Polyvascular Atherosclerotic disease

Echocardiographic and metabolic determinants
of adverse cardiac outcome

Jan-Peter van Kuijk

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Echocardiographic and metabolic determinants of adverse cardiac outcome

Echocardiografische en metabole determinanten van cardiale complicaties bij polyvasculair atherosclerotisch vaatlijden

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Overige leden:	Prof.dr. H.J.M. Verhagen
	Prof.dr.ir. H. Boersma
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Chapter 1

General introduction and outline of the thesis

INTRODUCTION

Peripheral Arterial Disease (PAD) is a multifactorial syndrome that most commonly affects people over 60 years of age.[1] With the aging of the population, the prevalence of atherosclerotic disease and its associated adverse outcomes will increase. It has to be noted that the process of established atherothrombosis is not limited to a single arterial location, giving it the character of a systemic and generalized disease. The Reduction of Atherothrombosis for Continued Health (REACH) registry demonstrated that one out of six patients with (i) PAD, (ii) cerebrovascular disease, or (iii) coronary artery disease had involvement of one or two other arterial beds.[1,2] Importantly, the presence of multiple affected arterial territories, called polyvascular disease, has been demonstrated to be an independent predictor of long-term cardiovascular outcome in the general population.[2-4]

In response to studies demonstrating the adverse prognosis of atherosclerotic disease, the need for adequate risk factor stratification and reduction has emerged. The importance of risk factor reduction in patients with PAD has resulted in universally recommended atherothrombotic risk factor reduction, with the objective of decreasing the high incidence of heart disease and cerebrovascular disease associated with PAD.[5,6] In patients with PAD scheduled for vascular surgery, risk factor stratification is directed at the detection of (a)symptomatic atherosclerotic disease in other vascular beds than the primary symptomatic arterial location. Early detection of polyvascular atherosclerotic disease has important consequences for risk factor reduction strategies, including life-style interventions and medical therapy.

OUTLINE OF THE THESIS

Part I: Prevalence and prognosis

Worldwide more than 230 million major surgeries are performed annually, and this number continuous to grow.[7] Peri- and postoperative complications mainly have a cardiac origin and it is estimated that 1% of the patients (approximately 2.300.000 patients) will have a myocardial infarction. The occurrence of cardiac complications during and after vascular surgery is strongly influenced by the presence of polyvascular disease. In **chapter 2**, a systematic review is performed adressing the prevalence of coronary artery disease in a high-risk population of patients with

abdominal aortic aneurysms. In addition, pathogenesis, risk factors and treatment possibilities are discussed.

Preoperative cardiovascular risk stratification is an important tool to estimate the patients' risk for peri- and postoperative complications.[8] **Chapter 3** discusses the role of ankle-brachial index (ABI) measurements in addition to coronary heart disease risk estimation in a population-based cross-sectional study.

Another important location of atherosclerotic disease is the common carotid artery. Cerebrovascular disease has a major impact on the patients' quality of life and is associated with severe physical and mental impairment. **Chapter 4** described the use of common carotid intima-media thickness measurements for perioperative risk estimation and the occurrence of cardiovascular events.

Several general population-based studies have described the influence of polyvascular disease during a follow-up period up to a maximum of 5 years. **Chapter 5** describes the results of a large study including almost 3000 patients undergoing vascular surgery. At baseline the number of affected vascular beds was determined and long-term prognosis during a follow-up period of 10 years was assessed. In **chapter 6** the same cohort of patients is evaluated for the presence of the so-called obesity paradox, in which underweight patients have an increased mortality risk while overweight is associated with an increased survival.

Echocardiography is an important tool to determine the presence of cardiac involvement in the atherosclerotic process. Left ventricular function describes the mechanical properties of the heart and is commonly used in clinical practice for determining the patients' cardiac risk. **Chapter 7** describes the prevalence and prognostic implications of asymptomatic left ventricular dysfunction in patients scheduled for vascular surgery. **Chapters 8 and 9** focus on the influence of perioperative cardiac ischemia on short- and long-term prognosis after vascular surgery.

Part II: Diabetes mellitus

Patients with PAD have a high prevalence of diabetes mellitus (DM). Diabetes mellitus (DM) is currently affecting over 40 million people in the European Union alone.[9] Importantly, the prevalence of DM is strongly related to age and the presence of atherosclerotic disease. Atherosclerosis is associated with an increased risk of insulin resistance, resulting in an increasing number of pre-diabetic PAD patients. The presence of DM is an important risk factor for cardiovascular

complications during and after surgery.[8] **Chapter 10** systematically reviews the prevalence of DM in vascular surgery patients. In addition, the current available literature for blood sugar monitoring and control during the perioperative phase is discussed.

The strong relation between atherosclerotic disease and DM has emerged the need for earlier detection of DM in vascular surgery patients. **Chapter 11** describes the role of two pre-operative testing methods for the detection of glucose regulation disorders (pre-diabetes) or DM.

The metabolic syndrome, also known as the insulin resistance syndrome or Syndrom X, is the concurrence of multiple metabolic abnormalities associated with cardiovascular disease. In the general population the prevalence of metabolic syndrome is 9 to 22%, and increases up to 50% in patients with known cardiovascular disease.[10,11] In **Chapter 12** the prevalence and prognostic implications of metabolic syndrome in a high-risk population of patients with occlusive and aneurysmatic PAD are evaluated.

Diabetes mellitus and left ventricular dysfunction have been separately associated with increased long-term mortality rates.[12] Treatment possibilities for systolic left ventricular dysfunction are well defined; however, there are few data available for the treatment of diastolic dysfunction. Consequently, it is important to know if there are differences in prognosis between systolic and diastolic dysfunction. In **Chapter 13** the influence of left ventricular dysfunction on long-term prognosis in patients with or without diabetes is discussed.

Part III: Renal disease

Chronic kidney disease (CKD) is a worldwide public health problem with poor outcomes and high costs and patients with PAD frequently have concomitant CKD.[13] Importantly, patients with CKD also frequently have associated cardiovascular disease, which is demonstrated by the fact that patients with CKD are more likely to die from a cardiovascular event than to develop kidney failure.[14] As the process of atherosclerotic disease is extended to the renal vasculature as well, we evaluated the prevalence and prognostic implications of polyvascular disease in a sub-cohort of vascular surgery patients with known CKD prior to surgery. These results are reported in **Chapter 14.**

Acute kidney injury is a common and serious complication in hospitalized patients and is associated with a high rate of in-hospital morbidity and mortality.[15]

Although episodes of acute kidney injury seem to be reversible, there is a silent, ongoing inflammatory and fibrotic process, that leads to structural kidney damage.[16] This process predisposes to a more rapid decrease in glomerular filtration rate, which is a well known risk factor for incident chronic kidney disease. In **Chapter 15** the association between temporary declines in renal function after vascular surgery and the development of CKD during long-term follow-up is assessed. In **Chapter 16** the influence of preoperative left ventricular dysfunction on the risk of postoperative acute kidney injury and long-term outcome is evaluated.

Phosphorus is essential for multiple and diverse biological functions, and it has been acknowledged as a marker of renal disease. There has been considerable interest in the relation between serum phosphorus levels and long-term cardiovascular outcome in several populations.[17,18] However, no studies evaluated short-term postoperative outcome. **Chapter 17** describes the results of a study that evaluated the predictive value of preoperative phosphorus levels on 30-day outcome after vascular surgery.

Part IV: Risk reduction strategies and future perspectives

Once cardiac risk has been assessed before surgery, risk reduction strategies to reduce perioperative and long-term complications have to be initiated. In part four of this thesis several possible risk reduction strategies are discussed, including (i) pharmacological therapy with statins, β-blockers, antiplatelet agents, and (ii) prophylactic coronary revascularization. In **Chapter 18** a systematic review of the current available literature regarding the influence of statin therapy on the expansion rate and rupture risk of patients with an abdominal aortic aneurysm is performed.

The presence of extensive coronary artery disease in patients scheduled for vascular surgery is an important risk factor for perioperative and early postoperative complications. However, results from two randomized, controlled trials demonstrated no benefit derived from preoperative revascularization on immediate postoperative outcome.[19,20] **Chapter 19** describes the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography-V trial, which assessed the potential long-term benefit of preoperative revascularization in high-risk vascular surgery patients. **Chapter 20** evaluated the double-edged sword on the prevention of cardiac complications versus the risk of severe bleeding complications in patients with dual antiplatelet therapy scheduled for noncardiac surgery.

Preoperative pharmacological therapy using β-blockers is recommended by the recent European Society of Cardiology guidelines addressing perioperative care.[21] Although multiple observational studies and randomized, controlled trials have been performed to evaluate the effect of perioperative β-blocker treatment, the duration of β-blocker treatment before surgery and its effect on cardiovascular outcome has not been evaluated yet.[22,23] In **Chapter 21** three different timing protocols for β-blocker therapy initiation are described, including the influence on preoperative heart rate, high-sensitive C-reactive protein levels, and postoperative outcome.

Future perspectives include the development of new diagnostic and therapeutic strategies in vascular medicine. Nowadays, screening for abdominal aortic aneurysms is not routinely performed. The high costs associated with routine conventional ultrasound and the need for well trained staff is the most important disadvantages. In **Chapter 22** the early results of a new portable ultrasound scanner, developed for abdominal aortic aneurysm screening, are described.

Chapter 23 focusses on the use of a new treatment modality, called remote ischemic preconditioning. An overview is given of the current medical treatment possibilities for patients undergoing vascular surgery, and the additional value of remote ischemic preconditioning is addressed.

Patients undergoing vascular surgery are characterized by a high prevalence of perioperative ischemia reflected by an asymptomatic release of troponin T. Nowadays, asymptomatic cardiac ischemia is not treated, although late outcome hereafter is severely compromised. **Chapter 24** describes the design of a new trial in which patients are randomized to either clopidogrel or placebo for the treatment of asymptomatic perioperative troponin T release after vascular surgery.

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PART I

PREVALENCE AND PROGNOSIS

Chapter 2

Coronary artery disease in patients with abdominal aortic aneurysm

Jan-Peter van Kuijk
Willem-Jan Flu
Martin Dunkelgrun
Jeroen J. Bax
Don Poldermans

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INTRODUCTION

Abdominal aortic aneurysms (AAA) and coronary artery disease (CAD) have traditionally been regarded as two separate vessel disorders with a common background. Atherosclerosis has always been considered as the basic pathophysiologic process. However, during the last decade, evidence has emerged with differences between AAA and CAD. Firstly, data regarding the prevalence of AAA and CAD are different. Secondly, the risk profiles between AAA and CAD differ, mainly regarding gender, age and diabetes mellitus. Thirdly, despite the intensive treatment of CAD and improved outcome, the prevalence of AAA has not changed during the last decade. In this review we will discuss the characteristics of CAD in patients with AAA. In the first part we focus on epidemiological data of CAD in AAA patients. The pathophysiology of both AAA and CAD will be described in the second part. There is a common pathway between pathophysiology and risk profiles that is discussed in the third chapter. Based on the presence of risk factors and their influence on cardiovascular events, the preoperative work-up and testing for CAD in AAA has gained an important role. The role of (non)-invasive testing will be described in the fourth chapter. The treatment of AAA traditionally consisted solely of surgery. However, due to the influence of CAD on adverse outcomes, medical intervention is potentially useful. Surgical approaches for the treatment of both AAA and CAD, and most importantly, their influence on long-term outcome will be discussed in the fifth chapter.

