1-4.2; respectively). During the long-term follow-up 238 (21%) patients died. Mortality risks were high among patients with moderate-severe CKD without AVS (adjusted HR 2.0; 95% CI 1.2-3.4) and were highest in patients with combined moderate-severe CKD and AVS (adjusted HR 2.2; 95% CI 1.4-3.4).

Conclusions

Aortic valve sclerosis is highly prevalent in moderate 3b CKD and severe CKD in vascular surgery patients, and its presence in these patients is associated with an increased mortality risk. The mechanisms responsible for the association of CKD with AVS need to be explored in future studies.

BACKGROUND

Chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min per 1.73 m^2, is a major health problem, with an estimated prevalence of 5% in the general population[1-3], increasing five- to sevenfold in patients with prevalent cardiovascular disease[4-8]. About half of patients with CKD have a moderate decline in eGFR (30-59 mL/min per 1.73 m^2) and the majority of these patients are at greater risk for cardiovascular morbidity and mortality than to progress to end-stage renal disease, defined as CKD requiring renal replacement therapy[1, 3, 6-11].
In patients with end-stage renal disease the prevalence of cardiac calcifications, such as aortic valve sclerosis (AVS) and mitral annular calcification, is high[12-15], and its presence is a strong predictor for adverse cardiovascular events[13, 15] and all-cause mortality[14, 15], as it is in the general population[16-18]. In patients with CKD not requiring dialysis the association with cardiac calcifications and its prognostic value as a risk factor for all-cause mortality has been mainly extrapolated from population based-studies[19-21].
Chronic kidney disease is common in patients with peripheral arterial disease[5-8], as well as AVS[22, 23]. We recently demonstrated that the presence of aortic valve calcium in vascular surgery patients was associated with negative postoperative and long-term outcomes[23].
In the present study we examine the hypothesis different stages of CKD will be associated with AVS in vascular surgery patients, after adjusting for traditional cardiovascular risk factors. Moreover, we also examine the prognostic impact of CKD and AVS on long-term survival.

METHODS

Patients

The study sample was derived from an observational cohort of 1484 vascular surgery patients at the Erasmus Medical Center in Rotterdam, during the period between 2002 and 2011. The institutional review board approved the study and the study complied with the declaration of Helsinki. According to Dutch law, written informed consent is not required in observational studies in which patients are not subjected to interventions and in whom data are collected from routine clinical care. All patients underwent elective open or endovascular surgery, including lower extremity arterial repair, abdominal aortic repair (stenotic or aneurysmatic) and carotid surgery. Patients were screened prior to surgery at the outpatient clinic, by physical examination, laboratory measurements, electrocardiograms and lung function tests, and a detailed medical history was obtained from every patient. This included coronary heart disease (history of angina pectoris, myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting), heart failure (by history) and cerebrovascular disease (history of transient ischemic attack or cerebrovascular accident). Baseline characteristics were recorded including age, gender and cardiovascular risk factors: diabetes mellitus (by history or requirement of anti-diabetic medication), hypertension (blood pressure ≥ 140/90 mmHg

in non-diabetic patients, blood pressure ≥ 130/80 mmHg in diabetic patients, or the use of antihypertensive medication), hypercholesterolemia (low-density lipoprotein cholesterol ≥ 135 mg/dl or requirement of lipid-lowering medication), chronic obstructive pulmonary disease (based on preoperative pulmonary function testing and classified according to the Global Initiative on Obstructive Lung Diseases) and smoking status. High-risk surgery was defined as open aortic or peripheral vascular surgery[24]. Medication use was recorded for aspirin, oral anticoagulants, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, diuretics, nitrates and statins.

Kidney function

Blood samples were obtained prior to surgery for serum creatinine level assessment in all patients, and during long-term follow-up. Kidney function was estimated by using the simplified Modification of Diet in Renal Disease (MDRD) prediction equation, defined as eGFR = 186.3 x (serum creatinine)$^{-1.154}$ x age$^{-0.203}$ x (0.742 for women)[25]. Kidney function was considered normal when eGFR > 60 mL/min per 1.73 m^2; stages 1 and 2 of the K/DOQI guidelines were combined in the present study due to increasing uncertainty at values greater than 60 mL/min per 1.73 m^2 [26], and because proteinuria measurements were not available[1, 2]. Glomerular filtration rate 30-59 mL/min per 1.73 m^2 was defined as CKD with moderate reduction in GFR; it was sub-classified into stages 3a and 3b with eGFR of 45-59 mL/min per 1.73 m^2 and 30-44 mL/min per 1.73 m^2, respectively[2, 27]. These categories were chosen since eGFR < 45mL/min per 1.73 m^2 is considered a more advanced state of kidney disease within stage 3 CKD. Chronic kidney disease with severe GFR reduction was defined as eGFR < 30 mL/min per 1.73 m^2, in which stages 4 and 5 were combined, including 12 patients requiring chronic dialysis, because of a small number of subjects in both groups.

Echocardiography

Aortic valve evaluation with transthoracic echocardiography was completed in 1172 patients (preoperatively in 1064 patients and within 30-days postoperatively in 78 patients), using a portable Acuson Cypress Ultrasound System (Acuson, A Siemens Company, Mountain View, CA) with a 7V3c transducer or a portable Vivid-I Ultrasound System (Vivid-I, GE Healthcare, Solingen, Germany) with a 3S-RS transducer. Aortic valve evaluation included assessment of valve anatomy and calcification. Continuous-wave Doppler echocardiography was used to measure aortic jet velocity. Aortic valve sclerosis (AVS) was defined by thickening and/or calcification of one or more leaflets of a tricuspid valve not inducing stenosis, i.e. with a maximal velocity < 2.5 m/s, stenosis was defined as a jet velocity > 2.5 m/s[28]. Echocardiographic Doppler measurements of the aortic valve have a low intra- and interobserver variability[29, 30] and flow velocity is the most observer- and machine-independent parameter[31].

Follow-up and endpoints

Median follow-up duration was 2.5 years (interquartile range 1.1-4.0 years). The primary endpoint of interest was the association between AVS and different CKD stages.

The secondary endpoint was long-term all-cause mortality, which was ascertained from the civil registries. The follow-up data were complete in all patients.

Statistical analyses

Continuous variables are reported as mean ± standard deviation (SD) and dichotomous data as numbers and percentages. Continuous variables were compared with analysis of variance and categorical data with chi-squared tests. Logistic regression models were used to examine whether CKD was associated with AVS. The odds ratio (OR) for AVS was estimated in patients with moderate CKD, further classified as stage 3a CKD and stage 3b CKD, and for those with severe CKD, using patients with normal kidney function as the referent group. Covariates in the multivariable-adjusted model included age, gender, coronary heart disease, cerebrovascular disease, diabetes mellitus, hypertension and hypercholesterolemia. These covariates were chosen on the basis of biological plausibility. In secondary analyses, cumulative long-term survival was determined using the Kaplan-Meier method and compared with the log-rank test. Long-term mortality risk was evaluated with Cox proportional hazards models. Patients were stratified into the following groups: (i) normal kidney function without AVS (referent group), (ii) normal kidney function with AVS, (iii) moderate 3a CKD without AVS, (iv) moderate 3a CKD with AVS, (v) moderate-severe CKD without AVS and (vi) moderate-severe CKD with AVS. For mortality analyses moderate-severe CKD was defined as eGFR < 45 mL/min per 1.73 m^2, in which patients with CKD stages 3b, 4 and 5 were combined because there were too few cases for meaningful subgroup analyses. Sensitivity analyses were performed excluding chronic dialysis patients. Because the long-term mortality risk in patients undergoing high-risk surgery might be different from patients undergoing other vascular surgery procedures, we performed additional sensitivity analyses in both patient groups. Multivariable analyses were primarily adjusted for potential confounders (age, gender, coronary heart disease, heart failure, cerebrovascular disease, hypertension, hypercholesterolemia, diabetes mellitus and high-risk surgery).

For all tests, a *P* value <.05 (2-sided) was considered significant. All statistical analyses were performed using SPSS 17.0 statistical software (SPSS Inc., Chicago, Ill).

RESULTS

Patients

The study cohort consisted of 1484 vascular surgery patients, of whom 1172 patients had complete echocardiographic aortic valve evaluation. Patients with aortic valve stenosis (n=30) were excluded; therefore the final study sample comprised 1142 patients. Of these patients, 551 (48%) underwent abdominal aortic repair, 331 (29%) underwent lower extremity arterial repair, and 246 (22%) underwent carotid surgery. Open vascular surgery was performed in 642 (56%) patients, and high-risk surgery (open aortic or peripheral vascular surgery) was performed in 472 (41%) patients. Aortic valve sclerosis was diagnosed in 416 (36%) patients. Baseline characteristics in patients with and without AVS

are shown in Table 1. Compared to patients without AVS, patients with AVS were older (67 ± 11 vs. 71 ± 9 years; $P < 0.001$) and had higher incidence of coronary heart disease (37% vs. 45%; $P = 0.02$), heart failure (8% vs. 12%; $P = 0.03$), diabetes mellitus (22% vs. 28%; $P = 0.01$) and hypertension (62% vs. 77%; $P < 0.001$). Regarding medication, patients with AVS more often used oral anticoagulants (21% vs. 15%; $P = 0.01$), beta-blockers (87%

Table 1 | Baseline characteristics by aortic valve sclerosis

	Normal AoV [N=726]	**AoV sclerosis** [N=416]	**P-value**
Demographics			
Age (mean ± SD)	67 (11)	71 (9)	<0.001
Male (%)	536 (74)	313 (75)	0.59
Medical history (%)			
Coronary heart disease	270 (37)	185 (45)	0.02
Cerebrovascular disease	234 (32)	149 (36)	0.22
Heart failure	58 (8)	50 (12)	0.03
Diabetes Mellitus	156 (22)	117 (28)	0.01
Hypertension	449 (62)	321 (77)	<0.001
Hypercholesterolemia	660 (91)	374 (90)	0.58
COPD	220 (45)	153 (45)	0.98
Smoker, current	323 (45)	165 (40)	0.09
Kidney function			
eGFR (mean ± SD)	79 (± 25)	72 (± 28)	<0.001
CKD (%)	147 (20)	139 (33)	<0.001
Surgery type (%)			
Open	400 (55)	242 (58)	0.29
Carotid	102 (26)	65 (27)	
Abdominal aorta	158 (40)	90 (33)	0.52
Lower extremity	137 (34)	87 (36)	
Medication (%)			
Aspirin	488 (68)	270 (65)	0.36
Oral anticoagulants	105 (15)	89 (21)	0.01
Beta-blockers	575 (80)	360 (87)	0.01
Calcium antagonists	125 (17)	93 (22)	0.04
ACE-inhibitors	196 (27)	132 (32)	0.10
Angiotensin II antagonists	117 (16)	89 (21)	0.03
Diuretics	163 (23)	119 (29)	0.02
Nitrates	62 (9)	52 (13)	0.03
Statins	574 (80)	336 (81)	0.61

Abbreviations: AoV aortic valve; ACE angiotensin converting enzyme; CKD chronic kidney disease; COPD chronic obstructive pulmonary disease; eGFR estimated glomerular filtration rate

vs. 80%; $P = 0.01$), calcium antagonists (22% vs. 17%; $P = 0.04$), angiotensin II receptor blockers (21% vs. 16%; $P = 0.03$), diuretics (29% vs. 23%; $P = 0.02$) and nitrates (13% vs 9%; $P = 0.03$) than patients without AVS.

Relationship of CKD with AVS

Chronic kidney disease defined as eGFR < 60 mL/min per 1.73 m^2 was present in 286 (25%) patients; 162 (14%) patients had moderate 3a CKD (eGFR 45-59 mL/min per 1.73 m^2), 83 (7%) had moderate 3b CKD (eGFR 30-44 mL/min per 1.73 m^2) and 41 (4%) had severe CKD (eGFR < 30 mL/min per 1.73 m^2). In patients with severe CKD 12 patients requiring chronic dialysis were included.

In patients with CKD cardiovascular disease including coronary heart disease and heart failure, and risk factors including diabetes and hypertension, were more common than in patients with normal kidney function (for coronary heart disease, heart failure and hypertension: $P < 0.001$; diabetes mellitus $P = 0.01$). Regarding medication, there were no differences in the use of aspirin, beta-blockers and statins in patients with CKD. However, ACE-inhibitors and angiotensin-II receptor blockers were more often prescribed in patients with CKD (ACE-inhibitors: $P < 0.001$; angiotensin-II receptor blockers: $P = 0.03$). The prevalence of AVS according to kidney function increased from 32% in patients without CKD to more than 50% in moderate 3b CKD and severe CKD ($P < 0.001$) (Table 2).

Patients with CKD were more likely to have AVS than patients without CKD. In unadjusted analyses, the odds of AVS in patients with moderate 3a CKD was 1.6 times higher compared to patients with normal kidney function (OR 1.6; 95% CI 1.1-2.2). In patients with moderate 3b CKD and severe CKD the odds of having AVS was even higher (moderate 3b CKD: OR 2.6; 95% CI 1.6-4.1; severe CKD: OR 2.7; 95% CI 1.4-5.0; respectively) (Table 2). Multivariable analyses, adjusting for age, gender, cerebro- and cardiovascular disease and other important cardiovascular risk factors, demonstrated that both patients with moderate 3b CKD as well as patients with severe CKD were (nearly) two times more likely to have AVS (moderate 3b CKD: OR 1.9; 95% CI 1.2-3.0; severe CKD: OR 2.2; 95% CI 1.1-4.2; respectively). On the other hand, moderate 3a CKD was no longer associated with AVS after multivariable adjustment (OR 1.2; 95% CI 0.9-1.8) (Table 2).

Prognostic Impact of CKD and AVS on Long-term Mortality

Serum creatinine levels were measured in 1022 (90%) patients during the long-term follow-up. The median follow-up period between surgery and the last serum creatinine level recorded was 358 days (interquartile range 18-874 days). In 768 (75%) patients kidney function (according to eGFR) remained stable, and in 169 (17%) patients kidney function worsened during follow-up, displayed by progression to higher CKD categories. During the long-term follow-up 238 (21%) patients died. The number of deaths in patients with moderate 3a CKD without AVS was 27 (30%) and 17 (24%) in moderate 3a CKD with AVS. Patients with more advanced kidney disease (stages 3b, 4 and 5 combined) had the highest mortality rates; in moderate-severe CKD without AVS 19 (35%) patients died, and mortality increased to 31 (45%) patients in moderate-severe CKD with AVS ($P < 0.001$) (Figure 1 and Table 3A).

After adjusting for potential confounders, moderate 3a CKD without AVS, but not moderate 3a CKD with AVS, was associated with long-term mortality (moderate 3a CKD without AVS: HR 1.6; 95% CI 1.0-2.6; moderate 3a CKD with AVS: HR 1.2; 95% CI 0.7-2.0; respectively). Mortality risks were high among patients with moderate-severe CKD without AVS (HR 2.0; 95% CI 1.2-3.4) and were even higher in patients with combined moderate-severe CKD and AVS (HR 2.2; 95% CI 1.4-3.4) (Table 3A). Sensitivity analysis excluding dialysis patients did not change these hazard ratios. Sensitivity analyses in patients undergoing high and non-high risk surgery demonstrated similar results (Table 3B). Mortality risks were high in patients with moderate-severe CKD without AVS (HR 3.0; 95% CI 1.5-5.8 in high-risk surgery and HR 1.2; 95% CI 0.5-2.8 in non-high-risk surgery) and even higher in patients with combined moderate-severe CKD and AVS (HR 1.8; 95% CI 1.0-3.5 in high-risk surgery and HR 3.9; 95% CI 2.0-7.3 in non-high risk surgery) (Table 3B).

DISCUSSION

In this cohort of vascular surgery patients, the prevalence of AVS and of CKD, defined by an eGFR < 60 mL/min per 1.73 m^2 is high, consistent with other published reports in patients with vascular disease[4-8, 22]. Aortic valve sclerosis was present in more than 50% of patients with moderate 3b CKD and severe CKD. After adjustment for cardiovascular risk factors, a strong association between moderate 3b CKD and severe CKD with AVS was still present. Mortality was high in all CKD patients, and significantly increased in those with more impaired kidney function (eGFR < 45 mL/min per 1.73 m^2) and when AVS was present.

Table 2 I Prevalence and association of aortic valve sclerosis with chronic kidney disease

	Prevalence	**Univariate**		**Multivariate ***	
	AVS (%)	**OR**	**[95% CI]**	**OR**	**[95% CI]**
normal kidney function	32	Reference		Reference	
eGFR > 60 mL/min/1.73m^2					
moderate 3A CKD	43	1.6	1.1-2.2	1.2	0.9-1.8
eGFR 45-59 mL/min/1.73m^2					
moderate 3B CKD	55	2.6	1.6-4.1	1.9	1.2-3.0
eGFR 30-44 mL/min/1.73m^2					
severe CKD (stage 4,5)	56	2.7	1.4-5.0	2.2	1.1-4.2
eGFR < 30 mL/min/1.73m^2					

Abbreviations: AVS aortic valve sclerosis; CI confidence interval; CKD chronic kidney disease; eGFR estimated glomerular filtration rate; OR odds ratio. * Adjusted for age, gender, coronary heart disease, cerebrovascular disease, diabetes mellitus, hypertension and hypercholesterolemia

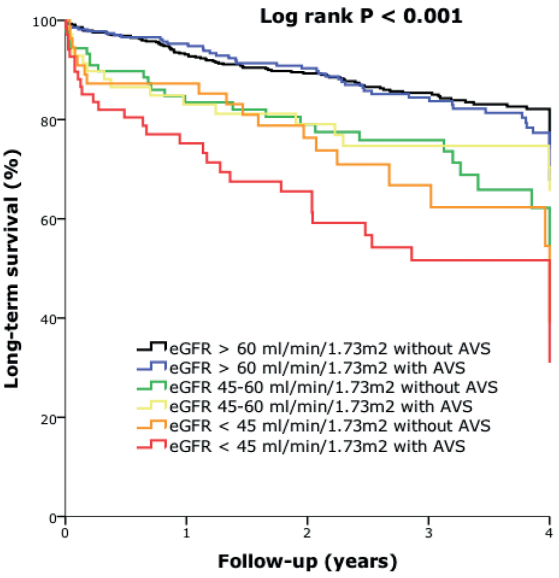

Figure 1 I Kaplan-Meier curves of long-term survival according to kidney function with or without aortic valve sclerosis. *Abbreviations: AVS aortic valve sclerosis; eGFR estimated glomerular filtration rate*

Table 3A I Long-term mortality according to kidney function with or without aortic valve sclerosis

			All patients [N=1142]			
			Univariable		Multivariable *	
	AVS	Mortality (%)	HR	[95% CI]	HR	[95% CI]
normal kidney function eGFR > 60 ml/min/1.73m²	-	16	Reference		Reference	
normal kidney function eGFR > 60 ml/min/1.73m²	+	18	1.2	0.9-1.7	1.0	0.7-1.4
moderate 3A CKD eGFR 45-59 ml/min/1.73m²	-	30	2.1	1.4-3.3	1.6	1.0-2.6
moderate 3A CKD eGFR 45-59 ml/min/1.73m²	+	24	1.8	1.1-3.1	1.2	0.7-2.0
moderate-severe CKD (stage 3B, 4, 5) eGFR < 45 ml/min/1.73m²	-	35	2.6	1.6-4.3	2.0	1.2-3.4
moderate-severe CKD (stage 3B, 4, 5) eGFR < 45 ml/min/1.73m²	+	45	3.8	2.5-5.8	2.2	1.4-3.4

Abbreviations: AVS aortic valve sclerosis; CKD chronic kidney disease; eGFR estimated glomerular filtration rate.
* Adjusted for age, gender, coronary heart disease, heart failure, cerebrovascular disease, hypertension, hypercholesterolemia, diabetes mellitus and high-risk surgery. ** P-value for interaction term kidney function and AVS was .819

Table 3B I Long-term mortality according to kidney function and surgery risk with or without aortic valve sclerosis

		High-risk surgery patients [N= 472]			Non-high-risk surgery patients [N=670]		
			Multivariable *			Multivariable *	
	AVS	Mortality (%)	HR	[95% CI]	Mortality (%)	HR	[95% CI]
normal kidney function eGFR > 60 ml/min/1.73m^2	-	19	Reference		15	Reference	
normal kidney function eGFR > 60 ml/min/1.73m^2	+	25	1.3	0.8-2.1	14	0.8	0.5-1.3
moderate 3A CKD eGFR 45-59 ml/min/1.73m^2	-	38	1.7	0.9-3.1	25	1.8	1.0-3.4
moderate 3A CKD eGFR 45-59 ml/min/1.73m^2	+	32	1.2	0.6-2.6	19	1.0	0.5-2.2
moderate-severe CKD (stage 3B, 4, 5) eGFR < 45 ml/min/1.73m^2	-	48	3.0	1.5-5.8	23	1.2	0.5-2.8
moderate-severe CKD (stage 3B, 4, 5) eGFR < 45 ml/min/1.73m^2	+	47	1.8	1.0-3.5	43	3.9	2.0-7.3

Abbreviations: AVS aortic valve sclerosis; CKD chronic kidney disease; eGFR estimated glomerular filtration rate.
*Adjusted for age, gender, coronary heart disease, heart failure, cerebrovascular disease, hypertension, hypercholesterolemia and diabetes mellitus

In line with previous studies, AVS is a frequent complication in patients with end-stage renal disease[12-15] and is associated with increased cardiovascular and all-cause mortality in these patients[14, 15]. However, this is the first study to show a considerable association between AVS and moderate 3b CKD and AVS. In the Framingham Heart Study and in the Cardiovascular Health Study no associations were observed between less severe CKD and AVS; CKD was defined as eGFR < 60 mL/min per 1.73 m^2 in the Framingham Heart Study and as eGFR < 45 mL/min per 1.73 m^2 in the Cardiovascular Health Study, respectively[19, 21]. Aortic valve calcification, determined by electron beam tomography, had only a modest association with CKD in the Multi-Ethnic Study of Atherosclerosis (MESA), which defined CKD as eGFR < 60 mL/min per 1.73 m^2 [20].

Valvular calcification in patients with end-stage renal disease has been regarded to be the result of passive degeneration, due to dysregulation of the mineral metabolism with elevated levels in serum phosphate[11, 12, 32], and of an active process of inflammation, similar to atherosclerosis[32, 33]. Whether atherosclerotic risk factors or factors unique to kidney disease are causally related to valvular calcifications in moderate CKD remains unclear. Aortic valve sclerosis and atherosclerosis have an overlap in traditional cardiovascular risk factors[34] and share pathophysiologic mechanisms, such as inflammation, lipid deposition, endothelial dysfunction and calcification[35, 36]. Patients with peripheral arterial disease have a high atherosclerotic burden, and cardiovascular risk factors associated with AVS were

more prevalent in this study population compared to aforementioned studies[19-21]. However, after adjustment for these risk factors a significant association between moderate 3b CKD and AVS remained. These findings suggest that factors other than atherosclerotic risk factors might be responsible for calcification in patients with moderate CKD. Abnormalities or complications related to declining kidney function, like abnormalities in mineral metabolism, might be a potential explanation for the association of moderate 3b CKD with AVS in this study cohort of vascular surgery patients. Disturbance of mineral metabolism starts early during kidney function decline[1]. In fact, higher serum phosphate levels, within the normal laboratory range, have been associated with valvular calcifications in patients with early CKD (mean eGFR 50.6 mL/min per 1.73 m^2)[37].

Patients with moderate CKD (eGFR 30-59 mL/min per 1.73 m^2) have an increased mortality risk. The results of the present study are consistent with previous studies[1, 3, 6-11] and demonstrate that mortality risk is increased both in patients with moderate 3a CKD as well as in patients with more impaired kidney function (eGFR < 45 mL/min per 1.73 m^2; in which CKD stage 3b, 4 and 5 were combined). The high prevalence of cardiovascular disease and risk factors in vascular surgery patients with CKD might be responsible for this increased mortality risk. However, after multivariable analysis adjusting for these confounders, the association with increased mortality remained. Other factors, like lower use of certain drugs and CKD specific factors, probably contributed to the increased mortality risk as well. Although underutilization of cardio- and nephroprotective drugs in patients with CKD was reported previously[38, 39], patients in the current study were prescribed aspirin in 67%, statins in 80% and beta-blockers in 82%. Angiotensin blockade in the form of ACE-inhibitors or angiotensin-receptor blockers were used in 45%. In subgroup analyses of CKD patients, there were no differences in the use of aspirin, beta-blockers and statins. However, CKD patients more often received angiotensin blockade. Non-traditional, CKD specific factors including anemia[40, 41], calcium-phosphate disorders[42, 43], inflammation[44] and a procoagulant state, expressed by high levels of fibrinogen[45], are also related to mortality in patients with moderate CKD and could possibly explain the increased mortality risk in this cohort of vascular surgery patients.

Aortic valve sclerosis in patients with eGFR < 45 mL/min per 1.73 m^2, was associated with a 2.2 times higher mortality risk compared to patients with normal kidney function without AVS, even after exclusion of chronic dialysis patients. The Framingham Heart Study was the only other study that evaluated mortality risk of valvular calcification in patients with less severe CKD (defined as eGFR < 60 mL/min per 1.73 m^2). In this study, the risk of death increased threefold in patients with CKD and mitral annular calcification[19]. Valvular calcification progresses more rapidly in patients with kidney disease[32] and some patients with AVS in the present study may have progressed to aortic valve stenosis during follow-up. Severe, asymptomatic aortic valve stenosis (jet velocity ≥ 4 m/sec) is associated with reduced survival[46, 47], and even mild and moderate stenosis (jet velocity 2.5 to 3.9 m/sec) carries an increased mortality risk[48]. The increased mortality risk in patients with eGFR < 45 mL/min per 1.73 m^2 with AVS might be attributable to the development of aortic valve stenosis over time, but it is unlikely that it is fully responsible for the observed increase. Moreover, sensitivity analyses in patients undergoing high and non-high-risk surgery yielded

similar results, with the highest mortality risks in patients with combined eGFR < 45 mL/min per 1.73 m^2 and AVS. Previous studies have not shown an association between surgery risk and long-term mortality[49, 50], and differences in hazards in the present study might have been caused by small numbers of patients in the high and non-high risk surgery groups. In conclusion, it seems that valvular calcification acts as a risk marker for patients with eGFR < 45 mL/min per 1.73 m^2, in a similar way it does for patients with end-stage renal disease[14, 15, 33].

Several limitations of the present study should be considered. First, CKD was assessed by estimated GFR with the MDRD formula[25], but more sensitive markers like cystatin may be preferred. Also, calcium, phosphate and parathyroid hormone levels were not available; this would have been useful in analysis for the association of AVS with different CKD stages. Second, results obtained in vascular surgery patients may not be applicable to the general population, although multivariable analyses were used to adjust for potential confounders. Third, data on mitral and aortic annular calcification were not available. Preoperative echocardiographic evaluation of patients undergoing noncardiac surgery is recommended in patients with heart failure to evaluate left ventricular function and in patients with severe valvular heart disease, particularly aortic valve stenosis, because these conditions are associated with a high risk of perioperative cardiovascular complications[24]. However, data on mitral and aortic annular calcification are not routinely collected. Another limitation lies in the fact that this is an observational cohort and not a prospective chosen cohort of patients with CKD. However, we were interested whether the presence of AVS in different CKD stages (particularly those not requiring dialysis) would be associated with an increased long-term mortality risk, as described in patients with end-stage renal disease as well as in the general population. Since both AVS and CKD are common in vascular surgery patients, we were able to study this question in the current patient cohort. However, causality between aortic valve calcification, CKD and outcome cannot be established. Cross-sectional data were collected, and follow-up measurements of creatinine and repeated echocardiography were not routinely performed.

CONCLUSIONS

In this study of vascular surgery patients, a strong and independent association between moderate 3b CKD (eGFR 30-44 mL/min per 1.73 m^2) and severe CKD (eGFR < 30 mL/min per 1.73 m^2) with AVS was demonstrated. The presence of AVS in patients with eGFR < 45 mL/min per 1.73 m^2 was associated with an increased mortality risk, besides the risk of CKD itself. The results of the present study need confirmation in other patient populations. The mechanisms responsible for the association of CKD with AVS need to be explored in future studies.

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PART III

BLOOD TYPE, HEMOGLOBIN AND BLOOD TRANSFUSIONS

CHAPTER 4

ABO blood type does not influence the risk of cardiovascular complications and mortality after vascular surgery

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ABSTRACT

Objectives

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

Methods

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

Results

Non-O blood type was present in 2627 (56%) patients. Within 30 days after surgery, 129 (4.9%) non-O and 112 (5.5%) O patients suffered a cardiovascular event ($P = 0.42$). Non-O blood type was not associated with increased mortality during long-term follow-up (aHR 0.96; 95% CI 0.88 – 1.04, with a median follow-up of 4 years). Antiplatelet and anticoagulant drugs did not interact with the relationship between ABO blood type and long-term outcome.

Conclusion

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

INTRODUCTION

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

Several studies reported an increased risk of thrombotic events, including myocardial infarction, ischemic stroke, peripheral arterial disease and venous thrombo-embolism, in people with non-O blood types in the general population.[6-10]

It is unclear whether or not ABO blood type influences outcome after vascular surgery. We conducted the current study to evaluate the effect of ABO blood type on both perioperative cardiovascular complications and long-term survival after vascular surgery.

MATERIALS AND METHODS

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

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

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

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

All data was tabulated according to O and non-O blood type. Categorical variables are described as numbers and percentages. Continuous variables were described as means ± standard deviation. Duration of follow-up was described as median with interquartile range. Categorical data were compared using a Chi-Square test. Continuous data were compared using ANOVA. Cumulative long-term survival was determined using the Kaplan-Meier method and log-rank test. Logistic regression analysis was performed to evaluate the effect of non-O blood type on 30-day cardiovascular events. Cox regression analysis was performed to assess the effect of non-O blood type on long-term survival. Subgroup analysis was performed for age (>65, <65), gender, statin use, and antiplatelet/anticoagulant medication use. Multivariate regression analyses were adjusted for high-risk type of surgery, gender, age, hypertension, diabetes mellitus, smoking status, renal failure, ischemic heart disease, hypercholesterolemia, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, the use of beta-blockers, statins, antiplatelet and anticoagulant drugs. We reported crude and adjusted odds ratios and hazard ratios and their 95% confidence intervals. For all tests, a $P < 0.05$ (two-sided) was considered significant. All analyses were performed using PASW version 17.0 statistical software (SPSS inc., Chicago, IL).

RESULTS

The study population consisted of 4679 consecutive patients who underwent elective vascular surgery. Abdominal aortic repair was performed in 1814 (39%) patients, lower extremity revascularization in 1834 (39%) patients and carotid surgery in 1027 (22%) patients, respectively. The median follow-up was 4 (IQR 2 – 8) years. The majority of patients were men (73%) and the mean age was 66 ± 12 years. Non-O blood type was present in 2627 (56%) patients. Of all patients, 52% had no or one risk factor, 31% had two risk factors and 17% had three or more risk factors according to the Revised Cardiac Risk Index. O and non-O groups differed significantly regarding male gender (74% vs. 72%, P=0.04), ischemic heart disease (34% vs. 37%, P=0.02), aspirin use (48% vs. 45%, P=0.04). There were no

significant differences between O and non-O groups regarding other comorbidities, medication use, age and surgical characteristics, as demonstrated in Table 1.

During 30-day follow-up 241 (5.2%) patients had a cardiovascular event, including 132 (2.8%) cardiovascular deaths, 66 (1.4%) non-fatal myocardial infarctions, and 36 (0.8%) non-fatal strokes, as presented in Table 2. No significant differences between O and non-O blood types were observed regarding stroke (1.0% vs. 0.6%, *P*=0.09), non-fatal myocardial infarction (1.5% vs. 1.4%, *P*=0.51), cardiovascular death (2.8% vs. 2.8%, *P*=1.00), and cardiovascular events (5.5% vs. 4.9%, *P*=0.42). Within 30 days of surgery, 228 patients died of any cause. No significant difference was observed between O and non-O blood type (4.9% vs. 4.8%, *P*=0.89). Multivariate analyses demonstrated that non-O blood type was not associated with 30-day cardiovascular events (odds ratio (OR) 0.87, 95% confidence interval (CI) 0.67 – 1.13, *P*=0.32).

During long-term follow-up 1233 (47%) patients with non-O blood type died, compared with 981 (48%) patients with O blood type (*P*= 0.60). Cumulative survival for all patients

Table 1 | Baseline characteristics according to blood type

	O [N=2052]	**Non-O** [N=2627]	**P-value**
Demographics			
Mean age (SD)	67 (11)	66 (11)	0.23
Mean BMI (SD)	26 (4)	26 (4)	0.28
Male gender (%)	1527 (74)	1884 (72)	0.04
Surgery type (%)			
Carotid surgery	470 (23)	557 (21)	
Abdominal aortic surgery	810 (40)	1004 (38)	0.09
Peripheral arterial surgery	769 (38)	1065 (41)	
Medical history (%)			
Congestive heart failure	122 (6)	178 (7)	0.25
Cerebrovascular disease	648 (32)	766 (29)	0.08
Hypertension	985 (48)	1188 (45)	0.06
Diabetes mellitus	366 (18)	463 (18)	0.88
Current smoking	663 (32)	863 (33)	0.71
Creatinin >2mg/dL	190 (9)	270 (10)	0.26
Ischemic heart disease	690 (34)	973 (37)	0.02
COPD	800 (39)	1018 (39)	0.88
Revised Cardiac Risk Index			
Cardiac risk factors (SD)	1.6 (1.0)	1.6 (1.0)	0.28
Medication use (%)			
Aspirin	979 (48)	1175 (45)	0.04
Anticoagulants	686 (33)	904 (34)	0.49
Beta-blockers	949 (46)	1173 (45)	0.29
Statins	770 (38)	965 (37)	0.58

Abbreviations: COPD Chronic Obstructive Pulmonary Disease

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

Table 2 | 30-day outcome according to blood type

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

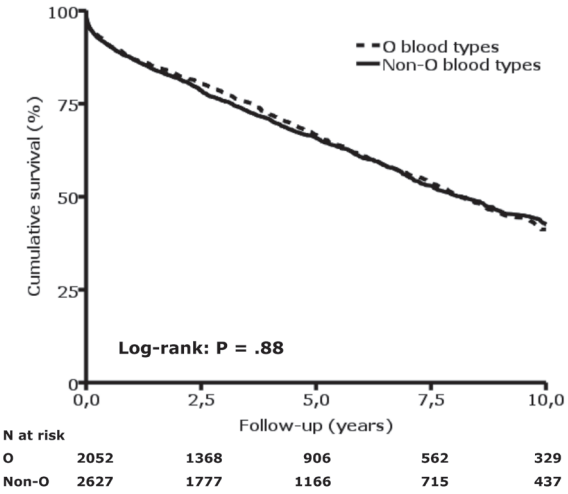

Figure 1 | Kaplan Meier estimates for long-term all-cause mortality, stratified according O and non-O blood type

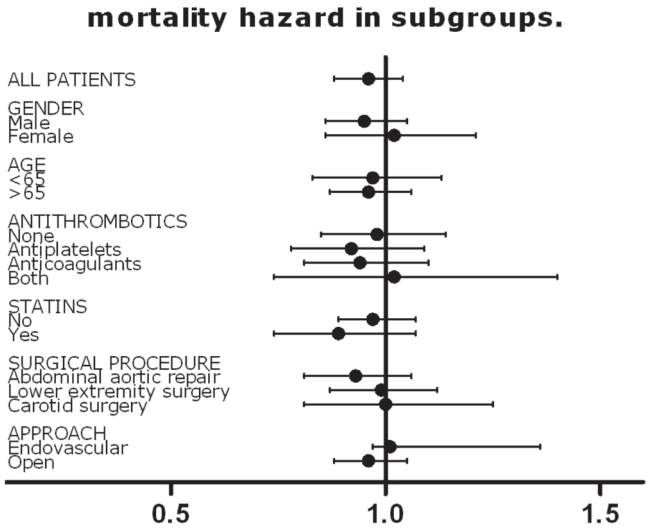

Figure 2 | Non-O blood types and long-term mortality hazard in subgroups

DISCUSSION

The current study demonstrated that non-O blood type was not associated with an increased prevalence of either 30-day cardiovascular events or long-term mortality, as compared with O blood type. After adjusting for cardiovascular risk factors, age, gender, smoking, and medication use, the odds ratio for 30-day cardiovascular events and hazard ratio for long-term mortality were 0.87 (95% CI 0.67 – 1.13) and 0.96 (95% CI 0.88 – 1.04). Von Willebrand factor is an important factor in hemostasis. It mediates platelet adherence to the subendothelium in vascular injury and serves as a carrier protein of clotting factor VIII, increasing plasma half-life of clotting factor VIII from 2 to 12 hours.[12-13] Increased levels of Von Willebrand factor are associated with an increased risk of both arterial and venous thrombosis.[14-18]

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

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

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

To our knowledge, no data were available on the effect of ABO blood type on cardiovascular events and prognosis in peripheral arterial disease patients. In the current study, we found no evidence of such relationships. These findings are comparable to the results reported by Ketch et al., who reported no difference in 1-year mortality between non-O and O blood type in a cohort of 1198 patients who underwent a percutaneous coronary intervention for acute myocardial infarction (HR 0.89; 95% CI 0.63 – 1.25).[24] In contrast, Carpeggiani et al. reported an increased long-term mortality in patients with non-O blood type in a cohort consisting of 4901 patients hospitalized for coronary artery disease, with a hazard ratio of 1.24 (95% CI: 1.01-1.52).[25] Their results were driven mainly by a strong relation found in women under the age of 65 (HR 4.61; 95% CI 1.93-11.00). In a subanalysis of women under 65, we found no significantly increased long-term mortality for non-O blood types (HR 0.95; 95% CI 0.69 – 1.30).