EPIDEMIOLOGY

Prevalence of diseases in the general population is investigated by population-based screening studies. However, the prevalence of AAA and concomitant cardiovascular disease is difficult to determine, as there is a lack of objective data. Current data suggest that many individuals with AAA suffer from co-existing atherotrombotic risks such as coronary heart and cerebrovascular disease. (*Figures 1 to 3*)

Subjective data

The REACH registry included 68.236 patients with established CAD, CVD, PAD or at least three atherotrombotic risk factors.[1,2] At baseline 1.722 (2.52%) patients had known AAA as well, and no screening for AAA was performed in the remaining patients. This large registry provides subjective data about the concomitant presence of CAD and AAA. Data on the incidence of AAA in the general population is limited. Due to increased life expectancy, the incidence is increasing.[3] However;

two other aspects have influenced the incidence as well. Firstly, during and about a decade after the Second World War, the risk profile changed because of changes in smoking habits. Secondly, the easy availability of ultrasound diagnostic tools nowadays, has increased the identification of asymptomatic AAA.

Figure 1. *Prevalence of AAA in patients with established CAD*

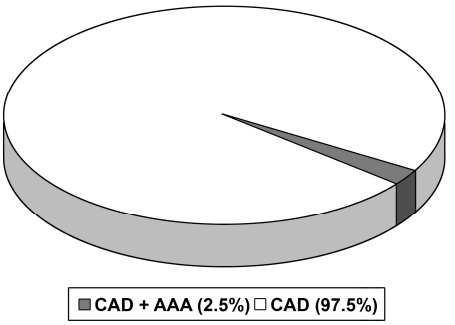
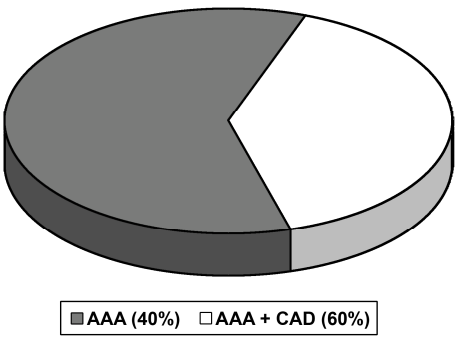


Figure 2. *Prevalence of CAD in patients with established AAA*



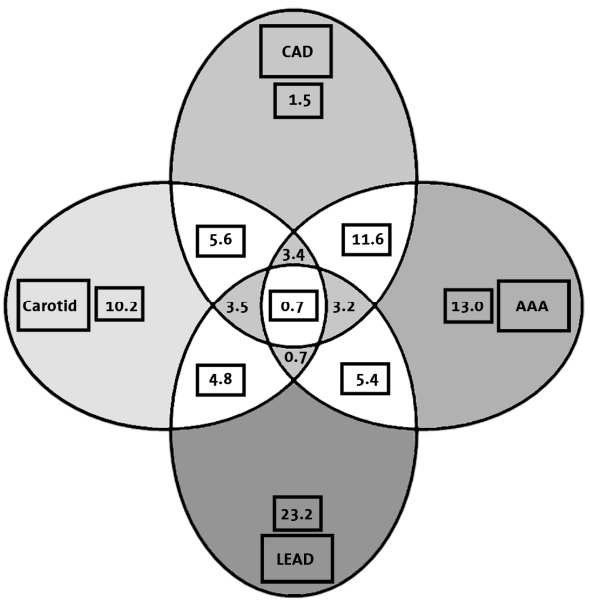
Objective data

Screening studies provide objective data regarding the prevalence of AAA. A Norwegian population-based study of 6.386 civilians, showed a prevalence of AAA in 263 (8,9%) men and 74 (2,2%) women, respectively.[4] The prevalence of AAA varies with gender and is roughly three times higher in men then that it is in women. Age is the most influential factor on prevalence. About 6% of men have an aortic diameter of more than 2.9 cm by the age of 65 years, with an estimated increase in prevalence of 6% per decade.[5] A meta-analysis of 14 population-based screening studies, including 110.000 patients, showed a prevalence ranging from 4.1% to 14.2% in men and 0,35% to 6,2% in women.[6] The prevalence of CAD in patients with AAA is analyzed more accurately by cardiovascular testing. In 1984, Hertzer was the first to describe the strong relationship between abdominal aortic aneurysms and CAD.[7] Coronary angiography (CAG) was performed in 1.000 patients with a primary peripheral vascular diagnosis. In 263 patients the primary diagnosis was AAA. Severe, correctable CAD was present in 81 patients (31%). Only 16 patients (6%) were classified as having normal coronary arteries. Several other studies analyzed the prevalence of CAD in AAA by performing CAG as well. As shown in *Table 1*, the average prevalence of CAD in patients with established AAA varies between 31 to 90%.

ETIOLOGY

Aortic aneurysms can be occlusive, aneurysmatic or a combination. Most AAA are called non-specific, as no direct pathogenic mechanism can be identified. Traditionally, AAA has been regarded as a consequence of atherosclerosis, mainly because it is invariably associated with atherosclerotic wall damage, supported by the presence of risk factors such as age, male gender, smoking, hypercholesterolemia, hypertension and a positive family history.[8] Recently, the REACH trial investigators analyzed these risk factors and found distinctions between CAD and AAA in cardiac risk profiles that were already proposed in the last decade.[1]

Figure 3. *The presence of concomitant vascular disease. Data are based on analysis of our own vascular surgical population*



Abbreviations: AAA; Abdominal Aortic Aneurysm, CAD; Coronary Artery Disease, Carotid; Carotid surgery or a history of cerebrovascular disease, LEAD: Lower Extremity Arterial Disease

In 1992, Tilson was the first to propose different pathogenic mechanisms, compared to athero-occlusive disease.[9] In 2003, Lederle *et al.* summarized the following aetiologic differences between AAA and CAD: (i) patients with severe systemic or aortic occlusive disease do not primarily have aortic aneurysms, (ii) aortic aneurysm has greater male predominance, (iii) aortic aneurysm is often

familial and occurs in genetic diseases unrelated to occlusive disease, and (iv) aortic aneurysm is uncommon in patients with diabetes mellitus.[10-13] This supports the hypothesis that AAA may represent arterial disease with an inherent pathophysiology. Specific causes of aneurismal dilatation include infection, mycotic aneurysms, trauma and connective tissue disorders (Ehlers-Danlos type IV, Marfan Syndrome).[14]

Table 1 **Prevalence of CAD in populations with established AAA**

	AAA*	CAG**	CAD prevalence		Defined stenosis***
Hertzer [7]	263	263 (100%)	Mild	58% (144pt)	>50%
			Moderate	31% (81pt)	
			Severe	5% (12pt)	
Bayazit[15]	125	125 (100%)	Mild	25% (31pt)	>70%
			Moderate	22% (28pt)	
			Severe	6% (7pt)	
Kishi[2]	102	102 (100%)		65% (66pt)	>75%
Islamoglu[8]	81	43 (53%)		84% (36pt)	Unknown
Kioka[9]	94	94 (100%)		46% (43pt)	>75%
Kieffer[10]	133	84 (63%)		43% (36pt)	>70%
Sukhija[11]	110	78 (71%)		90% (70pt)	>50%
Takahashi[16]	159	145 (91%)		27% (43pt)	>75%
Total	908	789		45% (total CAG)	Variable
				47.5% (total pt)	

** Number of patients with established AAA. ** Number of patients in whom a CAG was performed. ***Definition of percentage of coronary artery stenosis.*

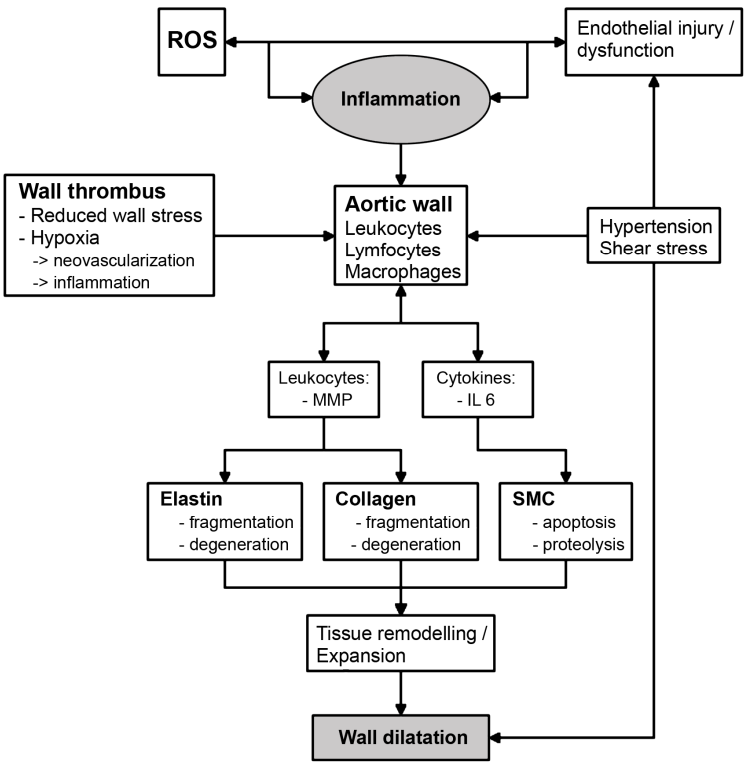
PHYSIOLOGY

Mechanical properties of the aortic wall are provided by elastic fibers and fibrillar collagen. The viscoelastic properties of the aortic wall are created by the formation of a network of elastic fibres, together with associated proteins. The network is stabilized by cross-links, which can be degraded by specific proteases. Together with smooth muscle cells (SMC), elastic fibers are most abundant in the medial layer of the aortic wall. Another significant component of the media and the surrounding fibrious adventitia is collagen. Structural integrity of the vascular wall is provided by two types of fibrillar collagen, namely type I and III. A third component, which is involved in the organisation of the aortic wall, are proteoglycans.[14]

PATHOPHYSIOLOGY

AAA development is clearly associated with connective tissue alterations in the aortic wall. The pathophysiologic process of both CAD and AAA contain several shared factors, of which the process of atherosclerosis is regarded as the most important. The process of atherosclerosis leads to either aortic occlusive, aneurysmatic or a combined disease (*Figure 4*). The generally accepted starting point for the process of atherogenesis is an injury of the vascular endothelium.[15] Contributing factors are infection, shear stress forces, angiotensin II, increased oxidative stress and cytokine release. This combination leads to endothelial activation and dysfunction.[16]

Figure 4. *Schematic representation of the inflammatory processes leading to aortic wall dilatation*



Abbreviations: ROS; reactive oxygen species, MMP; matrix metalloproteinases, IL-6; Interleukin 6, SMC; smooth muscle cells

Inflammation

The major process mediating accelerated progression of atherosclerosis and its complications is inflammation.[15] Supporting evidence for this association includes

an increase in CRP levels and a local influx of inflammatory cells into the aortic wall.[17] Atherosclerotic plaques are characterized by an accumulation of intracellular lipid droplets and formation of foam cells.[15] AAA have a lymphomonocytic infiltrate in the arterial wall as well. This infiltrate consists of inflammatory cells in the media and adventitia, derived from aortic blood and from medial neovascularisation.[17] Histological features of aneurismal tissue are: (i) fragmentation of the elastic fibers, and (ii) decreased concentration of elastin. The loss of elastic fibres seems to be an early step in the pathophysiological process of developing an AAA. Mycotic aneurysms develop through localized inflammation of the aortic wall. This process of inflammation is different from that in atherosclerosis, although both can lead to aneurysmatic dilatation.

Matrix metalloproteinases

Matrix Metalloproteinases (MMP) are the most potent proteolytic enzymes that degrade elastic and collagen fibres. Infiltrating leukocytes are important sources of MMP and serine proteases. These degrade elastin and collagen, thereby weakening the aortic wall.[18] As a defence mechanism, tissue inhibitors of MMP are increased in the aneurysm wall as well.[19] Unfortunately, as the process progresses, the balance between proteases and antiproteases favors the proteolysis.[20]

Smooth muscle cells

The infiltration of immune cells into the aortic wall exacerbates tissue injury through release of cytokines, such as Interleukin-6 (IL-6). This will lead to recruitment of immune cells and the induction of smooth muscle cell apoptosis. Reduction of SMC density in the elastic media is a key event in aneurysmatic dilatation. Physiologically, SMC have a protective influence on inflammation and proteolysis.[21] However, proteinases released from dying SMC, contribute to further matrix degeneration.[22]

Thrombus formation

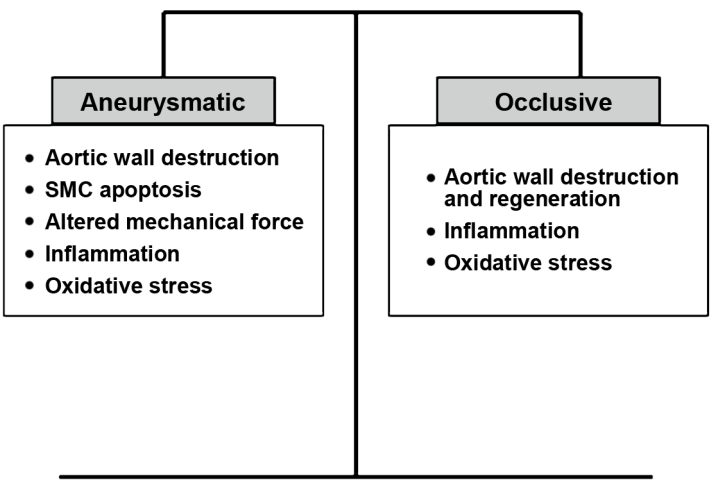
In CAD patients, thrombus formation is an important step in plaque instability. In AAA, most patients have an associated mural thrombus as well. As blood flow is maintained there is persistent remodelling of the thrombus components. On one hand, the thrombus can reduce aneurismal wall stress. On the other, its increasing thickness leads to local hypoxia at the inner layer of the media. This results in increased medial neovascularisation and inflammation.[23] Fontaine *et al.* showed that plasminogen and its activator (uPA) are present in the thrombus of the aneurismal wall, which might result in local generation of plasmin, an activator of MMP.[24]

Oxidative stress

Oxidative stress can be defined as tissue damage occurring secondary to increased production and/or decreased destruction of Reactive Oxygen Species (ROS). ROS play causal roles in many chronic (inflammatory) disease states, including atherosclerosis and hypertension.[25] Localized inflammatory responses enhance the production of ROS, leading to progressive cell and tissue damage. Increasing evidence points to these factors in the pathogenesis of AAA.[17] The influence of ROS is widespread in the process of inflammation, including the activation of MMP and the plasminogen-plasmin system. In the case of MMP activation, ROS acts as a promoter of further wall degeneration. However by activating the plasminogen-plasmin system, oxidative stress can activate Plasminogen Activator Inhibitor type 1 (PAI-1). This is an endogenous inhibitor of plasminogen, which is decreased in human aneurismal aortic wall tissue. The activation of PAI-1 by oxidative stress may serve to oppose vascular remodelling, thereby limiting AAA progression.[26]

In conclusion, the pathogenesis of CAD and AAA share several aspects, in which atherosclerosis plays a pivotal role. Insights regarding the differences in pathophysiological backgrounds between AAA and CAD are changing. Processes involved in further development of either occlusive or aneurysmatic diseases consist at least of an imbalance between: i) destruction and regeneration of the aortic wall by enhanced matrix proteolysis, ii) increased SMC apoptosis, iii) altered mechanical forces, and iv) most importantly the process of inflammation. All these processes are strongly influenced by oxidative stress (*Figures 4 and 5*).

Figure 5. *Schematic representation of the factors influencing the imbalance between aneurysmatic and occlusive aortic disease. SMC: smooth muscle cells*



RISK FACTOR PROFILES

The cardiovascular risk profile is well established. Not all patients with atherosclerosis develop an AAA, therefore it is conceivable that the pathophysiology and risk profile of AAA are different. Supporting evidence for a distinct cardiovascular risk profile between AAA and established atherotrombotic disease like CAD and PAD has been provided.[10,11,13]

Gender and age

The prevalence of AAA increases with age. Epidemiological screening studies have identified age and male gender as non-modifiable risk factors for AAA. The REACH trial found that patients with AAA were significantly more often male and older, compared to patients without.[1] The ADAM Program included 126.196 veterans, mean age 66 years, without a history of AAA.[10,11] An AAA of 3,0 cm or larger was detected in 5.283 participants (4.2%). Again, risk factor analysis identified male gender and age to be strongly associated with the development of AAA. On the contrary, female gender had a negative association with AAA. Coronary artery disease and AAA share the same relationship regarding age, but not gender.

Genetics

Familial clustering of abdominal aortic aneurysms has drawn attention to a possible genetic background of the disorder. Monogenic disorders associated with an increased risk of aortic aneurysm, like Marfan´s Syndrome and Ehlers-Danlos, are rare. In 1977, Clifton suggested AAA as one of the most common familial diseases.[27] In first degree relatives, the frequency of the disorder was 15-19% compared to only 1-3% in unrelated patients.[28] Three important aspects create a high suspicion of familial AAA. When the proband is: (i) female, (ii) young, and (iii) AAA rupture is present. Kuivaniemie *et al.* provided a multinational study with 233 families including 653 affected members.[28] The inheritance mode was autosomal recessive in 72% of the families and autosomal dominant in 25%.[28] Having a first-degree relative with an AAA was associated with an odds ratio of 1.9 to 2.4 for developing an AAA.[29] Several candidate genes on chromosome 19 have been proposed, such as LDL related protein 3 (LPR3).[30] However, no concluding genetic profile can be established at this moment. To study the genetic associations, very large numbers (up to 12000 for alleles present in 5% of the population) of patients are required.[31] Currently, ongoing multi-center studies are generating data. These will possibly identify candidate genes, which play a crucial role in the development of AAA.

Hyperlipidaemia

High levels of serum cholesterol and other lipids have an established role in the pathogenesis of atherosclerosis. In the ADAM trial, an odds ratio of 1.44 (95% CI: 1.27 to 1.63) was found for the association of high cholesterol levels and AAA.[10] A positive correlation between a history of, or treatment for, high serum total cholesterol and LDL-cholesterol concentrations and the presence of AAA was shown in screening studies.[32-34] However, in 1995, the Rotterdam study showed a negative correlation.[35] A very strong relation between low HDL cholesterol levels and a high risk for AAA in both genders was shown by Singh.[4] The risk of having an AAA was 70 percent lower in subjects with HDL cholesterol levels ≤1.20 mmol/L. A weak relation was found between high serum total cholesterol and AAA, and no relation was found between serum triglyceride (TGC) levels and risk for AAA.[4]

Diabetes mellitus

The ADAM program found that diabetes, together with female gender and black race, had a negative association with the development of AAA. As diabetes is a clinical risk factor for atherosclerosis, this finding surprised the investigators.[10] However as described above, the pathophysiology of AAA is only partly associated with the process of atherosclerosis. The effect of diabetes on the vessel wall mainly includes an increasing stiffness. Mainly, this effect is present in the medial layers of the peripheral arteries. It has been proposed that increasing stiffness could stabilize the aorta and resist aneurysmatic dilatation. However, in AAA patients, aortic stiffness was found to be increased as well.[36,37] This relatively surprising negative association was, however, confirmed by several leading studies.[1,6,29] In our own analysis we found a negative association of DM with AAA as well. The investigators of the REACH trial suggested a difference in abdominal aortic wall constitution between diabetic and non-diabetic individuals.[1] However, to our knowledge no clear pathophysiological explanation for the negative relationship between diabetes and AAA has been provided.

Hypertension

The main pathophysiological effect of hypertension is directed by increased shear stress on the arterial wall. The increased mechanical stretch induces production of ROS by the SMC. Reactive oxygen species induce mobilization of pressure normalizing chemokines and inflammatory parameters. However, as described above, ROS has detrimental effects on blood pressure by a multitude of possible mechanisms.[25] These mechanisms play a leading role in the process of atherosclerosis and are suspected to play a role in the pathogenesis of AAA as well. Studies regarding the role of hypertension as a risk factor for AAA have varying results. On the one hand, because the definition of hypertension is often based on

whether the patient is receiving treatment for this condition or not. On the other hand, because the understanding of the pathophysiological processes have changed. Previously, it was assumed that hypertension was an established risk factor for AAA, both in the pathogenesis and risk of rupture.[38] Vardulaki found a strong role of hypertension in the development, growth rate and risk of rupture of AAA.[39] Current or former use of antihypertensive medication was associated with an increased risk of AAA in both genders in a study by Singh *et al.*[4] They found odds ratios in men and women of 1.61 (95% CI: 1.16 to 2.24) and 2.02 (95% CI 1.14 to 3.57), respectively. In the ADAM screening program, an odds ratio of 1.23 (95% CI 1.14 to 1.32) was detected.[10] However, current prospective studies have shown a relatively weak association of hypertension with AAA prevalence.[10,33,39,40] Recently, the REACH trial showed an increased mortality in patients with AAA and current high blood pressure.[1] Nowadays, the possible explanation is that hypertension is a poor predictor for the development of AAA in the general population, but an important risk factor for expansion and rupture.[41]

Tobacco smoking

Smoking is the most important and well established risk factor for AAA. However, the mechanisms between smoking and AAA formation remain, at least in part, unknown. Smoking leads to endothelial damage of the arterial wall, with a subsequent inflammatory process and plaque formation. Aortic wall elasticity decreases as smoking stimulates elastase and MMP production by macrophages.[36,42] However, smoking also promotes coronary and cerebral vascular disease through a variety of other mechanisms. These include: i) adverse effects on lipids, ii) hemodynamic stress, iii) oxidant injury, iv) enhanced thrombosis, and v) increased blood velocity. In several large studies, smoking was the most important variable associated with an increased risk of AAA development.[2,4,6,11,41,42] Additional studies compared a history or current smoking to non-smoking in AAA development. Odds ratios for this risk between current smokers and non-smokers varied between 2.89 and 8.0 (95% CI 2.63 to 12.6).[4,6] In a systematic review the relative risk of smoking for aortic aneurysms was compared to that for CAD, cerebrovascular disease and PAD.[43] Relative risk for aortic aneurysms in current smokers was generally 3 to 6, compared with 1-2 for CAD and cerebrovascular disease. These differences in risks have negative implications for the theory of a common cause of vascular disease and aortic aneurysms. This relation was confirmed in the ADAM trial. After adjusting for smoking habits, both trials showed a modest independent association between atherosclerosis and aortic aneurysms. The duration of smoking habits reveals a stronger odds ratio for AAA than the number of cigarettes smoked daily.[39] Wilmink *et al.* found a clear dose-response relationship with the duration of smoking.[42] Each year smoked, increased the

relative risk by 4% (95% CI 2 to 5%). Ex-smokers are 3 times more likely to develop an AAA compared with non-smokers. The effect of smoking cessation has been investigated as well, and showed a slow decrease in risk for AAA of 4% per year. Singh *et al.* stated that the risk of AAA after 20 years of smoking cessation was not statistically significant different from the risk of current smokers.[4] This relative slow decline in risk after cessation of smoking differs strongly between AAA and CAD. Patients with CAD, who stop smoking, reduce their risk of myocardial infarction by up to 50% in 1 year. Their remaining risk approaches that of those who never smoked after 10 years. However, although there is a relative slow decrease in the risk of AAA development, more and more attention is given to the importance of smoking cessation. This has important consequences for AAA prevention, decreasing the growth rate and declining the risk of rupture.