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

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

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

We assessed only the fenotype and not genotype of the ABO blood group. The highest levels of clotting factor VIII and Von Willebrand factor are observed in $A_1A/A_1B/BB$, intermediate levels in A1O/BO and the lowest levels in OO genotype.[29] Possibly, by comparing O to non-O instead of A1A/A1B/BB to OO, the effects of ABO on prognosis were diluted.

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

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

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PART III

BLOOD TYPE, HEMOGLOBIN AND BLOOD TRANSFUSIONS

CHAPTER 5

The impact of haemoglobin levels on postoperative cardiovascular outcome in vascular surgery patients: results of an observational cohort study

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ABSTRACT

Context
Although low preoperative haemoglobin (Hb) levels are a well-known risk factor for adverse outcome, little is known about postoperative Hb levels and Hb decrease.

Objectives
The aim of this study was to evaluate the prognostic impact of both pre- and postoperative Hb levels (divided into low, intermediate and high tertiles) as well as Hb decrease, defined as preoperative minus postoperative Hb (g/dL), on postoperative cardiovascular events in vascular surgery patients.

Design
Observational cohort study.

Setting
Erasmus University Medical Centre, Rotterdam, the Netherlands, from 1 January 2002 to 31 December 2011.

Patients
1,484 patients underwent elective open or endovascular abdominal aortic repair (aneurysmatic or stenotic), lower extremity arterial repair or carotid surgery. Patients for whom pre- or postoperative Hb levels were not available were excluded.

Main outcome measures
The study endpoint was 30-day postoperative cardiovascular events, including myocardial infarction, heart failure, arrhythmias, stroke, asymptomatic troponin-T release and cardiovascular death.

Results
In 1,041 patients both pre- and postoperative Hb levels were available. Thirty-day cardiovascular events occurred in 221 (21%) patients. Multivariable logistic regression analyses, adjusting for age, gender, Revised Cardiac Risk Index (high-risk surgery, coronary heart disease, heart failure, cerebrovascular disease, diabetes mellitus, renal insufficiency), hypertension and hypercholesterolaemia, demonstrated that low preoperative Hb (8.7-12.9 g/dL) was associated with 30-day events (Odds Ratio (OR) 1.7; 95% confidence interval (CI) 1.1-2.5). Intermediate (10.6-12.1 g/dL) and low (7.4-10.5 g/dL) postoperative Hb and Hb decrease were also associated with an independently increased risk of 30-day events (intermediate Hb: OR 1.7; 95% CI 1.1-2.7; low Hb OR 3.1; 95% CI 2.0-4.8; and Hb decrease OR 1.2; 95% CI 1.1-1.3, respectively). Sensitivity analyses excluding patients with transfusions (n=314) demonstrated that only postoperative Hb levels remained associated with a high risk of 30-day cardiovascular events (intermediate Hb: OR 1.8; 95% CI 1.0-3.3 and low Hb: OR 2.0; 95% CI 1.0-4.0).

Conclusions

Pre- and postoperative Hb levels and Hb decrease are all related to 30-day cardiovascular events in elective vascular surgery patients. Postoperative Hb levels are the strongest predictor of 30-day cardiovascular events.

INTRODUCTION

The preoperative haemoglobin (Hb) level, particularly preoperative anaemia, is known to be associated with postoperative mortality and cardiac events in patients undergoing non-cardiac surgery.[1-4] Although preoperative anaemia is common,[2-4] the Hb level is not taken into consideration in guidelines for preoperative risk stratification in non-cardiac surgery, which mainly focus on screening for the presence of cardiorespiratory disease.[5] However, anaemia may be less well tolerated in patients with diminished cardiopulmonary reserve.[6] Low Hb levels, both pre- and postoperative, can be corrected by the administration of red blood cell (RBC) transfusions, which aim to reduce tissue ischemia by restoring oxygen supply.[7]

Only few randomized trials evaluated transfusion thresholds in high-risk patients.[8-10] No survival differences were observed for liberal (maintaining Hb > 10.0 g/dL) versus restrictive (maintaining Hb > 7.0 g/dL[8,10] or Hb > 8.0 g/dL[9,10]) RBC transfusion strategies.[8-10] Although these studies evaluated transfusion thresholds based on single Hb levels, Karkouti et al. demonstrated that not the lowest intraoperative Hb, but the maximum percent decrease in Hb level from baseline, was inversely related to postoperative outcome in cardiac surgery patients.[11]

Vascular surgery patients are another category of high-risk patients, in whom the presence of underlying coronary artery disease is common[12] and contributes to an increased risk of postoperative cardiac events.[13] It is unknown which Hb levels are associated with adverse postoperative outcomes in these patients, and if these levels differ from current transfusion guidelines. Therefore, the present study was undertaken to evaluate the prognostic impact of preoperative and postoperative Hb levels and Hb decrease on 30-day postoperative cardiovascular events in a cohort of vascular surgery patients.

METHODS

Study sample

The study sample was derived from an observational cohort of 1,484 vascular surgery patients who underwent elective vascular surgery, between January 2002 and December 2011, at the Erasmus University Medical Centre, Rotterdam, the Netherlands. Patients for whom pre- or postoperative Hb levels were not available were excluded. All patients underwent an open or endovascular surgical procedure, including abdominal aortic repair (aneurysmatic or stenotic), lower extremity arterial repair or carotid surgery. The study complies with the declaration of Helsinki and the study protocol (MEC-2011-510) was approved by the Erasmus MC Medical Ethical Committee (Chairpersons Prof H. Tilanus and Prof H. Metselaar) on 22 March 2012. For the purpose of this observational study patients were not subject to acts, neither was any mode of behaviour imposed, otherwise than as part of their regular treatment. Therefore, according to Dutch law, written informed consent for a patient to be enrolled in this study was not required.[14]

Baseline characteristics

Patients were screened prior to surgery at the outpatient clinic. The medical history, physical examination, laboratory measurements, electrocardiograms, transthoracic echocardiography and lung function tests were retrieved from the patients' medical records. The medical history included coronary heart disease (previous or current angina pectoris, previous myocardial infarction or coronary revascularization), heart failure, and cerebrovascular disease (ischemic or hemorrhagic stroke or transient ischemic attack). Baseline data included age, gender, diabetes mellitus, hypertension, hypercholesterolaemia, renal dysfunction (estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m^2), and chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification)[15] and smoking status. Also, the use of aspirin, oral anticoagulants, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, diuretics, nitrates and statins was retrieved from the medical records. The cardiac risk score was determined for every patient using the Revised Cardiac Risk Index (RCRI). The RCRI assigns one point to each of the following characteristics: high-risk surgery (open aortic or peripheral vascular surgery), coronary heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes mellitus, and renal insufficiency (serum creatinine > 2.0 mg/dL).[13]

Haemoglobin levels and red blood cell transfusions

Haemoglobin levels and the total number of packed RBC transfusions administered intra- and postoperatively (range 0 to 30 days postoperatively), were recorded retrospectively for all patients. During the study period, Hb levels were measured using a Sysmex XE-2100 (Sysmex, Kobe, Japan) haematology analyzer (within-run coefficient of variation < 1%).[16] Preoperative Hb (Hb_{pre}) was defined as the last Hb measurement prior to surgery with a maximum of 30-days preoperatively. Preoperative anaemia was defined as Hb_{pre} <13.0 g/dL in men and Hb_{pre} < 12.0 g/dL in women.[17] Postoperative Hb (Hb_{post}) was defined as the first Hb measurement after surgery, with a range of 0 to 3 days postoperatively. The Hb decrease (g/dL) was defined as the difference between Hb_{pre} and Hb_{post}.

The indication for RBC transfusion was determined according to Dutch transfusion guidelines (RBC transfusion recommended if Hb decreases < 8.0 g/dL or < 9.7 g/dL in patients with symptomatic cardiopulmonary disease), which did not change during the study period,[7] and on estimated intraoperative blood loss by discretion of the operating surgeon and the anaesthesiologist.

Study endpoint

The primary study endpoint was 30-day postoperative cardiovascular events, a composite of major cardiovascular events, cardiovascular death and asymptomatic TnT release. Thirty-day follow-up was completed retrospectively for all patients by patients' visits to the outpatient clinic, by letters from referring physicians, and by using the institutions' medical records. Mortality was ascertained from the municipal civil registries.

Major cardiovascular events were defined as non-fatal myocardial infarction, new or worsened congestive heart failure, severe cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention) and stroke (including transient ischemic attack). Myocardial infarction was defined as the characteristic rise and fall of (postoperative) TnT levels above the 99th percentile (>0.03 µg/L) with either electrocardiographic or clinical signs of myocardial ischemia.[18] Asymptomatic TnT release was defined as the rise of (postoperative) TnT levels without electrocardiographic or clinical signs of myocardial ischemia. Cardiovascular death was defined as any death from a cerebro-cardiovascular cause, including death following myocardial infarction, congestive heart failure, arrhythmia, stroke, surgery related bleeding complications and sudden unexpected death, and was determined by reviewing death certificates and the institution's medical records.

Statistical analysis

Continuous variables are described as mean ± standard deviation (SD) and dichotomous data as numbers and percentages. Continuous data were compared using analysis of variance and categorical data using chi-squared tests.

Preoperative Hb levels were divided into tertiles (high Hb_{pre}: Hb 14.5 – 17.0 g/dL; intermediate Hb_{pre}: Hb 13.1 – 14.3 g/dL; low Hb_{pre}: Hb 8.7 – 12.9 g/dL) and tertiles were also calculated for postoperative Hb levels (high Hb_{post}: Hb 12.2 – 14.8 g/dL; intermediate Hb_{post}: Hb 10.6 – 12.1 g/dL; and low Hb_{post}: Hb 7.4 – 10.5 g/dL). Logistic regression analyses were used to study the associations between Hb levels and Hb decrease towards 30-day postoperative cardiovascular events, with the high tertile being the reference category in the analyses of pre- and postoperative Hb levels. For postoperative Hb analyses and Hb decrease, patients who experienced an event that occurred before Hb_{post} was measured were excluded (n=9). Multivariable analyses were primarily adjusted for potential confounders, including age, gender, RCRI (high-risk surgery, coronary heart disease, heart failure, cerebrovascular disease, diabetes mellitus, renal insufficiency), hypertension and hypercholesterolaemia. In an additional multivariable analysis adjustments were made for medication use (aspirin, oral anticoagulants, beta-blockers, calcium antagonists, ACE-inhibitors, angiotensin-receptor blockers, diuretics, nitrates and statins).

Sensitivity analyses were performed in patients who did not receive RBC transfusions in order to rule out confounding caused by RBC transfusions. We decided to choose this method instead of adjusting for confounding by RBC transfusions in multivariable analyses, because residual confounding can still be present in the latter analysis.

For all tests, a *P* value <.05 (2-sided) was considered significant. All statistical analyses were performed using IBM SPSS 20.0 statistical software (SPSS Inc., Chicago, Ill).

RESULTS

Study sample

The study cohort consisted of 1,484 patients who underwent elective vascular surgery. The Hb levels were measured maximal 30-days preoperatively in 1,341 (90%) patients, and 0-3 days postoperatively in 1,087 (73%) patients. In 1,041 (70%) patients both pre- and postoperative Hb levels were available, and this comprised the final study sample. In 56% of the excluded patients, the pre- or postoperative Hb level was measured outside the defined time intervals. Patients who were excluded more often underwent endovascular surgery (60% vs. 35%, $P < 0.001$), and lower extremity arterial repair (50% vs. 24%, $P < 0.001$) and less frequently abdominal aortic repair (27% vs. 56%, $P < 0.001$), compared to the final study sample. Furthermore, excluded patients had a lower prevalence of renal dysfunction (18% vs. 29%, $P < 0.001$), had less beta-blocker use (76% vs. 84%, $P < 0.001$), and received less RBC transfusions (3% vs. 30%, $P < 0.001$). No other differences in baseline characteristics were observed.

Baseline characteristics

Baseline characteristics of the study sample are displayed in Table 1. Mean age was 69 (± 10) years and 75% were male.

During the 30-day follow-up 221 (21%) patients suffered from a cardiovascular event: 103 (10%) major cardiovascular events, 98 (9%) asymptomatic TnT release and 20 (2%) cardiovascular deaths. Patients who experienced a cardiovascular event were older, had more coronary heart disease, renal dysfunction and heart failure ($P < 0.001$ for all). In addition, they had more diabetes mellitus ($P = 0.006$) and hypertension ($P = 0.044$), and were more often referred for open surgery ($P < 0.001$).

Regarding medication, patients with a cardiovascular event more frequently used calcium antagonists ($P = 0.044$), ACE-inhibitors ($P = 0.017$), diuretics ($P = 0.001$) and nitrates ($P = 0.014$).

Haemoglobin levels and red blood cell transfusions

The mean pre- and postoperative Hb levels are presented in Table 1. Preoperative anaemia (Hb_{pre} <13.0 g/dL in men and Hb_{pre} < 12.0 g/dL in women)[17] was present in 246 (24%) patients, of which 119 (15%) in men and 127 (48%) in women, respectively ($P < 0.001$). Its presence was more common in patients who reached the primary endpoint: in 76 (34%) patients with an event versus 170 (21%) patients without an event ($P < 0.001$). The mean Hb decrease (difference between Hb_{pre} and Hb_{post}) was 2.2 (± 1.6) g/dL (Table 1), and 2.1 (± 1.3) and 2.2 (± 2.2) in transfused and non-transfused patients, respectively ($P = 0.204$). Of note, in 71 (7%) patients the difference between Hb_{pre} and Hb_{post} did not show a decrease but an increase instead. In addition, 48 (68%) of these patients received a postoperative RBC transfusion.

In 314 (30%) patients RBC transfusions were administered postoperatively, of which the majority of 265 (84%) were administered within 3 days of surgery. Of the patients who received RBC transfusions 143 (46%) patients had preoperative anaemia. Of all patients

Table 1 | Baseline characteristics

	Final study sample [N= 1041]	**No CV event** [N=820]	**CV event** [N=221]	**P-value**
Demographics				
Age (mean ± SD)	69 (10)	68 (10)	71 (10)	< 0.001
Men	776 (75%)	607 (74%)	169 (77%)	0.459
Coronary heart disease	443 (43%)	326 (40%)	117 (53%)	< 0.001
Cerebrovascular disease	344 (33%)	271 (33%)	73 (33%)	0.996
Renal dysfunction	297 (29%)	189 (23%)	108 (49%)	< 0.001
Heart failure	116 (11%)	71 (9%)	45 (20%)	< 0.001
Anaemia	246 (24%)	170 (21%)	76 (34%)	< 0.001
Diabetes Mellitus	247 (24%)	179 (22%)	68 (31%)	0.006
Hypertension	706 (68%)	544 (67%)	162 (74%)	0.044
Hypercholesterolaemia	919 (88%)	729 (89%)	190 (86%)	0.229
COPD	362 (45%)	279 (44%)	83 (50%)	0.157
Smoker, current	424 (41%)	331 (40%)	93 (42%)	0.851
Haemoglobin (g/dL)				
preoperative (mean ± SD)	13.5 (1.9)	13.7 (1.8)	13.0 (2.1)	< 0.001
postoperative (mean ± SD)	11.4 (1.8)	11.6 (1.7)	10.6 (1.7)	< 0.001
decrease (mean ± SD)	2.2 (1.6)	2.1 (1.5)	2.4 (2.0)	0.016
Red blood cell transfusion				< 0.001
no RBC transfusion	728 (70%)	653 (80%)	75 (34%)	
RBC transfusion	314 (30%)	167 (20%)	147 (66%)	
on day of surgery	184 (59%)	109 (65%)	75 (51%)	
day 1-3 postoperatively	81 (26%)	40 (24%)	41 (28%)	
day 4-30 postoperatively	49 (15%)	18 (11%)	31 (21%)	
Surgery type				< 0.001
Open	678 (65%)	501 (61%)	177 (80%)	
Endovascular	363 (35%)	319 (39%)	44 (20%)	
Medication				
Aspirin	660 (64%)	525 (64%)	135 (61%)	0.428
Oral anticoagulants	191 (18%)	151 (19%)	40 (18%)	0.919
Beta-blockers	872 (84%)	678 (83%)	194 (88%)	0.061
Calcium antagonists	209 (20%)	154 (19%)	55 (25%)	0.044
ACE-inhibitors	324 (31%)	241 (30%)	83 (38%)	0.017
Angiotensin II antagonists	181 (18%)	139 (17%)	42 (19%)	0.476
Diuretics	260 (25%)	185 (23%)	75 (34%)	0.001
Nitrates	105 (10%)	73 (9%)	32 (15%)	0.014
Statins	804 (78%)	639 (78%)	165 (75%)	0.311
Revised Cardiac Risk Index				< 0.001
0-1 risk factor	546 (53%)	482 (59%)	64 (29%)	
2 risk factors	308 (30%)	225 (28%)	83 (38%)	
≥ 3 risk factors	184 (18%)	110 (14%)	74 (34%)	

Abbreviations: ACE angiotensin converting enzyme; COPD chronic obstructive pulmonary disease; CV cardiovascular; RBC Red blood cell; SD standard deviation

who received a RBC transfusion, 183 (58%) received ≤ 2 RBCs and 131 (42%) patients received > 2 RBCs. A total of 147 (47%) transfused patients suffered from a cardiovascular event (Table 1).

Study endpoint

Multivariable logistic regression analyses, adjusting for potential confounders, demonstrated that for preoperative Hb levels, low Hb_{pre} was associated with an increased risk of 30-day cardiovascular events (OR 1.7; 95% CI 1.1-2.5) (Table 2). For postoperative Hb levels a stepwise increase in the risk of 30-day cardiovascular events was observed, with an OR 1.7 (95% CI 1.1-2.7) for intermediate Hb_{post} and an OR 3.1 (95% CI 2.0-4.8) for low Hb_{post} (Table 2). The Hb decrease was associated with an increased 30-day cardiovascular event risk as well (OR 1.2; 95% CI 1.1-1.3) (Table 2), with comparable odds after excluding patients in whom the difference between Hb_{pre} and Hb_{post} showed an increase (OR 1.3; 95% CI 1.1-1.4). Reported odds ratios did not change after additional adjustment for medication use.

Sensitivity analyses in patients without RBC transfusions demonstrated that the increased risk of 30-day cardiovascular events was no longer present neither for low Hb_{pre} (OR 1.8; 95% CI 0.9-3.4), nor for Hb decrease (OR 1.0; 95% CI 0.9-1.2) (Table 2). On the other hand, after exclusion of patients who received RBC transfusions, the 30-day cardiovascular event risk remained high both for intermediate Hb_{post} (OR 1.8; 95% CI 1.0-3.3) and for low Hb_{post} (OR 2.0; 95% CI 1.0-4.0) (Table 2).

DISCUSSION

In this observational cohort of vascular surgery patients we found that preoperative Hb levels, as well as postoperative Hb levels and Hb decrease were all inversely related to 30-day cardiovascular events. In order to reduce bias caused by RBC transfusions, sensitivity analyses were performed excluding patients who received intra- or postoperative RBC transfusions. These sensitivity analyses demonstrated that postoperative Hb levels, but not preoperative Hb levels and Hb decrease, remained associated with a high risk of 30-day postoperative cardiovascular events. To our knowledge, this is the first study that evaluated the prognostic impact of both pre- and postoperative Hb levels as well as Hb decrease on 30-day postoperative cardiovascular events in a high risk population of vascular surgery patients.

Our findings that low preoperative Hb levels were associated with postoperative cardiovascular events are in line with the results of several other studies.[1-4] Of note, the prevalence of preoperative anaemia in our cohort of vascular surgery patients was 24%, which is remarkably lower than the reported prevalence of approximately 40% in non-cardiac surgery patients in previous studies.[2,4] A possible explanation for the lower prevalence in the present study could be that in our cohort of high-risk patients in whom coronary heart disease is common, RBC transfusions were required prior to surgery in order to correct severe anaemia.[7]

Table 2 | Prognostic value of Hb levels on 30-day cardiovascular events

	Final study sample					Patients without RBC transfusions				
	CV events	Univariable		Multivariable*		CV events	Univariable		Multivariable*	
	n	OR	[95% CI]	OR	[95% CI]	n	OR	[95% CI]	OR	[95% CI]
Preoperative Haemoglobin										
High [Hb 14.5 – 17.0]	58	Reference		Reference		22	Reference		Reference	
Intermediate [Hb 13.1 – 14.3]	61	1.1	0.7-1.6	1.1	0.7-1.6	28	1.4	0.8-2.5	1.6	0.9-2.9
Low [Hb 8.7 - 12.9]	102	2.2	1.5-3.1	1.7	1.1-2.5	24	2.1	1.2-3.9	1.8	0.9-3.4
Postoperative Haemoglobin										
High [Hb 12.2 – 14.8]	40	reference		reference		20	reference		reference	
Intermediate [Hb 10.6 - 12.1]	67	1.9	1.2-2.9	1.7	1.1-2.7	33	1.8	1.0-3.3	1.8	1.0-3.3
Low [Hb 7.4 - 10.5]	105	3.7	2.4-5.5	3.1	2.0-4.8	21	2.4	1.2-4.6	2.0	1.0-4.0
Decrease in Haemoglobin										
Decrease	212	1.1	1.0-1.2	1.2	1.1-1.3	74	1.0	0.8-1.2	1.0	0.9-1.2

* adjusted for age, gender, hypertension, hypercholesterolemia and Revised Cardiac Risk Index (high-risk surgery, coronary heart disease, heart failure, cerebrovascular disease, diabetes mellitus, renal insufficiency)

Similar to low preoperative Hb levels, the Hb decrease was associated with an increased risk of 30-day cardiovascular events as well, with every 1.0 g/dL Hb decrease giving a 20% increased risk of developing a 30-day cardiovascular event. Only few studies evaluated the risk of Hb decrease on postoperative outcomes.[1,11] Carson et al. demonstrated a stepwise increase in the risk of postoperative death in general surgery patients: a Hb decrease of < 2.0 g/dL was associated with a low risk and a Hb decrease of ≥ 4.0 g/dL was associated with the highest risk, particularly in patients with prior cardiovascular disease.[1] Moreover, Karkouti et al. demonstrated that a 50% decrease from baseline Hb was associated with adverse events in cardiac surgery patients.[11] Importantly, the mean Hb decrease in our population was only 2.2 g/dL, by far not reaching the 50% Hb decrease described by Karkouti.

Compared to preoperative Hb levels and Hb decrease, postoperative Hb levels were the strongest predictor of postoperative cardiovascular events. Our results are consistent with several other studies, in which low postoperative Hb levels were associated with worse outcome.[1,19] In a retrospective cohort study of surgical patients who declined blood transfusions, postoperative Hb levels < 12.0 g/dL increased the risk of 30-day mortality.[1] In addition, Nelson et al. found that postoperative anaemia (haematocrit < 0.28%) was associated with postoperative cardiac events in high-risk vascular surgery patients.[19] However, this was a small study and no corrections for RBC transfusions were made.

The aim of RBC transfusions is to increase oxygen delivery in order to reduce tissue hypoxia. However, they carry risks as well, like transfusion transmissible infections,[6] and are associated with worse postoperative outcomes.[4,20,21] In observational studies it is impossible to gain insight into all factors that affected the decision to give RBC transfusions. Statistical analyses cannot fully adjust for (unknown) factors that might be causally related to adverse outcomes, and therefore we performed sensitivity analyses in patients without RBC transfusions. These analyses showed that the increased risk of 30-day cardiovascular events associated with low preoperative Hb and Hb decrease was no longer present, whereas postoperative Hb levels remained associated with a high risk of 30-day cardiovascular events. Several hypotheses may serve to explain the results of the sensitivity analyses. First, the number of patients with low preoperative Hb levels who did not receive RBC transfusions was probably too small to demonstrate a significant association. Furthermore, it can also be hypothesized that, although the duration of a low preoperative Hb level was unknown, vascular surgery patients with lower preoperative Hb levels have adapted to lower oxygen carrying capacity by increasing O2 extraction and therefore no association with postoperative cardiovascular events was observed.[6,22] Another possible explanation is that RBC transfusions might have influenced the risks of preoperative Hb levels and Hb decrease on 30-day cardiovascular events, leading to worse outcomes in the entire study sample. This hypothesis is probably best supported by the observation that the risk of 30-day cardiovascular events in patients with low postoperative Hb levels went down from 3.1 to 2.0 after excluding patients with RBC transfusions in the sensitivity analysis.

Several randomized controlled trials evaluated outcome between liberal (maintaining Hb > 10.0 g/dL) and restrictive (maintaining Hb > 7.0 g/dL[8,10], Hb > 8.0 g/dL[9,10] or Hb > 9.0 g/

dL[22]; respectively) RBC transfusion strategies in high-risk patients.[8-10,22] No significant differences in mortality were observed, neither in vascular surgery patients,[22] nor in intensive care unit patients, even not in a subgroup of patients with cardiovascular disease.[8,23] In elderly patients at high cardiovascular risk undergoing hip surgery, the rates of the primary endpoint (death or inability to walk) were equal in patients in the liberal and restrictive RBC transfusion group.[9] The results of these randomized trials suggest caution against RBC transfusion in stable patients with Hb > 7.0-8.0 g/dL and are in line with current transfusion guidelines that recommend RBC transfusion if Hb decreases below 6.0-7.0 g/dL.[7,24,25] In patients with diminished cardiopulmonary reserve, British guidelines recommend RBC transfusion when Hb is below 8.0 g/dL,[25] and Dutch guidelines even when Hb is below 9.7 g/dL.[7] However, the results of aforementioned trials and the guidelines do not support our findings that postoperative Hb levels < 12.1 g/dL in vascular surgery patients were associated with an increased risk of 30-day cardiovascular events; neither does it answer the question whether these patients should be treated and what the most appropriate treatment option is. A randomized trial in vascular surgery patients would offer the best opportunity to study transfusion thresholds, because the only RCT in vascular surgery was performed many years ago.[22]

Limitations

Several limitations of the present study should be considered. First, this study included an observational cohort of vascular surgery patients. Patient data, including Hb levels, RBC transfusions, and study endpoints were recorded retrospectively so causality between Hb levels, RBC transfusions and outcome cannot be established. Second, selection bias is a potential source of bias in our study. Pre- or postoperative Hb levels were measured within the defined time intervals in 70% of patients. Patients who were excluded more often underwent less invasive procedures and received less RBC transfusions. Results of the present study may not be applicable to other patient populations. Third, postoperative Hb levels and Hb decrease could have been influenced by intraoperatively administered RBC transfusions. In order to reduce this bias we have performed sensitivity analyses in patients without RBC transfusions.

In conclusion, in this cohort of vascular surgery patients, preoperative Hb levels, postoperative Hb levels and Hb decrease were all related to an increased risk of 30-day postoperative cardiovascular events. Postoperative Hb levels were the strongest predictor of 30-day events, and remained associated with a considerably increased 30-day cardiovascular event risk after exclusion of patients with RBC transfusions.

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PART III

BLOOD TYPE, HEMOGLOBIN AND BLOOD TRANSFUSIONS

CHAPTER 6

The impact of perioperative red blood cell transfusions on postoperative outcomes in vascular surgery patients

Submitted

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PART IV

OBESITY

CHAPTER 7

The obesity paradox in the surgical population

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ABSTRACT

Background

Despite the medical hazards of obesity, recent reports examining body mass index (BMI) show an inverse relationship with morbidity and mortality in the surgical patient. This phenomenon is known as the 'obesity paradox'. The aim of this review is to summarize both the literature concerned with the obesity paradox in the surgical setting, as well as the theories explaining its causation.

Methods

PubMed was searched to identify available literature. Search criteria included obesity paradox and BMI paradox, and studies in which BMI was used as a measure of body fat were potentially eligible for inclusion in this review.

Results

The obesity paradox has been demonstrated in cardiac and in non-cardiac surgery patients. Underweight and morbidly obese patients displayed the worse outcomes, both postoperatively as well as at long-term follow-up. Hypotheses to explain the obesity paradox include increased lean body mass, (protective) peripheral body fat, reduced inflammatory response, genetics and a decline in cardiovascular disease risk factors, but probably unknown factors contribute too.

Conclusions

Patients at the extremes of BMI, both the underweight and the morbid obese, seem to have the highest postoperative morbidity and mortality hazard, which even persists at long-term. The cause of the obesity paradox is probably multi-factorial. This offers potential for future research in order to improve outcomes for persons on both sides of the 'optimum BMI'.

INTRODUCTION

With advancement of medical care in modern societies, two distinct growing phenomena are observed, which pose new challenges to the surgeon. These are the overweight and obesity epidemic on the one hand, and the growing elderly population on the other hand.[1-3] These two categories of patients share a number of risk factors and associated comorbidities that predispose them to cardiovascular and other life-threatening complications.[4,5]

Body mass index (BMI), formerly known as Quetelet's index, has been introduced to public health science as a proxy of overall body fat content. It is calculated by dividing weight in kilograms by the square of height in meters. In late and even in upcoming years, much attention has been paid to this index and to other measures of total or abdominal fat, due to the increasing prevalence of overweight and obesity. Because of its simplicity, BMI has gained widespread acceptance and application in daily clinical practice. The World Health Organization (WHO) has defined different BMI categories (Table 1).[6,7]

Clinical research in the surgical population frequently focused on the prognostic value of certain clinical variables obtained from the preoperative assessment and the perioperative course.[8-11] Some of these variables are incorporated in guidelines regarding preoperative cardiovascular management in non-cardiac surgery,[12] which have been shown to reduce postoperative cardiac events and improve long-term outcomes. Furthermore, recognition and optimization of other, non-cardiac, chronic ailment conditions prior to surgery can also be beneficial, both in the perioperative stage as well as for the long-term.[13] Although several preoperative risk-scoring systems exist,[14] BMI has not been included, since it was not considered as an independent (preoperative) risk factor or predictor for postoperative and long-term outcomes.

The purpose of this article is to give an overview of the relationship between BMI and outcome in the surgical population, reporting both postoperative and long-term outcomes. Furthermore, the literature regarding the inverse relationship between BMI and outcome, known as the obesity paradox, as well as the theories explaining its causation, are reviewed.

Table 1 | BMI classification according to the WHO

	BMI (kg/m²)
Underweight	< 18.5
Normal	18.5 – 24.9
Overweight (pre-obese)	25 – 29.9
Obese	≥ 30.0
Obese class I (mild obese)	30 – 34.9
Obese class II (moderate obese)	35.0 – 39.9
Obese class III (morbid obese)	≥ 40.0

BMI Body Mass Index; WHO World Health Organization

METHODS

We performed a PubMed search to identify available literature up to January 1st, 2012. Search criteria included obesity paradox and BMI paradox, each of which was subsequently combined with additional search criteria including surgery, general surgery, cardiac surgery, outcome, and survival to narrow search results. Search criteria were restricted to English language, humans, and adults (age > 19 years). Original articles (observational, cohort, case-control, cross-sectional, longitudinal and experimental), systematic reviews and meta-analyses were considered for inclusion in the review. Eligible studies were first identified by title, and abstracts in which BMI was used as a measure of body fat were retrieved as full-text papers. Additional studies were identified after reviewing related PubMed citations and references of the included papers.

THE RISKS OF OBESITY IN THE SURGICAL PATIENT

The worldwide broadening of the obesity epidemic has also affected surgery, not only because more surgical patients are obese, but also because of an increase in obesity related diseases that require surgery.[1,4] Substantial data from literature showed the preponderance of cardiovascular risk factors in the overweight and obese population.[1,4,15] Moreover, increased body mass was found to be a predictor of increased cardiac risk, independent of cardiovascular risk factors.[16] Obesity is also known to be related to left-ventricular morphological changes and impaired diastolic function.[17] Therefore, the observation of a strong association between obesity and long-term mortality in several studies was not unexpected.[18,19]

However, the perioperative risks associated with obesity might have been overestimated. Increased anesthetic and surgical interest in obesity, particularly in bariatric surgery, might have led to better care of obese patients and lower perioperative complication rates.[20,21] Several prospective cohort studies with strict definitions of postoperative morbidity, demonstrated that in general (non-bariatric) surgery, postoperative complications like surgical site infections are related to obesity,[22-27] with the highest rates in morbid (class III) obese patients.[22,24,26,27] In addition, morbidly obese patients had the highest postoperative mortality rates.[23,24,26,27] On the other hand, the lowest postoperative mortality risk was reported in the overweight and obese class I and class II patients.[23,24,27] In several surgical oncology populations the postoperative mortality rates did not differ between normal weight and overweight and obese patients.[25,28-30] However, most data regarding the risks of obesity in the (non-bariatric) surgical population are obtained from large-scale studies in cardiac surgery patients. Since overweight and obesity are known to promote the progression of coronary heart disease,[7] it is not surprising that around two thirds of all coronary artery bypass grafting (CABG) surgery is performed in overweight and obese patients.[31,32] Similar to non-cardiac surgery, several prospective studies in CABG surgery demonstrated that obesity was shown to be related to postoperative morbidity, with the highest rates of deep sternal wound infection and prolonged ventilation and hospitalization in moderate

(class II) and morbid (class III) obese patients.[33-35] However, the majority of cardiac surgery studies, including CABG studies, did not report adverse associations with postoperative morbidity[31,32,36] or mortality in obese patients.[31,32,35-38] It is important to notice that current studies in various surgical populations do not make a distinction between obese surgical patients with normal metabolic profiles and those with diabetes, although it is widely known that diabetes adversely affects postoperative outcomes.

Despite the large body of evidence showing that postoperative mortality is not increased in the majority of obese patients undergoing surgery, much attention has been paid to the association with postoperative morbidity, which might have led to a negative attitude towards obesity as a co-morbid condition in patients requiring surgery.

THE OBESITY PARADOX

Recent epidemiological studies in the general population have shown a longer life expectancy in modern societies with prevalent overweight and obesity, compared to those that did not join the obesity epidemic.[39,40] The inverse relationship between body fat composition, particularly defined by the BMI, and all-cause mortality, is frequently referred to as the *obesity paradox*. The more comprehensive term *reverse epidemiology* also comprises the obesity paradox. It represents the unexplained counterintuitive relationship of traditional cardiovascular risk factors and mortality in various (patient) populations.[41-44]

Many studies in surgical populations have demonstrated a similar paradoxical relationship between BMI and postoperative mortality, with the highest postoperative mortality risks in the underweight and morbid (class III) obese patients (Figure 1).