SURGICAL TREATMENT AND RISK STRATIFICATION

Surveillance interval

Rupture of an AAA leads to death in 65-85% of the patients.[38,42,44-46] Elective surgical treatment of AAA consists of open surgical repair or endovascular stenting of the aneurysm. Timing of the procedure depends on: (i) aortic diameter, (ii) expansion rate, (iii) symptomacity, (iv) concomitant disease leading to perioperative mortality, and v) general health status. The American Society of Cardiology (ACC) / American Heart Association (AHA) guidelines and the Trans-Atlantic Inter-Society Consensus (TASC) provided a Class I recommendation (level of evidence: B) for the repair of infrarenal or juxtarenal AAA measuring 5.5 cm or larger. Intervention is not recommended if they measure a diameter of less than 5.0 cm in men and 4.5 cm in women, respectively (Level of Evidence: A).[47,48] The expansion rate differs between patients and is influenced by high blood pressure, smoking and inflammatory processes.[25,39,46] Evidence from two studies suggests that one-time ultrasound screening of men, at the age of 65 years, is sufficiently to identify nearly all those who are at risk.[49] Surveillance intervals differ between studies, mainly based on the use of varying criteria. The ACC/AHA recommends ultrasound or computed tomography (CT) scans every 6 to 12 months for AAAs measuring 4.0 to 5.4 cm in diameter.[47] However, other studies suggested an interval of 12-24 months for asymptomatic aneurysms smaller than 5.0 cm.[8,50,51]

Risk stratification

Pre-operative risk stratification and screening is performed in the presence of concomitant disease. The high frequency of perioperative cardiac complications reflects the high prevalence of underlying coronary artery disease [CAD].[7] Autopsy

studies demonstrated that in more than 50% of perioperative MI cases, a coronary plaque rupture could be identified at the site of MI.[52,53] It is now generally accepted that coronary plaque rupture leading to thrombus formation and subsequent vessel occlusion is an important cause of perioperative MI. Patients undergoing major vascular surgery (MVS), such as open or endovascular abdominal aneurysm repair, are at high-risk of developing postoperative myocardial complications.[54] During surgery there is an increased cardiac oxygen demand. In combination with perioperative tachycardia and increased myocardial contractility, this can result in an oxygen supply–demand mismatch in patients with coronary artery stenosis. Currently, the predominant theory holds that postoperative MI is triggered by surgical stress, caused by high catecholamine production associated with the following factors: (i) haemodynamic stress, (ii) vasospasm (iii) reduced fibrinolytic activity, (iv) platelet activation and (v) consequent hypercoagulability.[54] Postoperative cardiovascular outcome in patients undergoing MVS is influenced by cardiovascular risk factors, including: age >70, diabetes, MI, coronary revascularization, congestive heart failure, type of surgery and renal insufficiency.[55] The great majority of cardiac events in patients undergoing MVS are asymptomatic. Biagini *et al.* noted that in at least 69% of patients who experienced coronary artery disease by dobutamine echocardiography, silent ischemia was present.[56] In the growing elderly population, many major surgical interventions are performed in patients with increasing age, leading to an increased incidence of cardiovascular risk factors. In future times, a progressive influence of the patient's risk profile towards cardiovascular disease is to be expected with great impact on postoperative survival, especially in patients undergoing MVS such as open or endovascular abdominal aneurysm repair.

PREOPERATIVE SCREENING

In addition to risk stratification by obtaining the patients history and physical examination, preoperative screening and treatment is performed. Laboratory investigation includes assessment of the biomarkers N-terminal pro-B-type natriuretic peptide (NT-proBNP), High sensitive CRP (HsCRP) and cardiac troponin T. Recent studies showed that an increased plasma level of NT-proBNP is associated with adverse postoperative outcome, as it is a marker of left ventricular dilatation caused by fluid overload (e.g. CHF and renal dysfunction), pressure overload (e.g. aortic valve stenosis), cardiac arrhythmias and myocardial ischemia.[57] HsCRP is an inflammation marker for determining heart disease risk in those with undetected heart disease and risk of complications for those who have already had a cardiac event. Cardiac troponin T is a very sensitive and specific

indicator of myocardial damage. It is an important marker of all heart muscle damage, not only myocardial infarction.

Non-invasive cardiac testing

The REACH trial found an increased risk of 1.4 - 14.1% for adverse cerebro-cardiovascular events in AAA patients. Therefore, non-invasive cardiac testing is performed to assess: (i) the presence of ischemia, (ii) valve abnormalities, and (iii) left ventricular function. Tests can be performed in rest or during exercise, either by physiological stress or pharmacological induced stress.

Resting / Ambulatory ECG

A resting electrocardiogram (ECG) is performed to assess a baseline for the detection of ECG changes during the peri- and postoperative period. However, as this is a one-moment measurement, ambulatory (Holter) ECG monitoring can also be performed. The advantages of this test are that it is cheap and widely available. However, the presence of resting ECG changes (bundle branch block, left ventricular hypertrophy) may influence reliable ST segment analysis.

Exercise ECG

Exercise ECG's are performed either during treadmill walking or bicycle ergometry. Conventional exercise ECG is considered the most physiological form of stress. Compared to other non-invasive tests, exercise ECG has shown reasonable sensitivity and specificity for the prediction of perioperative cardiac complications.

Resting echocardiography

Without directly visualizing (most of) the coronary arteries, echocardiography has proven to be an excellent diagnostic tool in the detection and quantification of CAD. With two-dimensional transthoracic echocardiography ischemic segment 1 wall motion abnormalities can be detected. Visual assessment categorises wall motion as being normal or abnormal, in which wall motion abnormalities can be further characterized as hypokinetic, akinetic, or dyskinetic (*Table 2*). Although there is tremendous variability in the coronary artery blood supply to the myocardium, a model with 17 myocardial segments is recommended by the American Society of Echocardiography for visual interpretation of regional left ventricular wall motion abnormalities.[58] Therefore individual myocardial segments can be assigned to one of the 3 major coronary arteries with recognition that there is anatomic variability. Wall motion abnormalities at rest represent scarred myocardium caused by transmural infarction in which the epicardium is involved (STEMI). However, myocardial segments can have a normal function at rest and develop wall motion abnormalities during exercise or stress.

Stress echocardiography

During exercise or stress the myocardial oxygen demand is increased and ischemia occurs in patients with coronary artery stenosis. When cardiac myocytes are damaged, but still viable, they become dysfunctional. This dysfunctionality is a reversible process, characterized by an oxygen demand-supply mismatch. With the use of stress echocardiography this mismatch can be observed by: (i) detecting reversible ischemia, (ii) distinguishing ischemia from fixed wall motion abnormalities, and (iii) identifying regions supplied by a specific coronary vessel. When stress testing induces ischemia, it permits wall motion analysis during stress with the use of exercise or pharmacologically induced stress. As most patients with vascular disease are not able to reach sufficient exercise, stress echocardiography with the use of a pharmacological stressor is often used. During stress testing, either dobutamine or dipyridamole is administered. Prior to infusion of the stressor, images are recorded which serve as a baseline for comparison with stress images. Many reports have demonstrated that Dobutamine and Dipyridamole Stress Echocardiography (DSE) can predict perioperative events in patients undergoing vascular surgery.[59] Both tests have a high negative predictive value, however the positive predictive value is much lower. Kertai *et al.* reported a weighted sensitivity of 85% (95% CI: 74 to 97%) and a specificity of 70% (95% CI: 62 to 69%) for dobutamine stress echo in 850 patients from 8 studies.[60] Dipyridamole stress echo showed a similar high sensitivity, but a significantly lower specificity. For this reason, dobutamine stress echocardiography is preferred in clinical practice, unless patients have serious arrhythmias, severe hypertension or hypotension.

Table 2	**Regional wall function at rest**	
Normal	Normal inward systolic motion	4-10 mm systolic thickening
Hypokinesia	Reduced inward systolic motion	Reduced systolic thickening
Akinesia	Absent inward systolic motion	Absent systolic thickening
Dyskinesia	Abnormal outward systolic motion	Systolic thinning

Classification of wall function at rest in echocardiography

Radionuclide Ventriculography

Radionuclide ventriculography is used to assess the left ventricular ejection fraction. It is useful for measuring resting and exercise ejection fraction in CAD and valvular heart disease. A preoperatively assessed low ejection fraction (<35%) has a proven value for the prediction of perioperative cardiac complications. Compared to other tests, radionuclide ventriculography did not have a better predictive performance. Radionuclide ventriculography has been largely replaced by echocardiography, which is less expensive, does not require radiation exposure, and theoretically can measure ejection fractions as accurately.

Myocardial perfusion scintigraphy

Myocardial perfusion scintigraphy (MPS) has been widely used for the evaluation of patients undergoing vascular surgery and serves as a valuable diagnostic tool in preoperative risk stratification. The major goal of noninvasive risk stratification with MPS is to identify patients at high-risk for developing unrecognized myocardial infarction or myocardial ischemia during surgery. Nuclear imaging differs from other imaging techniques by focusing on physiologic processes in the left ventricle myocardium instead of anatomy. Both Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) scanners globally assess left ventricle function by detecting gamma radiation emitted by radiotracers, which are administrated intravenously in a small quantity. The detection of coronary artery disease is based on a difference in blood-flow distribution through the left ventricle myocardium. These perfusion abnormalities can be explained by insufficient coronary blood-flow based on coronary artery stenosis. In patients with significant CAD and transmural MI, a reduced radiopharmaceutical signal is observed after maximal vasodilatation due to a decrease or loss in regional perfusion. Myocardial perfusion scintigraphy is a diagnostic tool with low specificity, however the negative predictive value derived from a normal scan is high in predicting future myocardial infarction and cardiac death. A meta-analysis conducted by Kertai *et al.* reported a sensitivity of 83% (95% CI, 77% to 89%) and a much lower specificity of 47% (95% CI, 41% to 57%) for thalium-201 MPS to predict perioperative cardiac events.[60]

Table 3 **Non-invasive testing**

Type of test	Sensitivity (%)	Specificity (%)
Resting ECG	50 (32-69)	91 (87-96)
Exercise ECG	52 (21-84)	70 (57-83)
Rest Echocardiography	74 (60-88)	69 (60-78)
Stress Echocardiography	74 (53-94)	86 (80-93)
Radionuclide Ventriculography	73 (77-89)	49 (41-57)
Myocardial perfusion scintigraphy	85 (74-97)	70 (62-79)

Summary of sensitivity and specificity of non-invasive tests. Adjusted from Kertai et al.[67]

Invasive cardiac testing

Coronary Angiography

Coronary angiography is used for directly visualizing the coronary arteries. With the use of contrast agents, X-ray can directly visualize wall irregularities and occlusive disease. Invasive cardiac testing by CAG is the golden standard for investigating the presence of CAD, and the positive and negative predictive value are high. However, because an arterial access route is needed the risk of

complications is higher as well. Therefore screening has to be performed primarily by non-invasive testing.