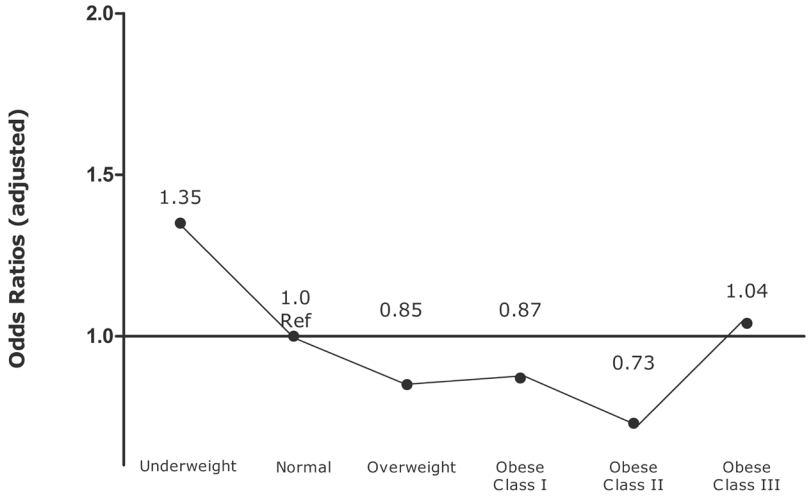

Figure 1 I Odds ratios (adjusted) for 30-day mortality after (non-bariatric) general surgery displayed by obesity class, with normal BMI class used as reference. *(Adapted with permission from Mullen et al, Ann Surg 2009[22]).*

The obesity paradox has been shown in various surgical populations, both in cardiac[31,32,34,36-38] and in non-cardiac surgery.[23,24,26,27]
The majority of studies examining the effects of BMI on surgical outcome merely studied short-term (i.e. postoperative) mortality; however some also reported long-term survival.[25,29,30,33,37,45-48] Underweight patients displayed the worse long-term survival, both in non-cardiac[45] and in cardiac surgery.[33,46,48] Overweight and obese patients showed conflicting results regarding long-term survival. Studies in vascular surgery,[45] oncology surgery[29,30] and cardiac surgery[37] reported survival benefit for overweight and obese patients, whereas other studies in oncology surgery[25] and cardiac surgery[47] did not demonstrate any association with long-term survival.
Table 2 gives an overview of different patient populations in which an inverse relationship between BMI and mortality was demonstrated. Most of these studies were conducted in Western populations; however, the obesity paradox has recently been described in East Asians as well.[59]

THE PARADOX THEORIES

Since the first observation of the obesity paradox, several suggestions were made to overcome the unexpected survival benefit of the overweight and obese. One suggestion was that the values of BMI cut-offs representing the categories defined by the WHO should be revised, so that overweight patients showing survival improvement should merge into the control group i.e. the normal BMI population.[60] However, it is important to consider

Table 2 I Populations showing the obesity paradox

Non-surgical Populations	Surgical Populations
Cardiac Disease	**Vascular surgery**
Acute coronary syndromes[50,51]	Peripheral arterial disease[23,45]
Percutaneous coronary interventions (PCI)[37]	Abdominal aortic aneurysm[24]
Coronary artery disease[55]	
Chronic atrial fibrillation[49]	**Cancer surgery**
Chronic heart failure[44,54]	Pancreaticoduodenectomy[30]
	Gastrectomy[29]
Chronic obstructive pulmonary disease[44,52]	
Renal disease	**Orthopedic surgery**
Chronic kidney disease[43]	Arthroplasty[58]
Maintenance dialysis[57]	**Cardiac surgery**
	Coronary artery bypass grafting[31,32,34,36-38]
Rheumatoid arthritis[44]	Left-ventricular assist device placement[46]
Acquired immunodeficiency[44]	
Intensive care unit patients[56]	
Hospitalized patients[53]	
Advanced age[44]	

that BMI does not discriminate between fat mass and lean mass, and as a result, BMI does not adequately reflect adiposity.[61,62] Therefore, it might be that overweight and (mild) obese persons do not have more fat, but instead have a preserved or increased lean body mass, which would offer a possible explanation for the survival benefit in these groups. Consequently, it has been suggested to omit the BMI completely as an index of body fat and replace it with more accurate indices such as waist circumference, waist-to-hip ratio and waist-to-height ratio, and with computed tomographic measurement of intra-abdominal fat content.[63-65]

Conversely, others have tried to find explanations for the occurrence of the obesity paradox, which was first recognized in chronic disease populations. Moreover, the obesity paradox has also been described in the general population.[19,60] Studies of BMI and cause-specific mortality in the general population, excluding persons with prior cardiovascular disease, cancer and chronic obstructive pulmonary disease (COPD), revealed that overweight was not associated with an increased risk of cancer or cardiovascular disease, and appeared to be relatively protective for survival.[66] However, excess mortality in the obese population was mainly attributable to cardiovascular disease and obesity-related cancers, including colon cancer, breast cancer, esophageal cancer, pancreatic cancer, uterine cancer, ovarian cancer and kidney cancer.[66,67] In contrast, upper aerodigestive cancers, COPD and other respiratory diseases could explain excess mortality in the underweight population.[66,67] Chronic diseases, including cardiovascular disease, cancer and COPD, are characterized by wasting and increased inflammatory responses, thereby offering possible explanations for the obesity paradox, which causation is probably multi-factorial.

THE BENEFITS OF OBESITY

Adipose tissue is a potential endocrine organ capable of secreting a variety of cytokines with opposing actions.[4] Tumor necrosis factor-α (TNF-α) is a pro-inflammatory and atherogenic macrophage-derived cytokine, and is known to promote cardiac and endothelial injury through its apoptotic and negative inotropic effects.[68] Adipocytes release soluble TNF-α receptors, which can neutralize TNF-α in various inflammatory wasting states.[69] Moreover, adipocytes secrete adipokines, of which adiponectin plays a key role in regulating inflammation and endovascular homeostasis and increasing insulin sensitivity in peripheral tissues.[70] Particularly visceral (abdominal) adiposity is associated with chronic inflammation, insulin resistance and enhanced progression of atherosclerosis.[4] On the other hand, peripheral (lower-body) fat has a protective effect.[71] These differences between visceral and peripheral adiposity are irrespective of gender.[71] However, since BMI cannot distinguish between visceral and peripheral adiposity, this might offer an explanation for the observed survival benefit in the obese population.

Inflammatory responses in obesity can also be reduced by the toxin-scavenging ability of adiposity. Lipopolysaccharides (LPS) are potent endotoxins that induce the release of pro-inflammatory cytokines.[72] Plasma concentrations of LPS are higher in chronic debilitating

disorders.[73-75] In overweight and obesity the negative effects of lipopolysaccharides are neutralized by the toxin-scavenging effect of adiposity, in which lipophilic end products of increased catabolism are sequestrated.[57] Furthermore, increased levels of lipoproteins, which are often observed in overweight and obesity, may offer a survival advantage in chronic diseases, because lipoproteins can actively bind to and neutralize circulating endotoxins, the so-called *endotoxin-lipoprotein hypothesis*.[76]

In addition, the prevalence of cardiovascular risk factors among the overweight and obese has declined in the past decades.[77] Although cardiovascular disease remains the leading cause of death among the obese, this decline in cardiovascular risk factors might have led to a decrease in cardiovascular related mortality, and therefore to a decrease in total mortality.[19] These findings are consistent with declining mortality rates from ischemic heart disease.[78,79] However, it may take several years to decades for obesity and its related cardiovascular disease to have its full impact on mortality.[80] Consequently, in studies without long-term (e.g. more than 15 years) follow-up, the effects of obesity on mortality might have been underestimated, suggesting survival benefit for the obese.

Finally, genetics might offer a different explanation for the survival advantage of the overweight and obese. The thrifty genotype theory is an old theory explaining obesity. This genotype emerged as an adaptive and selective gene-environment interaction in times of famine, and led to obesity when famines no longer occurred in the modern era.[81] This theory would explain the survival advantage of the overweight and obese, however, it is not supported by any substantial scientific evidence.[82] On the other hand, genetic

Figure 2 I Schematic representation of possible causes of the obesity paradox, showing its' multi-factorial origin with several (overlapping) hypotheses. *CVD cardiovascular disease.*

polymorphism in systems related to food intake, energy expenditure and BMI definition can result in variable effects on body composition, which might lead to differential effects on survival among the obese population.[83-85] Figure 2 gives an overview of the multi-factorial causation of the obesity paradox. In addition to the various aforementioned explanations, there might be currently unknown factors that also contribute to its' causation, as presented in the figure.

THE HAZARDS OF UNDERWEIGHT

The association of increased mortality in the underweight population might, at least in part, be attributable to *reverse causation*, which means that lower weight is not a cause but a result of chronic diseases that are related to poor outcome.[86] Chronic diseases that cause weight loss may remain unnoticed for months or even years, for example, in the case of cancer, chronic respiratory or cardiac diseases. Smoking is another potential confounding factor, because it is associated with both a decreased weight and an increased mortality risk.[86] In order to minimize the effects of reverse causation and smoking on mortality rates, deaths occurring in the initial follow-up period should be disregarded, and analyses should be restricted to patients without preexisting disease and to persons who had never smoked. However, studies that addressed these potential confounders still show increased mortality rates in the underweight population.[18,19,67]

COPD and other respiratory diseases are responsible for the vast majority of mortality in the underweight population.[66,67] This may be due to weight loss associated with COPD (reverse causation). However, low BMI in COPD has also been shown to be a risk factor for mortality, irrespective of disease severity.[87] In addition, skeletal muscle dysfunction is a common feature in COPD, and can be caused by muscle loss due to wasting and by intrinsic muscular alterations, in which the proportions of skeletal muscle fiber types change.[88] Skeletal muscle dysfunction is recognized to be an independent predictor of mortality in patients with COPD.[89] In underweight patients with COPD the intrinsic muscular alterations are aggravated,[90] and this could also explain the increased mortality risk in this group.

Wasting and inflammation could offer additional explanations for the mortality hazard of the underweight population. Improper nutrition and wasting in chronic illness can result in catabolic changes in skeletal muscle in lean subjects having minimal stores of fat, leading to cachexia.[91] Oxidative stress may be an important underlying cause for both wasting and inflammation.[92] Accumulation of oxidants results from a reduction in anti-oxidant capacity in the face of elevated metabolic requirements. These oxidants have pro-inflammatory effects, which eventually will lead to fatal complications. This cascade is called the "*malnutrition-inflammatory-cachexia complex*".[93] The deleterious effects of the malnutrition-inflammatory-cachexia complex occur rapidly, and the short-term risks of underweight outweigh the long-term (cardiovascular) risks associated with obesity.[93] The malnutrition-inflammatory-cachexia complex clearly explains the increased mortality risk in the underweight population.

IMPLICATIONS FOR THE SURGICAL POPULATION

As previously described, the obesity paradox has also been shown in the surgical population. The mechanisms explaining the survival benefit of the obese in the general population might also be applicable to the obese surgical patient. Moreover, it is speculated that overweight and mild obese patients have a more appropriate inflammatory and immune response to the stress of surgery than their leaner and morbid obese counterparts.[26,27] There is a close relationship between the immune and metabolic response systems, and proper function of each is dependent on the other.[94] Compared to normal weight patients, overweight and obese patients have a more sufficient nutritional reserve and might be functioning in a more efficient metabolic state, and as a result, the inflammatory and immune response to surgery might be more adequate. In contrast, both underweight and morbid obese patients are inefficient in energy expenditure, due to underlying malnutrition and metabolic excess. The inflammatory response to the stress of surgery is aggravated, which leads to further metabolic dysfunction and immunosuppression. Consequently, these patients suffer from adverse outcomes following surgery.[26,27]
In addition, recent weight loss of more than 10% of body weight and lower mean albumin levels, due to protein-energy malnutrition, are common in underweight patients and are indicators of malnourishment. Both conditions are well-known risk factors for adverse outcomes following surgery.[95-98] Several nutrition-screening tools can adequately assess malnourishment, and are able to identify patients who should benefit from nutritional support.[99] Peri- and postoperative nutritional support in malnourished underweight patients can improve outcomes following major surgery.[100-103] On the other hand, preoperative nutritional support in obese patients is not recommended,[101,102] although in obese patients nutritional deficiencies like iron deficiency, resulting in a higher prevalence of anaemia, are common.[21] Weight loss in obese patients prior to surgery is not recommended as well, because studies that evaluated this strategy showed conflicting evidence regarding postoperative outcomes.[21] In obese patients undergoing surgery, the highest priority should be on the recognition and adequate treatment of underlying cardiopulmonary comorbidities that negatively influence postoperative outcomes, including obstructive sleep apnea syndrome, in order to reduce postoperative complications.[21]

CONCLUSION

Despite the feeling that obese patients requiring surgery are at increased risk for adverse postoperative outcomes, surgery can be relatively safely performed in the higher BMI categories. However, patients at the extremes of BMI, both the underweight and the obese class III, seem to have the highest postoperative morbidity and mortality hazard, which even persists at long-term. The inverse relationship between BMI and mortality is referred to as the obesity paradox, and has been observed both in the general population as well as in several disease specific populations. Cancer and respiratory diseases, including COPD, are responsible for excess mortality in the underweight population, exerting its effects at relatively 'short'

long-term, i.e. within years. On the other hand, cardiovascular disease accounts for the majority of deaths among the obese, particularly at longer follow-up. Cancer, COPD and cardiovascular disease are characterized by wasting and inflammation, thereby offering possible explanations for the obesity paradox. Moreover, it is important to consider that BMI is not a measure of body fat distribution. Likely, the cause of the obesity paradox is multi-factorial. It is suggested that future research should be directed at more accurate indices of body fat, such as waist circumference or computed tomographic measurement of intra-abdominal fat content and its' relation with inflammation, in order to examine the association with survival and to evaluate whether the obesity paradox remains valid, not only in the general population, but also in disease specific populations. This provides more insight into the hazards of both underweight and (morbid) obesity and might lead to a more tailored approach, including dietary and drug strategies, in order to improve outcomes for patients at the extremes of BMI.

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PART IV

OBESITY

CHAPTER 8

The impact of obesity on postoperative and long-term outcome in a general surgery population: A retrospective cohort study

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ABSTRACT

Background

The obesity paradox has been demonstrated postoperatively in several surgical populations. However, only few studies reported long-term survival. This study evaluates the presence of the obesity paradox in a general surgery population, reporting both postoperative and long-term survival.

Methods

This retrospective study included 10,427 patients scheduled for elective, non-cardiac surgery. Patients were classified as underweight (BMI < 18.5 kg/m^2); normal weight (BMI 18.5 - 24.9 kg/m^2); overweight (BMI 25.0 - 29.9 kg/m^2); obesity class I (BMI 30.0 - 34.9 kg/m^2); obesity class II (BMI 35.0 - 39.9 kg/m^2); and obesity class III (BMI ≥ 40.0 kg/m^2). Study endpoints were 30-day postoperative and long-term mortality, including cause-specific mortality. Multivariable analyses were used to evaluate mortality risks in different BMI categories.

Results

Within 30-days after surgery, 353 (3.4%) patients died. Only overweight was associated with postoperative mortality, showing improved survival (Odds Ratio (OR) 0.7; 95% confidence interval (CI) 0.6-0.9). During the long-term follow-up 4,884 (47%) patients died. Underweight patients had the highest mortality risk (HR 1.4; 95% CI 1.2-1.6), particularly caused by high cancer related mortality. In contrast, overweight and obese patients demonstrated improved survival (overweight: HR 0.8; 95% CI 0.8–0.9; obesity class I: HR 0.7; 95% CI 0.7–0.8; obesity class II: HR 0.7; 95% CI 0.6-0.9; obesity class III: HR 0.7; 95% CI 0.5-1.0), mainly because of a strongly reduced risk of cancer related mortality.

Conclusions

In this surgical population the obesity paradox could be validated at long-term, mainly because of decreased cancer related mortality among the obese.

INTRODUCTION

Overweight and obesity are major health conditions that currently affect more than two-thirds of the US population, and the prevalence of obesity still continues to increase[1, 2]. In Europe obesity has also reached epidemic proportions, although there are large differences between European countries[3]. The obesity epidemic also affects surgery, not merely because of an increase in obese patients, but also because of an increase in obesity related disorders that require surgery[4, 5]. Despite the medical hazards associated with obesity[5], recent literature has demonstrated that obese patients show improved survival, a phenomenon referred to as the obesity paradox. The obesity paradox has been described in various populations, including the general population[6], and in patient populations with heart failure[7], coronary artery disease[8], dialysis[9] and peripheral arterial disease[10], among others. Moreover, several surgical populations have shown a similar survival benefit for the obese patient in the postoperative period[11-14]. However, the majority of these studies included specific surgical populations, and did not report long-term survival.
Therefore, this study was undertaken to evaluate the presence of the obesity paradox in a general surgery population, reporting both postoperative and long-term outcome, including cause-specific mortality.

MATERIALS AND METHODS

Patients

This retrospective study included 10,427 patients who underwent non-cardiac surgery between January 1991 and December 2008, in the Erasmus Medical Center, Rotterdam, the Netherlands. In all patients, height and weight measurements were obtained during preoperative evaluation at the anesthesia clinic. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.
Baseline clinical data were retrieved from medical records and included age, gender, ischemic heart disease (history of myocardial infarction or angina pectoris), heart failure, cerebrovascular disease (history of cerebrovascular accident and/or transient ischemic attack), cancer (current or previous malignancy), diabetes mellitus (treatment with insulin and/or fasting blood glucose ≥ 7 mmol/L), renal dysfunction (serum creatinine > 2.0 mg/dL), chronic obstructive pulmonary disease (COPD), and smoking status.

Classifications and Risk Stratification

The World Health Organization (WHO) classification was used to divide the patient population into the following BMI categories: underweight (BMI < 18.5 kg/m^2); normal weight (BMI 18.5 – 24.9 kg/m^2); overweight (BMI 25.0 – 29.9 kg/m^2); obese (BMI ≥ 30.0 kg/m^2), further divided in obesity class I (mild obesity: BMI 30.0 -34.9 kg/m^2); obesity class II (moderate obesity: BMI 35.0 -39.9 kg/m^2); and obesity class III (morbid obesity: BMI ≥ 40.0 kg/m^2)[15].