Summary
Resting ECG and ambulatory ECG have a relatively low sensitivity and specificity; therefore these tests have a low value in perioperative risk assessment. The ACC/AHA guidelines recommend an exercise ECG in the preoperative phase. However, vascular surgical patients frequently have abnormalities on their resting ECG, and are very often not able to perform adequate exercise. In those patients, stress echocardiography or MPS should be considered. Kertai *et al.* reported a similar sensitivity for dobutamine stress echocardiography compared to MPS, but a higher specificity and a better overall predictive performance. Stress echocardiography has an additional advantage in visualizing valvular or left ventricular dysfunction. Coronary angiography should be performed if indicated by non-invasive testing.

MANAGEMENT OF ABDOMINAL AORTIC ANEURYSMS AND CORONARY ARTERY DISEASE

In patients with an accurately assessed cardiac risk, two risk reduction strategies can be performed to reduce the incidence of peri –and postoperative cardiovascular events: prophylactic pharmacological treatment and/or preoperative coronary revascularization.

Pharmacological management

β-blocking agents
β-blockers have beneficial effects in congestive heart failure (CHF) by increasing the ejection fraction and reducing functional deterioration of the left ventricle in which heart rate reduction plays a pivotal role. After myocardial infarction, β-blocker use has a class I recommendation by the ACC/AHA.[61] During the perioperative phase mixed results for the use of β-blockers are available. However, in all studies outcome was improved in patients with known or suspected CAD. Poldermans *et al.* randomized 112 patients with more than 1 cardiac risk factor. Before surgery, a dobutamine stress echocardiography was performed. β-blocker therapy showed to improve peri-operative cardiac morbidity and mortality a 10-fold following major cardiovascular surgery.[62] However, during the past years, evidence is suggesting β-blockers to be ineffective in reducing cardiovascular events. The recent PeriOperative Ischemic Evaluation (POISE) study suggested a net harm of β-blockers in surgical patients.[63] Hereafter, use of β-blocking agents is recommended

to be used only in those patients who are on them already. The role of β-blockers (i.e. propanolol) for the prevention of aneurysm expansion has been investigated in only one randomized controlled trial, which showed no reduction in AAA growth rate. On the contrary, propanolol use significantly impaired quality of life.[64] The ACC/AHA guidelines on perioperative care strongly recommend the achievement and maintenance of a heart rate between 65-70 beats per minute.[61]

Statins

Irrespectively of their lipid lowering effects, statins seem to improve postoperative cardiac outcome by stabilizing coronary artery plaques and preventing atherosclerotic plaque rupture during surgery. Pleiotropic effects play a pivotal role and include: (i) increased expression of endothelial nitric-oxide-synthase, (ii) reduced production of endothelin-1, (iii) generation of reactive oxygen species, (iv) improvement of the trombogenic profile, and (v) reduction of inflammation.[65] Use of statins after AAA repair, has been associated with a 3-fold reduction in the risk of cardiovascular death.[29,66,67] Based on the Heart Protection study, it could be suggested that all patients should receive statin-therapy, irrespective of their cholesterol pattern.[68]

ACE-inhibitors

The influence of hypertension as a risk factor for the development of AAA is moderate. However, the influence of hypertension on the expansion of aneurysms is significant. According to the British Hypertension Society guidelines, an angiotensin converting enzyme (ACE) inhibitor should be preferred for the treatment of hypertension in patients with CAD and AAA.[66,69]

Anti-platelets

The presence of intraluminal thrombi creates possibilities for antiplatelet therapy in patients with AAA. Treatment with aspirin or clopidogrel is recommended in patients with stable CAD to prevent cardiovascular events.[70] Aspirin reduces platelet activation and vasoconstriction, thereby limiting the risk of non-fatal MI by 34%. In the setting of secondary prevention, aspirin reduces cardiovascular events by 27 and cardiovascular deaths by 18%.[71] In MVS aspirin is routinely used preoperatively and associated with improved peripheral bypass patency.[61] Addition of clopidogrel next to low-dose aspirin might be beneficial towards postoperative cardiac outcome, however the effect on the incidence of postoperative bleeding complications might be a potential problem that should be sorted out in future studies.

Future perspectives

Some studies suggested the use of MMP inhibitors. However, only a handful of small trials have been performed.[72] These showed some beneficial effects in decreasing the expansion of aneurysms. Much larger randomized trials will be necessary before these treatments can be evaluated properly. The role of non-steroidal inflammatory drugs (NSAIDs) in the treatment of AAA has not been established. A positive effect on the decrease of prostaglandin E2 and Interleukin 1 and 6 in the aneurysmatic tissue was shown.[22] With respect to the role of inflammation in the development of AAA, the role of NSAIDs in AAA prevention and treatment has to be investigated more thoroughly.

Revascularization

Patients with CAD detected by preoperative screening might benefit from prophylactic revascularization by coronary artery bypass grafting or percutaneous coronary intervention (PCI). However, the value of prophylactic revascularization is controversial and debated. The Coronary Artery Revascularization Prophylaxis (CARP) trial was the first that randomized trial that investigated the benefit of coronary revascularization before elective MVS. During short- and long-term follow-up, no reduction in the number of cardiovascular events was observed.[73] The optimal preoperative management of patients with (i) left main disease, (ii) severe left ventricle dysfunction, (iii) unstable angina pectoris and (iv) aortic stenosis has not been determined yet. Recent findings by Landesberg *et al.* suggest that intermediate-risk patients are most likely to benefit from preoperative coronary revascularization, in contrast to low-risk patients and high-risk patients.[74] In the current ACC/AHA guidelines routine prophylactic coronary revascularization is not recommended before non-cardiac surgery in patients with stable CAD.[61]

PERIOPERATIVE SURVEILLANCE AND POSTOPERATIVE SURVIVAL

Perioperative surveillance

The general assessment of postoperative patients with CAD should be focused on evaluating asymptomatic and unstable myocardial ischemia. The diagnosis of postoperative myocardial infarction is frequently difficult to make since it often presents atypically and may have a different etiology compared with non-operative myocardial infarction. The evaluation of postoperative myocardial infarction should include cardiac monitoring, electrocardiography, and serial cardiac enzyme measurements. Special attention should be given to perioperative volume infusion since excessive fluid administration is a common cause of decompensated heart failure in patients with CAD.

Postoperative survival

Postoperative survival is strongly influenced by the presence of associated cardiovascular disease. Crawford *et al.* showed that cardiac risk factors counted for the postoperative deaths in 95%.[75] Another study of 167 patients with in 45% CAG-established CAD showed a cardiovascular perioperative mortality of 13.8% after AAA repair.[76] Back *et al.* reviewed the amount of cardiac deaths during the follow-up of infrarenal AAA repair and found an average of 40%.[77] During the last two decades, reducing cardiac mortality associated with AAA repair has been an important goal. Correction of severe or unstable CAD before or coincident with AAA repair was performed in several studies, showing a decline in operative mortality.[78-80] The combined open repair has mortality rates similar to a consecutive approach.[79-81] However, a proposed combined approach with endovascular stenting seems to be associated with lower morbidity and mortality rates.[82]

CONCLUSION

The incidence and prevalence of AAA are rising. Risk factor analysis identified age and gender as the most influencing factors. With the rising population of the elderly, the influence of cardiovascular disease will increase as well. Risk stratification and subsequent life style intervention and preventive pharmacological interventions deserve more attention. Postoperative outcome is strongly influenced by the presence of concomitant CAD. Therefore, screening for cardiovascular disease in the preoperative phase will decrease the risk of cardiovascular events during the peri- and postoperative period. Treatment possibilities are traditionally directed at surgical aneurysm repair. However, as a consequence of the presence of concomitant cardiovascular disease, preoperative pharmacological treatment of both CAD and AAA has become an important topic. The present ACC / AHA guidelines recommend continuation of life style changes and pharmacological treatment after surgery, to reduce cardiovascular events in the postoperative period.

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Chapter 3

Prevalence of (a)symptomatic peripheral arterial disease; the additional value of ankle-brachial index on cardiovascular risk stratification

Jan-Peter van Kuijk
Willem-Jan Flu
Jeroen J. Bax
Don Poldermans

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PREVALENCE OF PERIPHERAL ARTERIAL DISEASE

The prevalence of peripheral arterial disease (PAD) in the general population varies between 7 and 21%.[1,2] This is strongly related to age, gender and the definition of PAD, defined by the ankle-brachial index (ABI) cut-off and/or the presence of intermittent claudication (IC). PAD is typically asymptomatic before progressing to clinical stages such as IC or even critical limb ischemia.[3] The ABI, as a screening tool, has emerged as an accurate and reliable marker of (a)symptomatic PAD and as a measure of systemic atherosclerotic burden. The getABI study detected a PAD prevalence of 18% in the primary-care setting, while only 2.8% of the patients were symptomatic.[2]

In this issue of the *Journal*, Ramos *et al.* identified the prevalence of symptomatic and asymptomatic PAD in a population-based cross-sectional study including 6.262 participants aged 35-79 years.[4] Furthermore, they evaluated the value of ABI measurement in addition to coronary heart disease (CHD) risk estimation. PAD, defined as an ABI <0.9, was present in 4.5% of the study population, of which only 0.62% presented with IC assessed by the Edinburgh questionnaire. Prevalence increased up to 14% in patients aged 75 to 79 years. These findings are in line with several previous population-based studies, demonstrating a relation between age and prevalence of PAD. Importantly; the vast majority of the patients were asymptomatic, addressing the importance of PAD detection in an early phase.[1,2]

CARDIOVASCULAR RISK STRATIFICATION AND TREATMENT

The present study evaluated the CHD risk for all participants of 35 to 74 years old free of cardiovascular disease, using the Framingham function adapted to Spain and validated in this population. The mean 10-year CHD risk in the subgroup of patients with ABI <0.9 was 9.2 in men and 3.0% in women. In 16.8% of the patients with ABI <0.9, 10-year CHD risk was moderate-to-high (≥10%). There was an inverse association between ABI and the 10-year CHD risk. Combining CHD risk estimation with ABI measurement changed the proportion of participants aged 35 to 74 years with CHD risk ≥10% from 6.1 to 8.7%. Over the last years, PAD has become an indicator disease for generalized atherosclerosis. Study results reported a high prevalence of coronary artery disease (CAD) and cerebrovascular disease (CVD) in PAD patients.[5,6] The Framingham CHD risk function was developed to provide a 10-year risk estimate for the development of CHD in patients free of cardiovascular history.[5] Ramos *et al.* demonstrated that including ABI <0.9 in the

screening process resulted in a considerable increased proportion of moderate-to-high risk population when combined with 10-year risk ≥10% by risk functions using x^2 tests.

High prevalence of multiple affected vascular beds (polyvascular disease) in patients with symptomatic PAD, but also in asymptomatic patients was reported by several studies.[2] The REACH registry indicated that in patients with symptomatic PAD, 1 out of 6 (17%) patients have concomitant CAD and/or CVD.[6] As patients with (a)symptomatic PAD have a high prevalence of polyvascular disease, the impact of polyvascular disease in asymptomatic PAD patients may have huge consequences as well for (i) the need for screening, (ii) preventive life-style modification, and (iii) medical treatment. The REACH registry demonstrated that PAD patients are generally ignored with respect to lifestyle changes and risk factor management.[6] Treatment goals according the current guidelines include aspirin and statins (low-intermediate risk (Lee-cardiac index <2) patients: target LDL level <100 mg/dL, high-risk (Lee Cardiac index ≥2) patients <70 mg/dL) for patients with PAD, and if necessary combined with antihypertensive drugs to achieve a target blood pressure below 140/90 mmHg.[7] In patients with ischemic heart disease additional recommended therapy consists of β-blockers. Furthermore, in case of diabetes mellitus and/or heart failure (left ventricular ejection fraction <40%), treatment should be extended with ACE-inhibitors or Angiontensin receptor blockers in case of intolerance.[8] Importantly, a recent study showed that there is a care-gap in medical treatment between guideline recommendations and clinical practice in PAD patients.[9] Therefore, especially for patients with polyvascular disease, medical treatment adherence according the current guidelines needs to be emphasized.

In conclusion, the current study demonstrated a prevalence of symptomatic and asymptomatic PAD that is in line with previous studies in the primary care setting.[2] The low prevalence of symptomatic PAD in these patients indicates that PAD can only be comprehensively diagnosed by systematic screening, including ABI measurement. The additional value of ABI measurement to CHD risk estimation outlines the impact of PAD as an indicator of atherosclerotic disease, which is often not limited to one arterial location. Therefore, screening for asymptomatic PAD in high-risk patients needs to be part of systematic screening for atherosclerotic disease. Development of less time-consuming ABI measurement techniques should be supported to enlarge the applicability of ABI measurement in the primary care setting. Furthermore, the high prevalence of asymptomatic PAD creates the need for optimal life-style modification and medical treatment, as stated by the current guidelines on PAD.

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Chapter 4

Intima-media thickness of the common carotid artery in vascular surgery patients: a predictor of postoperative cardiovascular events

Willem-Jan Flu
Jan-Peter van Kuijk
Sanne E. Hoeks
Ruud J. Kuiper
Olaf Schouten
Dustin Goei
Tamara A. Winkel
Yvette R.B.M. van Gestel
Hence J.M. Verhagen
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Background: Cardiovascular (CV) complications are the leading cause of morbidity and mortality in vascular surgery patients. The Revised Cardiac Risk (RCR) index, identifying cardiac risk factors, is commonly used for preoperative risk stratification. However, a more direct marker of the underlying atherosclerotic disease, such as the common carotid artery intima-media thickness (CCA-IMT) may be of predictive value as well. The current study evaluated the prognostic value of the CCA-IMT for postoperative CV outcome.

Methods: In 508 vascular surgery patients, the CCA-IMT was measured using high-resolution B-mode ultrasonography. We recorded the RCR factors: ischemic heart disease, heart failure, cerebrovascular disease, diabetes mellitus and renal dysfunction. Repeated Troponin T measurements and electrocardiograms were performed postoperatively. The study end point was the composite of 30-day CV events and long-term CV mortality. Multivariate regression analyses were used to assess the additional value of CCA-IMT for the prediction of cardiac events.

Results: In total, 30-day events and long-term CV mortality were noted in 122 (24%) and 81 (16%) patients, respectively. The optimal predictive value of CCA-IMT, using receiver-operating characteristic curve analysis, for the prediction of CV events was calculated to be 1.25 mm (sensitivity 70%, specificity 80%). An increased CCA-IMT was independently associated with 30-day CV events (OR 2.20, 95% CI: 1.38 to 3.52) and long-term CV mortality (HR 6.88, 95% CI: 4.11 to 11.50), respectively.

Conclusions: This study shows that an increased CCA-IMT has prognostic value in vascular surgery patients to predict 30-day CV events and long-term CV mortality, incremental to the RCR index.

INTRODUCTION

Cardiovascular (CV) complications are the leading cause of morbidity and mortality in vascular surgery patients.[1] Adequate preoperative evaluation is inevitable to: (i) identify patients at increased risk, (ii) initiate risk reduction therapy, and (iii) select optimal surgical and anaesthesia techniques. Heart failure, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus and high-risk surgery, as summarised in the Revised Cardiac Risk (RCR) index, have been identified as independent predictors of perioperative CV events.[2,3] However, a more direct marker of the underlying atherosclerotic disease, such as the common carotid artery intima-media thickness (CCA-IMT),[4] may be of predictive value as well. Although an increased CCA-IMT is associated with an increased risk for myocardial infarction and stroke,[5,6] limited information is available concerning the predictive value of an increased CCA-IMT for postoperative CV events in vascular surgery patients. This study evaluated the predictive value of the CCA-IMT for CV events in vascular surgery patients, incremental to the predictive value of the RCR index.

METHODS

Study population

The study population was derived from a cohort of 1.005 consecutive vascular surgery patients undergoing lower extremity artery, abdominal aortic aneurysm, abdominal aortic stenosis or carotid artery repair from 2002 to 2008. From 2004 to 2008, standard CCA-IMT measurements were performed, and 508 consecutive patients with CCA-IMT measurements were included during this time period, with exclusion of patients undergoing carotid artery repair. Both open and endovascular procedures were included. The study was approved by the hospital's ethics committee and performed with informed consent of all patients.

Baseline characteristics

Before surgery, a detailed history was obtained from every patient. Risk factors according to the RCR index were recorded such as: heart failure (defined as the presence of heart failure symptoms according the New York Heart Association classification or previous hospital admission for decompensated heart failure), ischemic heart disease (defined as history of angina pectoris, coronary revascularization or myocardial infarction), cerebrovascular disease (defined as a history of ischemic or hemorrhagic stroke), renal dysfunction (defined as serum creatinin >2 mg/dL) and diabetes mellitus (defined as fasting blood glucose ≥7.0

mmol/L or requirement for insulin and/or anti-diabetic medication). Cardiac risk score was determined for each patient according the RCR index with one point assigned to each characteristic. Furthermore; age, sex, body mass index, hypertension (blood pressure was measured during preoperative evaluation at the outpatient clinic and hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg in nondiabetic patients, systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg in diabetics, or the use of antihypertensive medication), hypercholesterolemia (low-density lipoprotein cholesterol >3.50 mmol/L), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification) and smoking status were recorded. Finally, use of the following medication was recorded: β-blockers, statins, aspirin, oral anticoagulants, angiotensin-converting enzyme inhibitors, calcium antagonists, and diuretics. Medication use was ascertained if medication was documented at least one month before surgery.

Measurement of the intima-media thickness

The CCA-IMT was measured according to the 'Mannheim Carotid Intima-Media Thickness Consensus' scanning and reading protocol recommendations.[7-9] Measurements were taken at 10 mm proximal to the carotid bifurcation in the near and far wall of the left and right common carotid artery. Repeated measurements were performed along a minimum of 10 mm length. Four measurements were taken from both the left and right common carotid artery, two of which in the near and two in the far wall. The maximal measurement, of these eight measurements, was used. Plaques (defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm)[7] when present, were not used in the CCA-IMT measurements. Measurements were electrocardiogram-gated at the peak of the QRS complex to control for changes in CCA-IMT during the cardiac cycle. Two sonographers, unaware of the clinical information for each patient, performed the measurements with an interobserver correlation of 96.2%.

Clinical cardiac outcome and follow-up

Serial electrocardiograms and troponin T measurements were obtained from all patients before surgery, postoperatively on day 1, 3, 7 and before discharge. Main study endpoints were (i) 30-day CV events defined as myocardial infarction, myocardial ischemia, and CV mortality, and (ii) long-term CV mortality. Myocardial ischemia was present when cardiac enzyme levels were elevated >0.03 ng/mL.[10] Myocardial infarction was present when cardiac enzyme levels were elevated >0.03 ng/mL in combination with electrocardiographic changes such as new-onset ST-T changes, new onset left bundle branch block or development of pathological Q waves.[11] Thirty-day follow-up was completed during regular follow-up visits at the

outpatient clinic and, if needed, by reviewing hospital records or the electronic patient file. Long-term mortality was assessed by approaching the municipal civil registries. All surviving patients received a mailed questionnaire and, if needed, survival status was completed by approaching the referring physician. Mortality was considered CV unless explicit proof of a noncardiac cause could be delivered. Mean follow-up was 1.8 ± 1.1 years.

Statistical analysis

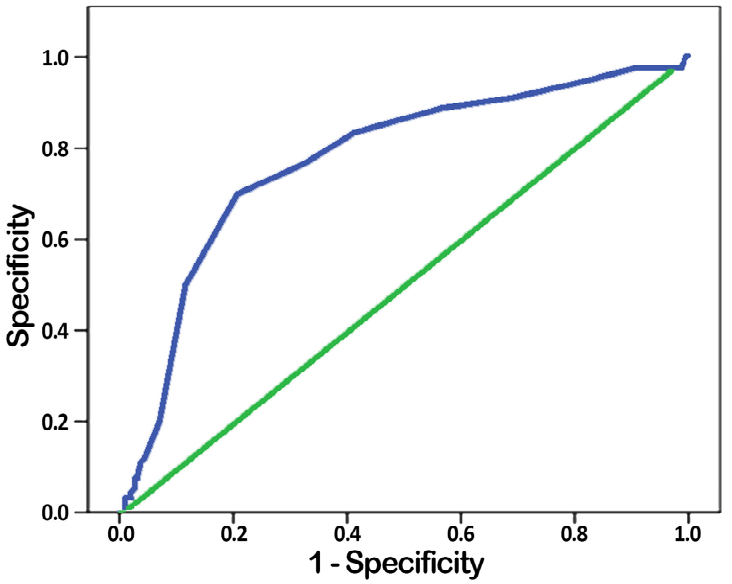
Dichotomous data are described as numbers and percentages. The continuous variables age and body mass index are described as means ± SD. Differences in baseline characteristics between CCA-IMT groups were evaluated using x^2 tests for categorical data. Continuous data were compared using one-way ANOVA. Receiver operating characteristic curve analysis was used to assess the optimal cutoff value of CCA-IMT for predicting 30-day CV events and long-term CV mortality. The optimal value of CCA-IMT for predicting 30-day CV events and long-term CV mortality was defined as the concentration with the largest sum of sensitivity plus specificity. Uni- and multivariate logistic regression analysis were performed to evaluate the prognostic value of an increased CCA-IMT towards 30-day CV events and Cox regression analysis towards long-term CV mortality. Multivariate regression analyses were adjusted for age, sex, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, current smoking, β-blocker use, statin use, and aspirin use. We report crude and adjusted ORs and HRs with their 95%-CI. For all tests, a $p < 0.05$ (two-sided) was considered significant. Cumulative long-term survival was determined by the Kaplan-Meier method. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Chicago, IL). No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the article, and its final contents.

RESULTS

A total of 508 patients undergoing lower extremity artery repair (N=245) and abdominal aortic aneurysm or abdominal aortic stenosis repair (N=263) were included in the study. Endovascular procedures comprised 38% of the studied surgical procedures. Mean age was 68 ± 11 years and 78% were men. Mean CCA-IMT (i.e. mean of the maximum CCA-IMT measurements) was 1.07 ± 0.35. In total, 30-day CV events were observed in 122 patients (24%) and long-term CV mortality in 81 patients (16%). The optimal predictive value of CCA-IMT for the prediction of

30-day CV events and long-term CV mortality was calculated to be 1.25 mm (sensitivity 70%, specificity 80%) (*Figure 1*).