Based on the guidelines of the European Society of Cardiology[16], the non-cardiac surgical procedures were classified into expected low cardiac risk (breast, dental, endocrine, eye, gynecology, orthopedic and reconstructive), intermediate cardiac risk (abdominal, carotid, endovascular aneurysm, head and neck, neurologic, pulmonary, renal, urologic, and remaining), and high cardiac risk (aortic, peripheral vascular and other vascular). For all procedures a distinction between cancer and non-cancer related surgery was determined. The Revised Cardiac Risk Index (RCRI), which is used to identify surgical patients at the highest risk for cardiovascular events, was determined for every patient. The RCRI assigns one point to each of the following characteristics: diabetes mellitus, renal dysfunction, ischemic heart disease, heart failure, and cerebrovascular disease[17].

Study Endpoints

The primary endpoints were 30-day postoperative mortality and long-term mortality. Length of hospital stay (LOS) was described as a secondary outpoint. Median follow-up duration was 5.4 years (interquartile range 2.2 – 9.7 years). Survival status was obtained from the hospital records and the civil registries. In 74 patients follow-up was missing (0.7%). Cause of death was classified as cardiovascular, cancer or other (non-cardiovascular, non-cancer), and was ascertained by examining medical records and autopsy reports. For patients without a definite cause of death, an assumption was made based on prior history. If prior history showed no significant morbidities, cause of death was classified as 'unknown' (6.6%). Cardiovascular mortality was defined as any death with a cerebro-cardiovascular cause and included death following myocardial infarction, cardiac arrhythmias, congestive heart failure, stroke and sudden unexpected death. Non-cardiovascular, non-cancer mortality included respiratory, infectious and other causes.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median and interquartile range (IQR), and categorical data as numbers and percentages. Continuous variables showing a normal distribution were compared using analysis of variance; otherwise, the Kruskal-Wallis and Mann-Whitney U test were applied. Categorical data were compared with chi-squared tests.

Data on smoking status were available in 8,887 (85%) patients and preoperative pulmonary function testing was performed in 9,953 (96%) patients, which was used to identify patients with COPD. Missing value analysis was used to impute the missing data on smoking status (n=1,540) and COPD (n=474). Regression substitution was performed to predict the missing values for smoking and COPD, using other variables without missing values (age, gender, height, weight, myocardial infarction, angina pectoris, heart failure, cerebrovascular accident, diabetes mellitus, and renal dysfunction) and available data on smoking status and COPD.

Logistic regression analysis was used to study the association between BMI category and 30-day postoperative outcomes. Long-term mortality risk was evaluated using a Cox proportional hazard model. When the categorical BMI variable was included in the model,

patients with normal BMI were taken as the referent group. Multivariable analyses were primarily adjusted for potential confounders, including age, gender, RCRI (ischemic heart disease, heart failure, cerebrovascular disease, diabetes mellitus, renal dysfunction), cancer, surgery risk, year of surgery, COPD, and smoking status. Cumulative long-term survival was determined by the Kaplan-Meier method and compared with the log-rank test.
Sensitivity analyses were performed in patients without missing values for smoking and COPD. Furthermore, to limit effects of pre-existing disease on baseline BMI, sensitivity analyses were performed 1) excluding patients with cancer, and 2) excluding all person-years and deaths in the first 5 years of follow-up[18].
For all tests, a 2-sided *P*-value of < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS 20.0 statistical software (SPSS Inc., Chicago, Ill).

RESULTS

Patients

The study population consisted of 10,427 non-cardiac surgery patients. According to the BMI categories, 475 (5%) patients were classified as underweight, 4,601 (44%) as normal weight, 3,500 (34%) as overweight, 1,851 (18%) as obese, with 1,311 (13%) patients with obesity class I, 368 (4%) patients with obesity class II, and 172 (2%) patients with obesity class III, respectively. Patient characteristics according to BMI classification are shown in Table 1.
The BMI among the study population attained a normal distribution, with a mean BMI of 25.8 (± 5.2) kg/m^2. Mean age of the study population was 58 (± 16) years and 59% were men. Underweight and obese class III patients were younger, whereas overweight patients were older than patients with a normal BMI. Gender also varied significantly by BMI category, with obese patients more often being females, and overweight patients more often being males ($P < 0.001$ for all).
Medical history revealed that the prevalence of diabetes mellitus increased from 30% in the lowest- to 49% in the highest BMI category ($P < 0.001$). Furthermore, ischemic heart disease and cerebrovascular disease were more common in the overweight and obese class I and class II patients, with a prevalence of > 10% for ischemic heart disease and 7% for cerebrovascular disease ($P < 0.001$ and $P = 0.005$ respectively). The prevalence of cancer decreased from 43% in the underweight patients to 16% in the obese class III patients ($P < 0.001$). Smoking prevalence showed a similar distribution ranging from 53% in the underweight to 29% in the obese class III patients ($P < 0.001$).
The majority (62%) of surgical procedures were classified as intermediate cardiac risk (Table 2). Low-risk surgery was most often carried out in obese class II and III patients (40%), whereas high-risk surgery was most often performed in overweight patients (16%) ($P < 0.001$) (Table 1). Of all surgical procedures, 2,461 (24%) was established as cancer-related surgery, of which 29% was performed in underweight patients and 9% in obese class III patients ($P < 0.001$).

Postoperative mortality and length of stay

Postoperative mortality differed between the BMI categories. Within 30-days after surgery, a total of 353 (3.4%) patients died. Underweight patients had the highest 30-day mortality rate (4.5%), compared to lower rates in the overweight (3.0%), obesity class I (3.1%), obesity class II (3.0%) and obesity class III patients (2.9%) ($P = 0.284$). After adjusting for potential confounders (age, gender, RCRI (ischemic heart disease, heart failure, cerebrovascular disease, diabetes mellitus, renal dysfunction), cancer, surgery risk, year of surgery, COPD, and smoking status), overweight patients showed a reduced postoperative mortality risk (OR 0.7; 95% CI 0.6-0.9), whereas other BMI categories showed no association with postoperative mortality risk (Figure 1).

Table 1 | Baseline characteristics of the study population

	Underweight [N=475]	**Normal weight** [N=4601]	**Overweight** [N=3500]	**Obesity Class I** [N=1311]	**Obesity Class II** [N= 368]	**Obesity Class III** [N=172]	**P-value**
Demographics							
Age (mean ± SD)	52 (± 19)	57 (± 16)	60 (± 15)	58 (±14)	56 (±14)	53 (±12)	< 0.001
Male (%)	52	62	65	49	30	20	< 0.001
Medical history (%)							
Ischemic heart disease	7	10	13	14	12	8	< 0.001
Cerebrovascular disease	3	6	7	7	7	4	0.005
Renal dysfunction	5	5	5	5	4	4	0.886
Heart failure	4	6	7	6	6	4	0.078
Diabetes Mellitus	30	36	41	45	48	49	< 0.001
Cancer	43	40	35	27	22	16	< 0.001
COPD	46	49	48	41	42	26	< 0.001
Smoker, current	53	40	32	29	26	29	< 0.001
Surgery risk (%)							< 0.001
Low	26	23	23	30	39	40	
Intermediate	65	64	61	59	54	56	
High	9	13	16	11	7	4	
Revised Cardiac Risk Index (%)							< 0.001
None	61	54	48	46	45	47	
1 risk factor	32	34	37	38	39	40	
2 risk factors	6	9	11	11	11	13	
≥ 3 risk factors	1	3	4	5	5	1	

Abbreviations: COPD chronic obstructive pulmonary disease; SD standard deviation

Table 2 | Surgical procedures

	N	(%)
Low Cardiac Risk *	**2596**	**25**
Breast	132	1.3
Dental	54	0.5
Endocrine	121	1.2
Eye	623	6.0
Gynecology	579	5.6
Orthopedic	939	9.0
Reconstructive	148	1.4
Intermediate Cardiac Risk *	**6461**	**62**
Abdominal	2417	23.2
Carotid	26	0.2
Head and neck	1382	13.3
Neurologic	338	3.2
Pulmonary	814	7.8
Renal and urologic	1022	9.8
Other	462	4.4
High Cardiac Risk *	**1370**	**13**
Aortic	185	1.8
Peripheral vascular	294	2.8
Other vascular	891	8.5

* cardiac risk in non-cardiac surgery based on ESC guidelines [15]

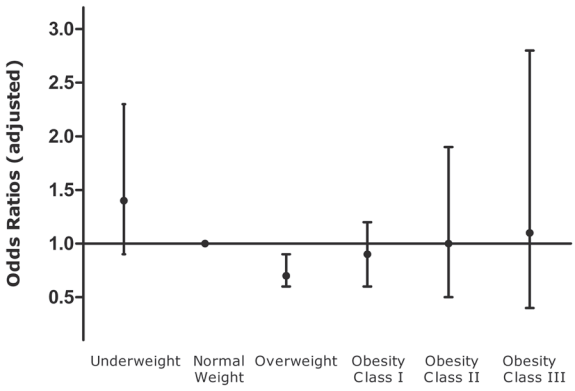

Figure 1 | Adjusted Odds Ratios for 30-day Postoperative Mortality According to BMI categories

The LOS also varied significantly by BMI category. The median LOS was 7.0 days (IQR 2.0-15.0 days) for normal weight patients, and 7.0 days (IQR 2.0-16.0 days) for underweight patients ($P = 0.7$). The LOS was significantly shorter for overweight and obese patients, compared to normal weight patients (overweight: median LOS 6.0 days (IQR 2.0-13.0) ($P = 0.001$); obesity class I: median LOS 5.0 days (IQR 1.0-12.0 days) ($P < 0.001$); obesity class II: median LOS 4.0 days (IQR 1.0-9.0) ($P < 0.001$); obesity class III: median LOS 4.0 days (IQR 1.0-10.0 days) ($P < 0.001$); respectively). When the analysis was stratified by surgical risk, LOS was shorter for obese patients compared to normal weight patients, particularly in intermediate risk surgery ($P < 0.001$) and high-risk surgery, although this difference was not significant ($P = 0.06$). On the other hand, in low-risk surgery LOS did not differ between BMI categories ($P = 0.5$).

Long-term survival

During the long-term follow-up, 4,884 (47%) patients died. Cumulative long-term survival according to BMI category is demonstrated in Figure 2 (log rank $P < 0.001$).

Mortality rates varied significantly among BMI categories: 276 (58%) patients in the underweight category; 2,361 (52%) patients in the normal weight category; 1,606 (46%) patients in the overweight category; 481 (37%) patients in the obese class I category; 115 (31%) patients in the obese class II category; and 45 (27%) patients in the obese class III category ($P < 0.001$) (Table 3). Multivariable regression analyses, adjusting for confounders, demonstrated that in underweight patients all-cause mortality risk was increased (adjusted HR 1.4; 95% CI 1.2–1.6), whereas overweight and obese patients showed improved survival (overweight: adjusted HR 0.8; 95% CI 0.8-0.9; obesity class I: adjusted HR 0.7; 95% CI 0.7–0.8; obesity class II: adjusted HR 0.7; 95% CI 0.6-0.9; obesity class III: adjusted HR 0.7; 95% CI 0.5-1.0 respectively) (Figure 3 and Table 3).

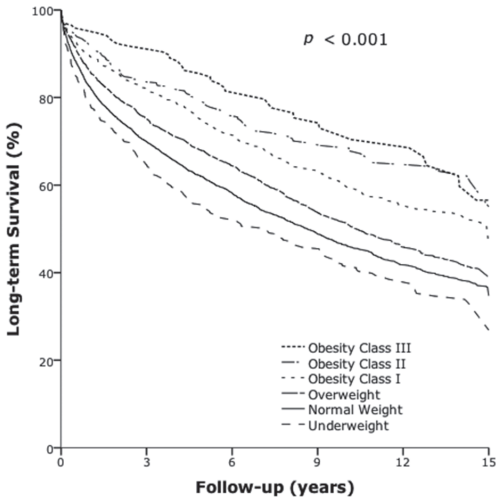

Figure 2 | Kaplan-Meier Curves for Long-Term Survival According to BMI Categories

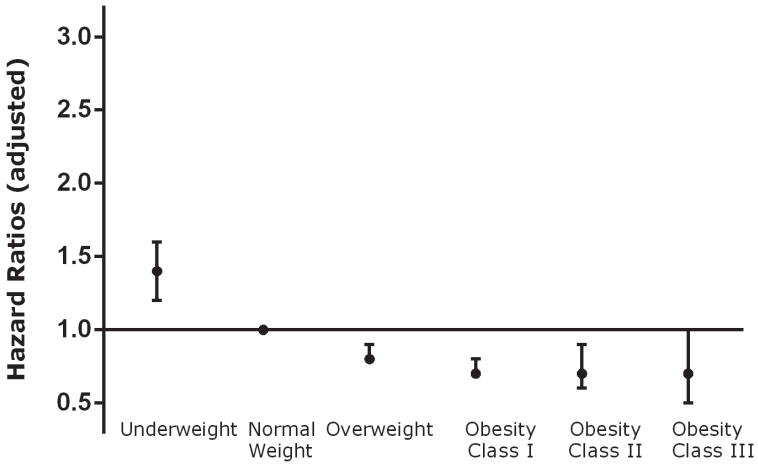

Figure 3 | Adjusted Hazard Ratios for Long-Term Mortality According to BMI Categories

Sensitivity analysis in patients without missing values on smoking and COPD did not change these hazard ratios. Moreover, sensitivity analysis excluding patients with cancer still showed that underweight was associated with an increased mortality risk (adjusted HR 1.6; 95% CI 1.3-1.9). Overweight, obesity class I and II remained associated with improved survival, with comparable hazard ratios as reported before, whereas obesity class III was no longer associated with mortality (adjusted HR 0.9; 95% CI 0.6-1.3). Sensitivity analyses excluding the first 5 years of follow-up yielded somewhat different results. In underweight patients mortality risk was still increased (adjusted HR 1.4; 95% CI 1.1-1.8), and overweight and obesity class I remained associated with improved survival (adjusted HR 0.9; 95% CI 0.8-1.0; and adjusted HR 0.8; 95% CI 0.7-1.0; respectively). On the other hand, both obesity class II and III was no longer associated with mortality (obesity class II: adjusted HR 0.8; 95% CI 0.6-1.1; obesity class III: adjusted HR 1.3; 95% CI 0.8-2.0).

Cause-specific mortality among the BMI categories is represented in Figure 4. Cardiovascular mortality accounted for 22% of deaths in underweight patients, and this increased to 42% in obesity class III patients ($P = 0.001$). Multivariable analyses showed that obesity class I was associated with improved cardiovascular survival (adjusted HR 0.8; 95% CI 0.7-1.0), whereas no associations with cardiovascular mortality risk were observed in the other BMI categories (Table 3).

Cancer related death was responsible for the majority (52%) of deaths in underweight patients, and this decreased to 24% in obesity class III patients ($P < 0.001$) (Figure 4). Underweight patients were 1.4 times more likely to die from cancer than normal weight patients (adjusted HR 1.4; 95% CI 1.1–1.6) (Table 3). In contrast, overweight and obese patients had a 20-50% reduced risk of cancer related mortality (overweight: adjusted HR 0.8; 95% CI 0.8-0.9; obesity class I: adjusted HR 0.7; 95% CI 0.6-0.8; obesity class II: adjusted HR 0.7; 95% CI 0.5-0.9; obesity class III: adjusted HR 0.5; 95% CI 0.3-0.9, respectively) (Table 3).

Table 3 | Mortality rates and Hazard Ratios for mortality from all-cause, cerebro-cardiovascular and cancer

	Underweight	Normal weight	Overweight	Obesity Class I	Obesity Class II	Obesity Class III
All-cause mortality						
%	58	52	46	37	31	27
unadjusted HR	1.2	1.0	0.9	0.6	0.5	0.4
(95% CI)	1.0-1.3		0.8-0.9	0.6-0.7	0.4-0.6	0.3-0.6
adjusted HR*	1.4	1.0	0.8	0.7	0.7	0.7
(95% CI)	1.2-1.6		0.8-0.9	0.7-0.8	0.6-0.9	0.5-1.0
Cerebro-cardiovascular mortality						
%	13	15	18	14	13	12
unadjusted HR	0.9	1.0	1.1	0.8	0.7	0.6
(95% CI)	0.6-1.1		1.0-1.2	0.7-1.0	0.5-0.9	0.4-1.0
adjusted HR*	1.2	1.0	0.9	0.8	1.0	1.3
(95% CI)	0.9-1.5		0.8-1.1	0.7-1.0	0.7-1.3	0.8-2.0
Cancer mortality						
%	31	24	19	12	10	7
unadjusted HR	1.4	1.0	0.8	0.5	0.4	0.2
(95% CI)	1.1-1.6		0.7-0.8	0.4-0.6	0.3-0.5	0.1-0.4
adjusted HR*	1.4	1.0	0.8	0.7	0.7	0.5
(95% CI)	1.1-1.6		0.8-0.9	0.6-0.8	0.5-0.9	0.3-0.9

* adjusted for age, gender, RCRI, COPD and smoking status, surgery risk, cancer related surgery and year of surgery

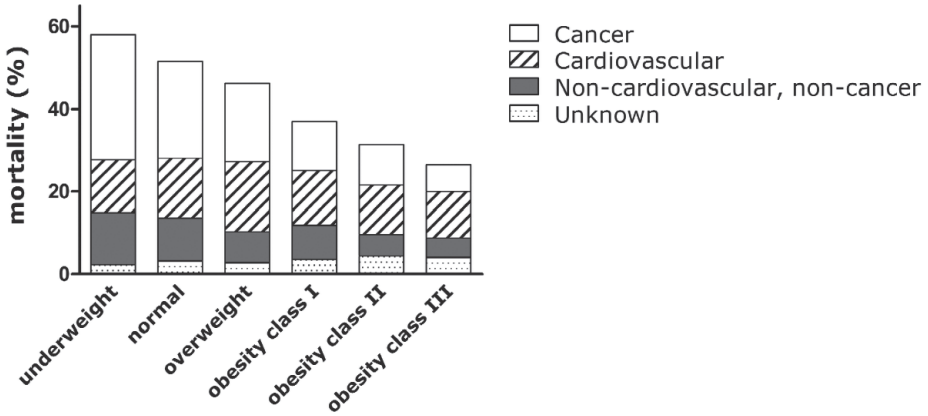

Figure 4 | Long-Term and Cause-Specific Mortality According to BMI categories

DISCUSSION

In this large sample of general surgery patients from a single Dutch hospital, only overweight was associated with 30-day postoperative mortality, showing improved survival, whereas obesity was not associated with postoperative mortality. However, long-term survival was significantly better for obese patients, clearly showing the presence of the obesity paradox in this surgical population. Furthermore, cause-specific mortality differed significantly between BMI categories, with cardiovascular mortality accounting for more than one third of deaths in overweight and obesity, and cancer being responsible for the majority of deaths in underweight patients.

Obesity was not associated with postoperative mortality risk in our study; however, postoperative death was reduced in overweight patients. Postoperative complications, like wound infections, are related to obesity and can lead to a longer hospital stay[12, 13], however, they do not affect survival. Although this study did not assess surgical complications, hospital stay was assessed and was shorter in patients with obesity classes I and II. Mullen et al. reported similar postoperative outcomes for the overweight and the obese, including lower mortality risks and reduced length of stay[13]. Increased awareness of the hazards of obesity by both surgeons and anesthesiologists[19, 20], might have led to improved perioperative care and lower postoperative (cardiac) complication rates. These improvements can be reflected by reduced length of hospital stay and no additional mortality risk for the obese patient in the present study.

Although the current study did not demonstrate the obesity paradox at 30-day postoperatively, its' presence could be confirmed at long-term. One of the hypotheses to explain the obesity paradox in our study might be that a decrease in cardiovascular related mortality in the overweight and obese patients, similar to observations in the general population[21], might have led to a decrease in all-cause mortality. A reduced cardiovascular mortality risk could be demonstrated for obesity class I patients, but was not observed in the overweight and obese class II and III patients. Probably the number of overweight and obese class II and III patients dying from cardiovascular causes was too small for meaningful subgroup analyses. However, considering that cardiovascular mortality was the leading cause of long-term mortality among the obese, this hypothesis might be less likely to explain the obesity paradox in the present study. Therefore, other explanations are probably warranted to explain the obesity paradox in our surgical population, which is mainly determined by decreased cancer related deaths among the obese.

One of the explanations could be that obese oncology patients were not, or less often, referred for surgery. In the present study, the prevalence of cancer was lowest among obese patients, and cancer related surgery was performed least often in obesity class III patients, which might have caused selection bias and supposed improved survival. In addition, although several site-specific cancers are associated with obesity[22], particularly with visceral adiposity[23], BMI cannot distinguish between visceral and peripheral adiposity. Visceral adiposity is less common in pre-menopausal women[23]. Therefore, visceral adiposity might have been less prevalent among the predominantly female obese patients in our study, particularly in obese class III patients, leading to a lower prevalence of cancer.

Another hypothesis is that overweight and obese patients had less disseminated cancer, as some studies have reported[13, 24], in that way leading to improved survival.
Although obesity is associated with several cancers, Calle et al. demonstrated an inverse association between overweight and obesity and death from lung cancer[25]. Decreased mortality rates from lung cancer could have reduced total cancer mortality rates among the overweight and obese in the present study. Similar to the current study, the population studied by Calle et al. included smokers. Smoking can be a potential confounder, because it is associated with both a decreased weight and an increased mortality risk[18]. Furthermore, smoking is related to an increased incidence of cancer. The effects of smoking on mortality cannot be separated from the effects of BMI on mortality in smoking-related diseases, like lung cancer. In the present study, the prevalence of smoking was higher in the underweight population compared to other BMI categories. This could offer another explanation for the obesity paradox in this surgical population.
Besides smoking associated weight loss, chronic diseases can also cause weight loss. Chronic diseases that cause weight loss may remain unnoticed for months or even years, for example in the case of cancer and COPD. Consequently, *reverse causation*, which means that lower weight is not a cause but a result of chronic diseases that are related to poor outcome, can be another confounder associated with mortality[10, 18]. In order to limit the effects of smoking and reverse causation on mortality risks, deaths occurring in the first years of follow-up should be disregarded, and analyses should be restricted to persons without prior disease and to persons who never smoked[18]. In the present study, underweight patients displayed the worst long-term survival, with nearly 60% mortality during follow-up. Furthermore, more than half of deaths were attributable to cancer. After exclusion of the first 5 years of follow-up, in order to limit the effects of pre-existing disease on baseline BMI, the obesity paradox was still present, with highest mortality risk in the underweight and improved survival in the overweight and obesity class I. Moreover, sensitivity analysis excluding patient with cancer demonstrated similar results. Unfortunately, in the present study analyses could not be restricted to never smokers, since information regarding former smoking was not available. In the study by Calle et al. the apparent inverse association between obesity and lung cancer mortality risk disappeared after restricting analyses to persons who never smoked[25].
Several limitations of the present study have already been mentioned, including the inability of BMI to differentiate between visceral and peripheral adiposity, and the unfeasibility to divide non-smokers into former and never smokers. In addition, information regarding medication use was not available. Furthermore, this is a retrospective observational study, and therefore causality between BMI and outcome cannot be established. Finally, data on smoking and COPD were incomplete. These patients were not excluded to prevent any bias, and established statistical methods were used to impute missing values. It was assuring that in sensitivity analyses excluding patients with missing values, reported hazard ratios did not change.

CONCLUSIONS

In this large retrospective study of general surgery patients, postoperative mortality risk was reduced in overweight, and not associated with other BMI categories. At long-term the obesity paradox could be validated, mainly due to decreased cancer related mortality among the overweight and the obese.

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Summary and discussion
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SUMMARY AND DISCUSSION

The atherothrombotic patient populations

Atherothrombosis, a collective term that includes peripheral arterial disease, coronary artery disease and cerebrovascular disease, is a leading cause of mortality, and is projected to remain the principal cause of death worldwide by 2020.[1] In **chapter 1** we have presented the various atherothrombotic patient populations by giving an overview of the results from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. The REACH Registry demonstrated that among patients with established atherothrombosis, patients with peripheral arterial disease generally have the worse prognosis. Two thirds of patients with peripheral arterial disease had polyvascular disease, defined as symptomatic involvement of more than one vascular bed. Although the risk factor profile among the three atherothrombotic patient populations was very much similar, optimal risk factor control by medical treatment and lifestyle interventions was least accomplished in patients with peripheral arterial disease. Therefore, it might be not surprising that cardiovascular event rates during follow-up were highest for these patients and for those with symptomatic polyvascular disease. Up to now, therapeutic strategies are similar for all atherothrombotic disease categories, irrespective of the presence of polyvascular disease. Therefore, it is of the utmost importance to achieve optimal risk factor control, particularly for patients with peripheral arterial disease and for those with polyvascular disease, in order to prevent future cardiovascular events.

Aortic valve calcification

Postoperative cardiovascular complications in patients undergoing non-cardiac surgery are common, particularly in patients undergoing high-risk surgery including vascular surgery. The majority of these adverse events are due to underlying coronary artery disease, a common comorbid condition in patients with peripheral arterial disease.[2] The Revised Cardiac Risk Index is commonly used to estimate a patient's individual risk of postoperative cardiovascular events, and is based on the surgical risk and the following comorbid conditions: coronary heart disease, congestive heart failure, prior cerebrovascular disease (including stroke and transient ischemic attack), insulin dependent diabetes mellitus and renal insufficiency (serum creatinin > 2.0 mg/dL).[3] However, other risk factors might contribute to an increased risk of postoperative cardiovascular events as well.

In **chapter 2** we have demonstrated that aortic valve calcification, a condition that is associated with cardiovascular mortality in the general population,[4] is common in vascular surgery patients. Aortic valve calcification included *aortic valve sclerosis*, defined by thickening and/or calcium of one or more cusps of a tricuspid valve not inducing stenosis, i.e. with a maximal velocity < 2.5 m/s (aortic jet velocity measured with continuous-wave Doppler echocardiography) and *aortic valve stenosis*, defined as a jet velocity > 2.5 m/s. Aortic valve sclerosis was present in 36% and stenosis in 3% of patients undergoing vascular surgery. Moreover, the presence of aortic valve calcification, particularly aortic valve stenosis, was associated with postoperative cardiovascular events and long-term mortality. It might be suggested that the presence of aortic valve calcification represents

a high atherosclerotic burden in vascular surgery patients. Although aggressive treatment with life-style modification and medical therapy is required in these patients, it is currently unknown whether these interventions influence the progression of aortic valve calcification in this patient category.

In the same cohort of vascular surgery patients we have shown a strong and independent association between moderate and severe chronic kidney disease (defined by an estimated glomerular filtration rate (eGFR) < 45 mL/min per 1.73 m^2) with aortic valve sclerosis (**chapter 3**). Although the long-term mortality rates were high in all patients with chronic kidney disease, the mortality risk increased significantly in those with moderate and severe kidney disease and when aortic valve sclerosis was present. It seems that aortic valve sclerosis acts as a risk marker for patients with eGFR < 45 mL/min per 1.73 m^2, in a similar way it does for patients with end-stage renal disease.[5] Obviously, these results need to be established in other patient populations. In addition, it remains to be elucidated if atherosclerotic risk factors or factors unique to kidney disease are causally related to aortic valve sclerosis in moderate kidney disease.

Blood type, hemoglobin and blood transfusions

The majority of adverse cardiovascular events in the postoperative phase are due to myocardial infarction, caused by thrombotic arterial occlusion at the site of a ruptured atherosclerotic plaque.[6] In the general population, non-O blood type has been linked to an increased risk of thrombotic events including myocardial infarction.[7] In **chapter 4** we have demonstrated that neither postoperative cardiovascular events, nor long-term mortality was related to non-O blood type in a large cohort of vascular surgery patients. The relationship between ABO blood type and postoperative events might have been influenced by the use of anti-platelet and anticoagulant medication. Perioperatively, aspirin therapy is not discontinued and thrombophrophylaxis using prophylactic doses of low molecular weight heparin (LMWH) in patients not receiving therapeutic doses of LMWH or oral anticoagulants, is administered routinely.

The use of aspirin and anticoagulants perioperatively is associated with an increased risk of bleeding. The resulting lower hemoglobin level might lead to the administration of red blood cell transfusions, particularly in patients who tolerate anemia poorly, including patients with a history of coronary heart disease.[8] In a cohort of high-risk vascular surgery patients, we found that preoperative hemoglobin levels, as well as postoperative hemoglobin levels and hemoglobin decrease were all inversely related to postoperative cardiovascular events (**chapter 5**). In order to rule out bias caused by the (intra- or postoperative) administration of red blood cell transfusions, sensitivity analyses were performed in patients who did not receive transfusions. These analyses demonstrated that only postoperative hemoglobin levels (< 12.1 g/dL) remained associated with a high risk of postoperative cardiovascular events.

Current transfusion guidelines do not recommend red blood cell transfusion in stable patients when hemoglobin is > 7.0-8.0 g/dL.[9,10] In patients with diminished cardiopulmonary reserve, American and British guidelines recommend red blood cell transfusion when hemoglobin is below 8.0 g/dL,[10,11] and Dutch guidelines even when hemoglobin is below

9.7 g/dL.[9] Although red blood cell transfusions aim to reduce tissue ischemia by increasing oxygen delivery, we have demonstrated a considerably increased dose-dependent risk of postoperative cardiovascular events and mortality in patients who received perioperative red blood cell transfusions (**chapter 6**). The guidelines and the results of chapter 6 suggest caution against red blood cell transfusion. However, they do not support the finding of chapter 5 in which postoperative hemoglobin levels < 12.1 g/dL in vascular surgery patients were associated with an increased risk of postoperative cardiovascular events; neither does it answer the question whether these patients should be transfused and what the most appropriate transfusion regimen is. Several limitations should be considered. First, the studies presented in chapters 5 and 6 comprised an observational cohort of vascular surgery patients. Importantly, a causal relation between hemoglobin levels, perioperative red blood cell transfusion and outcome cannot be assumed due to the study design. A randomized trial in vascular surgery patients would offer the best opportunity to study transfusion thresholds. Till then, transfusion guidelines should be followed accordingly, including preoperative hemoglobin measurement and ABO blood type determination in patients undergoing high-risk surgery.[9] Moreover, the primary focus should stay on measures to minimize blood loss, in order to avoid perioperative red blood cell transfusions.

Obesity

Overweight and obesity are major health conditions that have reached epidemic proportions, particularly in the Western world.[12,13] The obesity epidemic also affects surgery, not only because more surgical patients are obese, but also because of an increase in obesity-related diseases that require surgery. Despite the medical hazards associated with obesity, particularly cardiovascular disease,[14] recent literature has demonstrated that obese patients show improved survival, a phenomenon referred to as the *obesity paradox*.

In **chapter 7** we have presented a literature review regarding the obesity paradox in the surgical population. We were able to demonstrate the presence of the obesity paradox both in cardiac and in non-cardiac surgery populations. Underweight (BMI < 18.5 kg/m^2) and morbidly obese (BMI ≥ 40.0 kg/m^2) patients displayed the worse survival, both postoperatively as well as at long-term follow-up, although cause-specific mortality was not yet investigated. The cause of the obesity paradox is probably multi-factorial and we presented several hypotheses that serve to explain the paradox. The suggested hypotheses included increased lean body mass, (protective) peripheral body fat, reduced inflammatory response, genetics and a decline in cardiovascular disease risk factors, but probably unknown factors contribute too.

We have also confirmed the presence of the obesity paradox in a general surgery population (**chapter 8**). Not only postoperative, also long-term survival including cause-specific mortality was presented. In line with the results of the review described in the previous chapter, underweight patients had the highest long-term mortality risk, whereas overweight and obese patients showed improved survival. Cause-specific mortality differed significantly between BMI categories, with cancer being responsible for the majority of deaths in the underweight and cardiovascular mortality accounting for the majority of deaths among the overweight and the obese patients. One of the hypotheses to explain the obesity paradox

presented in the review included the decline in cardiovascular risk factors. However, considering that cardiovascular mortality was the leading cause of long-term mortality among the obese, this hypothesis might be less likely to explain the obesity paradox in this study. The paradox in this surgical population was mainly determined by decreased cancer related mortality among the overweight and the obese. The question whether this was caused by selection bias or by cancer specific determinants remains unanswered by this study. It is suggested that future research should be directed at more accurate indices of body fat distribution, for instance waist circumference, since it is known that BMI is not an adequate measure of body fat.

CONCLUSIONS

Atherothrombosis is a major worldwide health problem and will continue to be the leading cause of mortality in the next decade. By definition, patients undergoing vascular surgery have established atherothrombosis in one vascular bed, though the prevalence of polyvascular disease in these patients is high. For patients undergoing non-cardiac surgery, the risk of postoperative adverse cardiovascular events is estimated by the use of preoperative risk scores, particularly the Revised Cardiac Risk Index. We have evaluated the value of non-traditional risk factors, like aortic valve calcification, ABO blood type, hemoglobin, blood transfusions and BMI, on postoperative and long-term outcome in patients undergoing non-cardiac surgery and found that, except for ABO blood type, each of these risk factors contributed to adverse outcomes. Although the results of our studies suggest the use of these 'novel' risk factors in the estimation of the postoperative cardiovascular event and long-term mortality risk, it is probably most important to recognize and adequately treat the underlying comorbidity that is responsible for the negative outcomes, particularly coronary heart disease. Therefore, the primary focus for all patients with atherothrombotic disease should be on optimal risk factor control with medical therapy and lifestyle interventions according to guideline recommendations in order to prevent future cardiovascular events.

SAMENVATTING EN DISCUSSIE

De atherothrombotische patiënt populaties

Atherothrombose, een verzamelnaam die perifeer arterieel vaatlijden, coronaire hartziekten en cerebrovasculaire aandoeningen omvat, is een belangrijke oorzaak van sterfte, en zal naar verwachting wereldwijd de belangrijkste doodsoorzaak blijven tot 2020.[1] In **hoofdstuk 1** hebben we de verschillende atherothrombotische patiënt populaties gepresenteerd door een overzicht te geven van de resultaten van de REACH (Reduction of Atherothrombosis for Continued Health) Registry. De REACH Registry toonde aan dat onder patiënten met vastgestelde atherothrombose, patiënten met perifeer arterieel vaatlijden over het algemeen de slechtste prognose hebben. Twee derde van de patiënten met perifeer vaatlijden had polyvasculaire ziekte, gedefinieerd als de symptomatische betrokkenheid van meer dan een (arterieel) vaatbed. Hoewel het risicofactor profiel tussen de drie atherothrombotische patiënt populaties vergelijkbaar was, werd optimale regulatie van de risicofactoren door middel van medicamenteuze therapie en leefstijl interventies het minst bereikt in patiënten met perifeer arterieel vaatlijden. Daarom is het misschien niet verwonderlijk dat het percentage cardiovasculaire incidenten tijdens de follow-up het hoogst was voor deze patiënten en voor degenen met symptomatische polyvasculaire ziekte. Tot op heden is de therapeutische aanpak voor de verschillende atherothrombotische ziekte categorieën vergelijkbaar, ongeacht de aanwezigheid van polyvasculaire ziekte. Het is derhalve van het grootste belang om de risicofactoren zo optimaal mogelijk te reguleren, met name voor patiënten met perifeer arterieel vaatlijden en voor patiënten met polyvasculaire ziekte, om op die manier toekomstige cardiovasculaire incidenten te voorkomen.

Aortaklep calcificatie

Postoperatieve cardiovasculaire complicaties bij patiënten die niet-cardiale chirurgie ondergaan zijn gebruikelijk, vooral bij patiënten die hoogrisico chirurgie zoals vaatchirurgie ondergaan. De meerderheid van deze complicaties zijn het gevolg van onderliggende kransslagaderziekte, een frequent voorkomende aandoening bij patiënten met perifeer arterieel vaatlijden.[2] De Revised Cardiac Risk Index wordt gewoonlijk gebruikt om het individuele risico van een patiënt op postoperatieve cardiovasculaire complicaties in te schatten, en is gebaseerd op het chirurgisch (operatie) risico en de volgende comorbiditeit: coronaire hartziekte, chronisch hartfalen, cerebrovasculaire ziekte (waaronder beroerte en TIA), insuline afhankelijke diabetes mellitus en nierinsufficiëntie (serum kreatinine > 2.0 mg/dL).[3] Andere risicofactoren kunnen echter ook bijdragen aan een verhoogd risico op postoperatieve cardiovasculaire complicaties.