Figure 1: *Receiver operating characteristics curve analysis of common carotid artery intima-media thickness to predict postoperative cardiovascular events. Sensitivity and specificity are plotted for various levels*



In total, 145 patients (29%) had an increased CCA-IMT defined as a CCA-IMT ≥1.25 mm. Patients with an increased CCA-IMT were older (71 vs 67 years, p = 0.01) and more likely to be male (85 vs 75%, p = 0.013) compared to patients with a CCA-IMT <1.25 mm. Other factors associated with an increased CCA-IMT were a history of heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, β-blocker use, calcium-antagonist use and diuretic use. Baseline characteristics according the CCA-IMT groups are listed in *Table 1.*

30-day outcome

The study end point 30-day CV events was reached in 122 (24%) patients, of which 66 (18%) occurred in patients with a CCA-IMT <1.25 and 56 (39%) in patients with an increased CCA-IMT (p < 0.01) as shown in *Table 2*. During 30-day follow-up, 117 (23%) had a nonfatal myocardial event, of which 30 patients (26%) had a myocardial infarction and 87 patients (74%) had myocardial ischemia. In total, 61 (17%) patients with a CCA-IMT <1.25 and 56 (39%) patients with an increased CCA-IMT had a nonfatal myocardial event (p < 0.01).

Table 1 **Baseline characteristics according to CCA-IMT groups**

	All [N=508]	CCA-IMT <1.25 [N=363]	CCA-IMT ≥1.25 [N=145]	*p*-value
Demographics				
Age (± SD)	68 (11)	67 (11)	71 (10)	0.01
Male (%)	394 (78)	271 (75)	123 (85)	0.01
Body mass index (± SD)	26 (4)	26 (4)	26 (3)	0.70
Medical history (%)				
Heart failure	56 (11)	32 (9)	24 (17)	0.01
Ischemic heart disease	221 (44)	157 (43)	64 (44)	0.86
Cerebrovascular disease	83 (16)	45 (12)	38 (26)	<0.01
Renal dysfunction	103 (20)	63 (17)	40 (28)	0.01
Diabetes mellitus	124 (24)	83 (23)	41 ()28	0.20
Hypertension	340 (67)	235 (65)	105 (72)	0.10
Hypercholesterolemia	249 (49)	174 (48)	75 (52)	0.44
COPD	126 (25)	81 (22)	45 (31)	0.04
Smoker, current	221 (44)	156 (43)	65 (45)	0.70
RCR index (%)				
0-1 risk factors	250 (49)	196 (54)	54 (37)	<0.01
2 risk factors	145 (29)	101 (28)	44 (30)	<0.01
≥3 risk factors	111 (22)	64 (18)	47 (32)	<0.01
Surgery type (%)				
Open	314 (62)	220 (61)	94 (65)	0.376
Medication (%)				
β-blocker	397 (78)	274 (76)	123 (85)	0.02
Statin	343 (68)	241 (66)	102 (70)	0.39
Aspirin	287 (57)	211 (58)	76 (52)	0.24
Oral anticoagulant	87 (17)	57 (16)	30 (21)	0.18
ACE-inhibitor	153 (30)	111 (31)	42 (29)	0.72
Calcium-antagonist	92 (18)	56 (15)	36 (25)	0.01
Diuretic	121 (24)	77 (21)	44 (30)	0.03

Common carotid artery intima-media thickness (CCA-IMT), revised cardiac risk (RCR), standard deviation (SD), Chronic obstructive pulmonary disease (COPD)

Table 2 **CCA-IMT and postoperative outcome**

		CCA-IMT <1.25 [N=363]	CCA-IMT ≥1.25 [N=145]	Univariate	
30-day (%)				OR	[95%-CI]
Cardiovascular events	[N=122]	66 (18)	56 (39)	2.93	1.85-4.34
All-cause mortality	[N=25]	10 (3)	15 (10)	4.07	1.79-9.30
Long-term (%)				HR	[95%-CI]
Cardiovascular mortality	[N=81]	24 (7)	57 (39)	6.90	4.23-11.13
All-cause mortality	[N=113]	53 (15)	60 (41)	3.28	2.26-4.77

Confidence interval (CI), common carotid artery intima-media thickness (CCA-IMT), hazard ratio (HR), odds ratio (OR).

The study end point CV mortality was reached in 21 (4%) patients, of which 6 (2%) occurred in patients with a CCA-IMT <1.25 and 15 (10%) in patients with an increased CCA-IMT (p < 0.01). Multivariate analysis showed that the RCR index

was predictive for 30-day CV events (2 risk factors: OR 1.96, 95% CI: 1.12 to 3.43; ≥3 risk factors: OR 6.43, 95% CI: 3.66 to 11.28), as shown in *Table 3 (Model 1)*. When adding CCA-IMT to this model, an increased CCA-IMT was independently associated with 30-day CV events (OR 2.20, 95% CI: 1.38 to 3.52), as shown in *Table 3 (Model 2*).

Table 3 **Multivariate association between CCA-IMT and 30-day follow-up**

		Model 1 *		Model 2 **	
	[N=508]	OR	[95% CI]	OR	[95% CI]
Cardiovascular events					
RCR index ***					
1 risk factor	34/250	1.00		1.00	
2 risk factors	35/146	1.96	1.12-3.43	1.86	1.06-3.28
≥3 risk factors	53/112	6.43	3.66-11.28	5.70	3.21-10.11
CCA-IMT					
<1.25	66/363	-	-	1.00	
≥1.25	56/145	-	-	2.20	1.38-3.52
All-cause mortality					
RCR index ***					
1 risk factor	6/250	1.00		1.00	
2 risk factors	9/146	2.73	1.32-12.21	2.42	0.80-7.37
≥3 risk factors	10/112	4.02	0.90-8.22	2.92	0.93-9.15
CCA-IMT					
<1.25	10/363	-	-	1.00	
≥1.25	15/145	-	-	3.76	1.44-8.93

** Model 1: predictive value of RCR index for adverse outcome. Multivariate analyses were adjusted for age, gender, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, current smoking, β-blocker use, statin use and aspirin use.*

*** Model 2: additional value of CCA-IMT for prediction of adverse outcome additionally to clinical risk factors. Multivariate analysis adjusted for RCR risk factors and risk factors described in model 1. *** RCR risk factors: heart failure, ischemic heart disease, cerebrovascular disease, diabetes mellitus and renal dysfunction. Confidence interval (CI), common carotid artery intima-media thickness (CCA-IMT), odds ratio (OR), revised cardiac risk (RCR).*

Long-term outcome

During long-term follow up, 81 (16%) patients died due to a CV cause. Of these patients, 24 (7%) had a CCA-IMT <1.25 mm and 57 (39%) had an increased CCA-IMT (*Table 2*). Cumulative 5-year survival (log rank $p < 0.01$) is shown in *Figure 2*. Multivariate analysis showed that the RCR index was predictive for CV mortality for patients with 2 and ≥3 risk factors with HRs of 2.02 (95% CI: 1.05 to 3.88) and 3.81 (95% CI: 1.95 to 7.45), respectively (*Table 4, Model 1*). When including CCA-IMT in the model (*Table 4, Model 2*), an increased CCA-IMT was independently associated with CV mortality with an HR of 6.57 (95% CI: 3.93 to 10.96). The incremental value of CCA-IMT in the prediction of CV events is further illustrated in *Figure 3*.

Table 4 **Multivariate association between CCA-IMT and long-term mortality**

		Model 1 *		Model 2 **	
	[N=508]	HR	[95% CI]	HR	[95% CI]
Cardiovascular events					
RCR index ***					
1 risk factor	27/250	1.00		1.00	
2 risk factors	24/146	1.84	1.02-3.35	1.74	0.95-3.19
≥3 risk factors	35/112	3.66	2.08-6.43	2.97	1.67-5.29
CCA-IMT					
<1.25	24/363	-	-	1.00	
≥1.25	57/145	-	-	6.88	4.11-11.5
All-cause mortality					
RCR index ***					
1 risk factor	48/250	1.00		1.00	
2 risk factors	37/146	1.53	0.94-2.50	1.50	0.92-2.44
≥3 risk factors	40/112	2.49	1.53-4.04	2.14	1.31-3.49
CCA-IMT					
<1.25	53/363	-	-	1.00	
≥1.25	69/145	-	-	2.88	1.94-4.27

** Model 1: predictive value of RCR index for adverse outcome. Multivariate analyses were adjusted for age, gender, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, current smoking, ß-blocker use, statin use and aspirin use.*

*** Model 2: additional value of CCA-IMT for prediction of adverse outcome additionally to clinical risk factors. Multivariate analysis adjusted for RCR risk factors and risk factors described in model 1. *** RCR risk factors: heart failure, ischemic heart disease, cerebrovascular disease, diabetes mellitus and renal dysfunction. Confidence interval (CI), common carotid artery intima-media thickness (CCA-IMT), hazard ratio (HR), revised cardiac risk (RCR).*

Figure 2. *Cumulative long-term survival (Carotid artery intima-media thickness (CCA-IMT)*

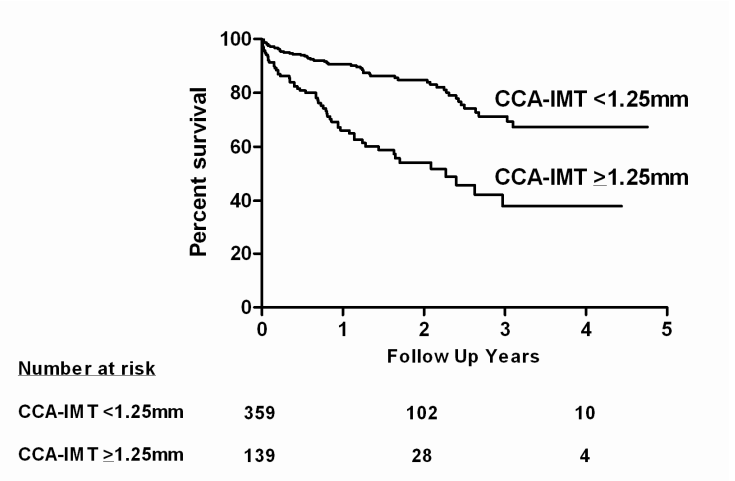
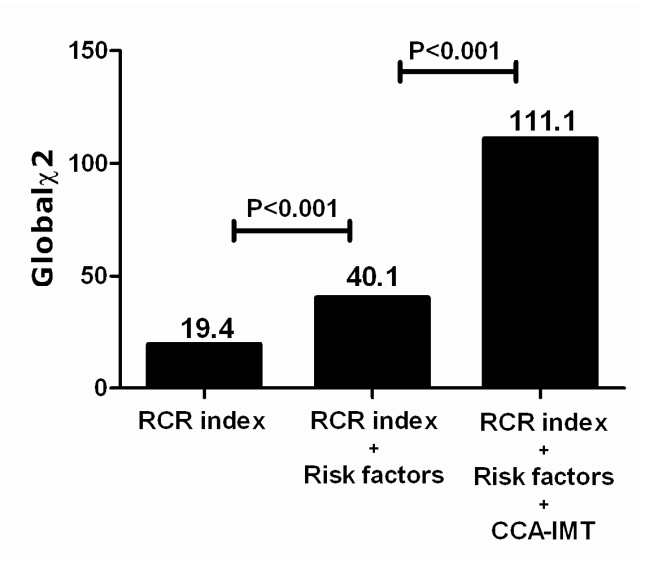


Figure 3: *Incremental value of CCA-IMT in the prediction of postoperative cardiovascular mortality*



Risk factors: age, gender, current smoking, hypercholesterolemia, chronic obstructive pulmonary disease. Common carotid intima-media thickness (CCA-IMT), revised cardiac risk (RCR).