In **hoofdstuk 2** hebben we aangetoond dat aortaklep calcificatie, een aandoening die in de algemene bevolking is geassocieerd met sterfte aan hart- en vaatziekten,[4] frequent voorkomt bij patiënten die een vaatchirurgische ingreep ondergaan. Aortaklep calcificatie omvat *aortaklep sclerose*, gedefinieerd door verdikking en/of kalk op een of meerdere cusps van een drieslippige aortaklep welke geen stenose veroorzaakt, dat wil zeggen met een maximale snelheid < 2.5 m/sec (snelheid over de aortaklep gemeten met continuous-

wave Doppler echocardiografie) en aortaklep stenose, gedefinieerd als een maximale snelheid van > 2.5 m/sec. Aortaklep sclerose was aanwezig in 36% en stenose in 3% van de vaatchirurgische patiënten. Bovendien was de aanwezigheid van aortaklep calcificatie, met name aortaklep stenose, geassocieerd met postoperatieve cardiovasculaire complicaties en sterfte op lange termijn. Het zou gesuggereerd kunnen worden dat de aanwezigheid van aortaklep calcificatie een uiting is van een hoge mate van atherosclerotische belasting in vaatchirurgische patiënten. Alhoewel agressieve behandeling middels leefstijl aanpassing en medicamenteuze therapie vereist is in deze patiënten, is het momenteel onbekend of deze maatregelen in deze patiënten categorie de progressie van aortaklep calcificatie zullen beïnvloeden.
In hetzelfde cohort vaatchirurgische patiënten hebben we een sterke en onafhankelijke associatie tussen matige en ernstige chronische nierfunctiestoornissen (gedefinieerd door een geschatte glomerulaire filtratiesnelheid (eGFR) < 45 ml/min per 1.73m^2) en aortaklep sclerose aangetoond (**hoofdstuk 3**). Hoewel de sterfte op lange termijn hoog was in alle patiënten met een chronische nierfunctiestoornis, nam het sterfterisico aanzienlijk toe in patiënten met matige en ernstige nierfunctiestoornissen en wanneer aortaklep sclerose aanwezig was. Het lijkt erop dat aortaklep sclerose een risicofactor is voor patiënten met een eGFR < 45 ml/min per 1.73m^2, zoals dit ook het geval is voor patiënten met terminale nierinsufficiëntie.[5] Vanzelfsprekend dienen deze resultaten bevestigd te worden in andere patiënt populaties. Bovendien zal moeten worden opgehelderd of atherosclerotische risico factoren of nierfunctiestoornis specifieke factoren oorzakelijk gerelateerd zijn aan aortaklep sclerose in matige chronische nierfunctiestoornissen.

Bloedgroep, hemoglobine en bloedtransfusies

De meerderheid van de cardiovasculaire complicaties die optreedt in de postoperatieve fase is het gevolg van myocardinfarct, veroorzaakt door arteriële thrombotische occlusie ter plaatse van een atherosclerotische plaque ruptuur.[6] In de algemene bevolking is non-O bloedgroep gerelateerd aan een verhoogd risico op thrombotische incidenten, waaronder myocardinfarct.[7] In **hoofdstuk 4** hebben we aangetoond dat noch postoperatieve cardiovasculaire complicaties, noch sterfte op lange termijn gerelateerd was aan non-O bloedgroep in een groot cohort vaatchirurgische patiënten. De relatie tussen ABO bloedgroep en postoperatieve complicaties zou beïnvloed kunnen zijn door het gebruik van plaatjes aggregatie remmers en anticoagulantia. Aspirine wordt perioperatief niet gestaakt en trombose profylaxe middels laagmoleculair heparine wordt routinematige toegepast bij patiënten die geen therapeutische dosering laagmoleculair heparine of orale anticoagulantia gebruiken.
Het gebruik van aspirine en anticoagulantia perioperatief is geassocieerd met een verhoogd risico op bloeding. Het daaruit voortvloeiende lagere hemoglobine gehalte zou kunnen leiden tot het toedienen van erytrocyten transfusies, met name bij patiënten die anemie slecht verdragen, zoals in patiënten met coronairlijden.[8] In een cohort van hoogrisico vaatchirurgische patiënten, hebben we gevonden dat zowel preoperatieve hemoglobine waarden, als ook postoperatieve hemoglobine waarden en afname in hemoglobine, allen omgekeerd gerelateerd waren aan postoperatieve cardiovasculaire

complicaties (**hoofdstuk 5**). Om bias ten gevolge van (intra- of postoperatief) toegediende erytrocyten transfusies uit te sluiten, werden subgroep analyses uitgevoerd in patiënten die geen transfusies hadden gehad. Deze analyses toonden aan dat alleen postoperatieve hemoglobine waardes (<12.1 g/dL) geassocieerd bleven met een hoog risico op postoperatieve cardiovasculaire complicaties.
Huidige transfusie richtlijnen bevelen geen erytrocyten transfusie aan in stabiele patiënten wanneer het hemoglobine > 7.0-8.0 g/dL.[9,10] In patiënten met een verminderde cardiopulmonale reserve adviseren Amerikaanse en Britse richtlijnen erytrocyten transfusie als het hemoglobine lager is dan 8.0 g/dL,[10,11] en Nederlandse richtlijnen zelfs wanneer het hemoglobine lager is dan 9.7 g/dL.[9] Hoewel bloedtransfusies tot doel hebben ischemie in de weefsels te reduceren door het verhogen van de zuurstof toevoer, hebben wij een aanzienlijk verhoogd, dosisafhankelijk risico op postoperatieve cardiovasculaire complicaties en sterfte aangetoond in patiënten die perioperatief erytrocyten transfusies kregen toegediend (**hoofdstuk 6**). De richtlijnen en de resultaten van hoofdstuk 6 wijzen op terughoudendheid van erytrocyten transfusies. Ze ondersteunen echter niet het resultaat van hoofdstuk 5 waarin postoperatieve hemoglobine waardes < 12.1 g/dL in vaatchirurgische patiënten geassocieerd waren met een verhoogd risico op postoperatieve cardiovasculaire complicaties, noch beantwoorden ze de vraag of deze patiënten getransfundeerd zouden moeten worden en wat het meest geschikte transfusie regime is. Een aantal beperkingen dient te worden overwogen. Ten eerste, de studie in zowel hoofdstuk 5 als 6 omvatte een observationeel cohort van patiënten die een vaatchirurgische operatie ondergingen. Het is belangrijk dat een causaal verband tussen hemoglobine waarde, perioperatieve erytrocyten transfusie en uitkomst niet kan worden aangetoond vanwege de onderzoeksopzet. Een gerandomiseerd onderzoek in vaatchirurgische patiënten biedt de beste mogelijkheid om transfusie grenzen te bestuderen. Tot die tijd dienen transfusie richtlijnen te worden gevolgd, inclusief preoperatieve bepaling van het hemoglobine gehalte en ABO bloedgroep determinatie in patiënten die hoogrisico chirurgie ondergaan.[9] Bovendien moet de primaire focus blijven op maatregelen om bloedverlies te beperken, teneinde perioperatieve bloedtransfusies te vermijden.

Obesitas
Overgewicht en obesitas zijn belangrijke gezondheidsproblemen die een epidemische omvang hebben bereikt, vooral in de Westerse wereld.[12,13] De obesitas epidemie beïnvloedt ook de chirurgie, niet alleen omdat meer chirurgische patiënten obees zijn, maar ook door een toename van obesitas gerelateerde aandoeningen die chirurgie vereisen. Ondanks de medische risico's die geassocieerd zijn met obesitas, met name cardiovasculaire ziekte,[14] heeft recente literatuur aangetoond dat obese patiënten een verbeterde overleving laten zien, een verschijnsel dat wordt aangeduid als de *obesitas paradox*.
In **hoofdstuk 7** hebben we een overzicht van de literatuur met betrekking tot de obesitas paradox in de chirurgische populatie gepresenteerd. We waren in staat om de aanwezigheid van de obesitas paradox zowel in cardiale als in niet-cardiale chirurgische populaties aan te tonen. Patiënten met ondergewicht (BMI < 18.5 kg/m^2) en morbide obesitas (BMI ≥ 40.0 kg/m^2) hadden de slechtste overleving, zowel postoperatief als op lange termijn,

hoewel de oorzaak van overlijden nog niet werd onderzocht. De oorzaak van de obesitas paradox is waarschijnlijk multifactorieel en we hebben een aantal hypotheses die de paradox zouden kunnen verklaren gepresenteerd. Deze hypotheses omvatten toegenomen 'lean' body mass, (beschermend) perifeer lichaamsvet, verminderde inflammatoire reactie, genetica en een afname in risicofactoren voor hart- en vaatziekten, maar waarschijnlijk dragen ook onbekende factoren bij.
We hebben de aanwezigheid van de obesitas paradox ook bevestigd in een algemeen chirurgische populatie (**hoofdstuk 8**). Niet alleen postoperatieve, ook lange termijn overleving inclusief oorzaak van overlijden werd gepresenteerd. In overeenstemming met de resultaten van het overzichtsartikel van hoofdstuk 7, hadden patiënten met ondergewicht het hoogste lange termijn sterfterisico, terwijl patiënten met overgewicht en obesitas verbeterde overleving lieten zien. De oorzaak van overlijden verschilde significant tussen de BMI categorieën, waarbij kanker gerelateerd overlijden verantwoordelijk was voor de meerderheid van de sterfgevallen in de ondergewicht groep en cardiovasculair gerelateerd overlijden voor de meerderheid van de sterfgevallen in de overgewicht en obese groepen. Een van de hypotheses die de obesitas paradox zou kunnen verklaren en die ook werd genoemd in hoofdstuk 7 betrof de afname in cardiovasculaire risicofactoren. Aangezien cardiovasculaire mortaliteit echter de hoofdoorzaak was van lange termijn mortaliteit onder patiënten met obesitas, is dit een minder waarschijnlijke verklaring voor de obesitas paradox in deze studie. De paradox in deze chirurgische populatie werd met name bepaald door een afname in kanker gerelateerde sterfte onder patiënten met overgewicht en obesitas. De vraag of dit is veroorzaakt door selectie bias of door kanker specifieke determinanten blijft onbeantwoord door deze studie. Toekomstig onderzoek zou zich wellicht moeten richten op meer accurate metingen van lichaamsvet, bijvoorbeeld taille omtrek, aangezien het bekend is dat de BMI geen goede afspiegeling is van de hoeveelheid lichaamsvet.

CONCLUSIES

Atherothrombose is wereldwijd een belangrijk gezondheidsprobleem en blijft de belangrijkste oorzaak van sterfte in de komende tien jaar. Per definitie hebben patiënten die een vaatchirurgische operatie ondergaan atherothrombose in een vasculair bed, hoewel de prevalentie van polyvasculaire ziekte bij deze patiënten hoog is. Voor patiënten die niet-cardiale chirurgie ondergaan, wordt het risico op postoperatieve cardiovasculaire complicaties geschat met behulp van preoperatieve risico scores, met name de Revised Cardiac Risk Index. Wij hebben de waarde van niet-traditionele risicofactoren, zoals aortaklep calcificatie, ABO bloedgroep, hemoglobine, bloedtransfusies en BMI, op zowel postoperatieve als op lange termijn uitkomsten onderzocht in patiënten die niet-cardiale chirurgie ondergingen en vonden dat, met uitzondering van ABO bloedgroep, elke van deze risicofactoren bijdroeg aan ongunstige uitkomsten. Hoewel de resultaten van onze studies het gebruik van deze 'nieuwe' risicofactoren in de schatting van het risico op postoperatieve cardiovasculaire complicaties en lange termijn sterfte suggereert, is het waarschijnlijk het meest van belang om de onderliggende comorbiditeit welke verantwoordelijk is voor de

negatieve uitkomsten, namelijk coronaire hartziekte, te herkennen en adequaat te behandelen. De primaire focus voor alle patiënten met atherothrombotische ziekte dient zich derhalve te richten op optimale regulatie van risicofactoren middels medicamenteuze behandeling en aanpassing van leefstijl volgens richtlijn aanbevelingen met het oog toekomstige cardiovasculaire incidenten te voorkomen.

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CURRICULUM VITAE

Tabita Maria Valentijn was born in Ter Aar on June 5th 1978. After graduating secondary school at the Groene Hart Lyceum in Alphen aan den Rijn in 1996, she started Medical School at the VU University, Amsterdam. After obtaining her medical degree in 2002, she subsequently worked at the department of Internal Medicine of the Spaarne Hospital in Haarlem, at the department of Internal Medicine of the Groene Hart Hospital in Gouda, and at the department of Cardiology of the Erasmus Medical Center in Rotterdam. Finally, in 2006 she started her residency in Cardiology at the Sint Antonius Hospital, Nieuwegein, under the supervision of dr. Wybren Jaarsma and dr. Jurriën ten Berg. From the beginning of 2011 she was allowed to interrupt her residency for a research period of 2 years. She started a PhD project at the departments of Anesthesiology and Vascular Surgery of the Erasmus Medical Center under the supervision of prof. dr. Robert Jan Stolker, prof. dr. Hence Verhagen and dr. Sanne Hoeks. In September 2013 she will finish her residency in Cardiology.

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Valentijn TM, Galal W, Hoeks SE, van Gestel YR, Verhagen HJ, Stolker RJ.
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The Impact of perioperative red blood cell transfusions on postoperative outcomes in vascular surgery patients.
(Submitted).

PHD PORTFOLIO SUMMARY

Name PhD student:	Tabita M. Valentijn
Erasmus MC Department:	Anesthesiology and Vascular Surgery
Research School:	COEUR
PhD period:	2011-2013
Promotors:	Prof. dr. R.J. Stolker, Prof. dr. H.J.M. Verhagen
Supervisor:	Dr. S.E. Hoeks

PHD TRAINING

	Year	Workload (ECTS)
General academic skills		
- Biomedical English Writing and Communication	Self taught	n.a.
Research skills		
- Research Integrity	2011	2.0
- Basiscursus regelgeving en organisatie voor klinisch onderzoekers (BROK)	2011	0.7
In-depth courses (e.g. Research school, Medical Training)		
- Principles of research in medicine (NIHES)	2011	0.5
- Reveal training (Biotronic)	2011	0.3
- CVOI beeldvorming	2011-2012	0.6
- CVOI nucleaire cardiologie	2012	0.3
- Cardiac MRI	2012	0.3
- Transoesphageale echocardiografie	2012	0.3
- CVOI acute myocarditis en hartfalen	2012	0.3
- Tour d'Horizon	2013	0.5
Presentations		
- Coeur PhD day	2011	0.5
- Poster presentations ESC congress	2011	0.6
- Oral presentation, Cardiometabolic Risk and Vascular Diseases, Rome	2011	0.3
- Oral presentation NVVC	2012	0.3
(Inter)national conferences		
- Nederlandse Vereniging voor Cardiology Congress, biannually	2011-2013	2.4
- European Society of Cardiology Congress, Paris	2011	1.5
- Cardiometabolic Risk and Vascular Diseases, Rome	2011	0.3
- Afscheidssymposium Thijs Plokker	2011	0.3
Seminars and workshops		
- Transthoracic echocardiography	2013	1.0
Other		
- Echocardiography and outpatient clinic	2011-2012	3.0

TEACHING ACTIVITIES

	Year	ECTS
Lecturing		
- Long-term risks and therapy of diabetes mellitus	2011	0.3
Supervising practicals and excursions		
- Echocardiography supervision outpatient clinic	2012	1.0
Supervising Master's theses		
- MSc student Leiden University (Jaap van Waning)	2011	0.6

Stellingen
behorende bij het proefschrift:

NOVEL INSIGHTS IN PERIOPERATIVE CARE

1. Aortaklep calcificatie komt frequent voor bij vaatchirurgische patiënten en is geassocieerd met een verhoogd risico op postoperatieve cardiovasculaire complicaties en nadelige lange termijn overleving. (*dit proefschrift*)

2. Bij vaatchirurgische patiënten zijn zowel matige als ernstige, niet-dialyse afhankelijke chronische nierfunctiestoornissen geassocieerd met aortaklep sclerose. (*dit proefschrift*)

3. Lage postoperatieve hemoglobine waardes waarvoor een bloedtransfusie volgens de richtlijnen niet is geïndiceerd, zijn geassocieerd met een hoog risico op cardiovasculaire complicaties. (*dit proefschrift*)

4. Erytrocyten transfusie in de perioperatieve fase van een vaatchirurgische operatie is gerelateerd aan een verhoogd risico op het optreden van cardiovasculaire complicaties en mortaliteit. (*dit proefschrift*)

5. Op de lange termijn kan de 'obesitas paradox' in een algemeen chirurgische populatie worden verklaard door een afname in kanker gerelateerde sterfte onder patiënten met overgewicht en obesitas. (*dit proefschrift*)

6. Poor lifestyle behaviors, including suboptimal diet, physical inactivity, and tobacco use, are leading causes of preventable diseases globally. However, the optimal population-level approaches to improve lifestyle are not well established. (*Circulation. 2012; 126: 1514-1563*)

7. Pure chocolade is goed voor het humeur, verbetert cognitieve prestaties en heeft een gunstig effect op verscheidene risicofactoren voor hart- en vaatziekten. (*nu.nl*)

8. Despite the "Go Red for Women" campaign, no decrease in time from symptom onset to presentation in female patients with myocardial infarction has been found. (*Am Heart J 2010; 160:80-87*)

9. Gravitation is not responsible for people falling in love. (*Albert Einstein*)

10. Voor vrouwen die een topfunctie ambiëren geldt nog steeds het adagium: 'look like a lady, act like a man and work like a dog'. (*Roger Woddis*)

11. Carpe diem.

Tabita M. Valentijn
Rotterdam, 24 september 2013


NOVEL INSIGHTS IN PERIOPERATIVE CARE
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