DISCUSSION

To our knowledge, our study is the first to describe the prognostic value of an increased CCA-IMT in patients undergoing vascular surgery. We have found a cutoff value (maximum CCA-IMT) of 1.25 mm, using receiver operating characteristic curve analysis, to be most indicative for the prediction of 30-day CV events and long-term CV mortality. In patients with an increased CCA-IMT, the occurrence of 30-day CV events was more than twice as high compared to patients with a CCA-IMT <1.25 mm. The occurrence of long-term CV mortality was more than five times higher in patients with an increased CCA-IMT compared to patients with a CCA-IMT <1.25 mm.

Atherosclerosis, a systemic inflammatory disease, is known to affect multiple sections of the arterial tree simultaneously. Previous studies have demonstrated a correlation between an increased CCA-IMT with cardiac risk factors and coronary atherosclerosis.[12-14] However, the extent of the atherosclerotic process is thought to differ between the vascular beds. In the general population, the median carotid IMT ranges from 0.5-1.0 mm,[15] and the CCA-IMT is considered increased being >1.0 mm.[16] In the prediction of myocardial infarction and stroke,

the Rotterdam Study found the average maximum CCA-IMT to be 1.03 ± 0.22 and divided the carotid IMT into quartiles based on the population distribution. Using maximal CCA-IMT cutoff values of 0.88, 0.99, and 1.12 mm, they have defined mild, moderate, and severe thickening of the carotid wall, irrespectively.[12,17] The Multi-Ethnic Study of Atherosclerosis study divided the maximal common carotid IMT in quartiles as well and found cutoff values of 0.74, 0.84, 0.97 and 2.45 mm, respectively.[18] Our study population consisted of major vascular surgery patients, which are prone to have atherosclerosis. In comparison, the Rotterdam study and Multi-Ethnic Study of Atherosclerosis study were population-based studies. As patients with operable vascular disease may have more diffuse and more severe vascular disease, this might explain our relatively high cutoff value for CCA-IMT to predict future CV events.

The carotid IMT is increasingly used as a surrogate marker of early atherosclerosis, which is associated with CV diseases such as myocardial infarction, stroke and peripheral arterial disease. Several studies have demonstrated that carotid IMT is associated with risk of CV events.[5,19] This study was performed to evaluate the predictive value of the CCA-IMT for preclinical stages of atherosclerosis. Therefore, focal thickened regions in the carotid arteries were excluded, as they reflect later stages of atherosclerosis. A meta-analysis performed by Lorenz *et al*,[12] in which 37.197 patients were included, provided data on the use of carotid IMT to predict myocardial infarction and stroke in the general population. In this study an absolute carotid IMT difference of 0.1 mm, was associated with an increased risk for myocardial infarction of 10 to 15% and an increased risk for stroke of 13 to 18%. However, as reported in the Mannheim Carotid IMT Consensus statement, the Food and Drug Administration does not yet approve carotid IMT as a surrogate marker of vascular events. Although, it is stated that carotid IMT is the most important candidate to be studied, as an independent marker for CV events.[7] To our knowledge, the prognostic value of an increased CCA-IMT has not been previously described in patients undergoing vascular surgery. Only limited information is available regarding the prognostic value of CCA-IMT in patients undergoing cardiac interventions. Lacroix *et al.*[20] evaluated whether CCA-IMT thickening was related to an increased risk of CV events after percutaneous transluminal coronary angioplasty. Univariatee analysis demonstrated that a CCA-IMT >0.7 mm was associated with increased CV events after percutaneous transluminal coronary angioplasty (p = 0.03). They concluded CCA-IMT could be useful to identify high-risk patients. Aboyans *et al.*[21] enrolled 609 patients undergoing coronary artery bypass grafting and hypothesized CCA-IMT could be used for perioperative and long-term risk stratification. However, in multivariate analysis, CCA-IMT failed to be an independent predictor for secondary

CV events after coronary artery bypass grafting. Both studies mentioned above included patients with known coronary artery disease and long-term follow-up included non-fatal CV events as well. This might explain our relatively high cutoff value for CCA-IMT to predict future CV events.

The "American Society of Echocardiography Carotid IMT task force" have stated that carotid IMT imaging should not be performed in patients with established atherosclerotic vascular disease or if the results would not be expected to alter therapy. They recommend prospective studies to investigate the effectiveness of carotid ultrasound imaging, in support to improve CV outcome.[5] It is suspected that 95% of the episodes of perioperative myocardial infarction and ischemia are asymptomatic,[1,22-25] and subsequently, these patients do not receive adequate treatment. We have shown that an increased CCA-IMT is an independent predictor of perioperative myocardial infarction and ischemia and could therefore contribute to optimize medical treatment as well. With current ultrasound scanners, CCA-IMT can be easily used in clinical routine for objective and reproducible cardiac risk assessment. Importantly, CCA-IMT has an additional value, incremental to subjective cardiac risk assessment using the RCR index. Validation of our results in future studies is needed to justify the recommendation of standard CCA-IMT measurements in preoperative risk stratification of vascular surgery patients.

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent a general population scheduled for elective major vascular surgery. Second, although two experienced investigators performed offline assessments of the obtained ultrasound images, we cannot rule out interobserver variability to have had minor influence on our results.[26] Third, we did not validate the CCA-IMT cutoff point in a prospective group of patients undergoing vascular surgery.

In conclusion, the present study shows that an increased CCA-IMT of ≥1.25 mm has a prognostic value in vascular surgery patients to predict 30-day CV events and long-term, incremental to the widely used RCR index.

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Chapter 5

Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease

Jan-Peter van Kuijk
Willem-Jan Flu
Gijs M.J.M. Welten
Sanne E. Hoeks
Michel Chonchol
Radosav Vidakovic
Hence J.M.Verhagen
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Aims: Patients with peripheral atherosclerotic disease often have multiple affected vascular beds (AVB); however, data on long-term follow-up and medical therapy are scarce. We assessed the prevalence and prognostic implications of polyvascular disease on long-term outcome in symptomatic peripheral arterial disease (PAD) patients.

Methods: Two thousand nine hundred and thirty-three consecutive patients were screened prior to surgery for concomitant documented cerebrovascular disease and coronary artery disease. The number of AVB was determined. Cardiovascular medication as recommended by guidelines was noted at discharge.

Results: Single, two and three AVB were detected in 1.369 (46%), 1.249 (43%) and 315 (11%) patients, respectively. During a median follow-up of 6 years, 1.398 (48%) patients died, of which 54% secondary to cardiovascular cause. After adjustment for baseline cardiac risk factors and discharge-medication, the presence of 2-AVB or 3-AVB was associated with all-cause mortality (HR 1.3, 95% CI: 1.2 to 1.5; HR 1.8, 95% CI: 1.5 to 2.2) and cardiovascular mortality (HR 1.5, 95% CI: 1.2 to 1.7; HR 2.0, 95% CI: 1.6 to 2.5) during long-term follow-up, respectively. Patients with 2- and 3-AVB received extended medical treatment compared with 1-AVB at time of discharge.

Conclusions: Polyvascular atherosclerotic disease in PAD patients is independently associated with an increased risk for all-cause and cardiovascular mortality during long-term follow-up.

INTRODUCTION

Peripheral arterial disease (PAD) is a multifactorial syndrome that most commonly affects people over 60 years of age.[1] As population age increases, the prevalence of atherosclerotic disease and its associated adverse outcomes will increase. Cardiovascular risk profiles have been established in several large studies, showing an equal risk factor distribution among all populations and across age groups and gender.[2,3] It has to be noted that the process of established atherothrombosis is not limited to a single arterial location. The Reduction of Atherothrombosis for Continued Health (REACH) registry showed that one out of 6 patients with PAD, cerebrovascular disease (CVD) or coronary artery disease (CAD) had involvement of 1 or 2 other arterial beds.[1,4] The REACH registry also demonstrated a substantial gap between recommended clinical guidelines and actual clinical practices in the care of patients with or at risk for atherothrombosis. A pattern of underutilization of established medical therapies and lifestyle interventions was shown throughout all geographic regions studies and vascular disease subtypes.[1] Consequently, patients with PAD have a three to six-fold increased risk for the occurrence of cardiovascular mortality compared with patients without PAD.[5,6] Therefore, the importance of risk factor reduction in patients with PAD has resulted in universally recommended atherothrombotic risk factor reduction, with the objective of decreasing the high incidence of heart disease and cerebrovascular disease associated with PAD.[7,8] However, although these large studies have identified the risk factor profiles and treatment protocols of atherosclerotic patients, most data are based on the screening of polyvascular disease, especially in the primary care setting. Therefore, the aim of the current study was to assess (i) the prevalence and number of affected vascular beds, and (ii) the prognostic implications of polyvascular disease on short- and long-term mortality in high-risk vascular surgery patients with symptomatic PAD.

METHODS

Study design and population

This retrospective single-centre study comprised a population of 2.933 consecutive patients with PAD, referred for elective major vascular surgery. All patients underwent a major vascular surgery procedure during the time period 1990 to 2008, and included lower extremity revascularization, abdominal aortic surgery (dilatating or stenotic) or carotid surgery. From 1990 until 2001, standard pre-operative screening included a detailed cardiac history, physical examination, electrocardiogram (ECG), standard laboratory measurements and additional

(stress)-testing if indicated. After 2002, standard pre-operative echocardiography was added to the screening program. The study complies the Declaration of Helsinki. Patient enrolment was performed after approval of the hospital's ethics committee and after informed consent of all patients (or their guardians) at time of inclusion.

Patient data

At baseline all medical records were reviewed to determine the presence of documented CAD and CVD. Patients undergoing lower extremity revascularization or abdominal aortic surgery were screened for the concomitant presence of documented CAD and CVD. Patients undergoing carotid surgery were screened for CAD and PAD. Coronary artery disease was defined as a documented history of ischemic heart disease [composite of angina pectoris, myocardial infarction (MI), percutaneous coronary intervention or coronary artery bypass grafting], using myocardial stress-testing (ergometry, stress-echocardiography, or CT-scan) or coronary angiogram. Patients with stable or unstable angina pectoris were classified as having documented CAD according the ESC guidelines.[9] The presence of coronary ischemia was established by one of the following techniques: exercise ECG [horizontal or down-sloping ST-segment depression or elevation (≥1mm (0.1mV) for ≥60-80ms after the end of the QRS complex)], or exercise testing with echocardiography, CT-scan (≥50% stenosis in one or more of the coronary arteries).[10] The presence of documented CVD was defined as a history of cerebrovascular accident or transient ischemic attack (TIA). Cerebrovascular accidents had to be confirmed by a CT-scanning report. The diagnosis of TIA had to be confirmed by a neurologist report. Lower extremity arterial disease was defined as current intermittent claudication with ankle-brachial-index <0.9, or a history of intermittent claudication with a previous intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention including amputation. Polyvascular disease was defined as the presence of 2 or 3-AVB. One-AVB included: PAD, 2-AVB: PAD and CAD or CVD, 3-AVB: PAD and CAD and CVD.

Finally, the use of the following medication was recorded at discharge: aspirin, statins, ß-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, oral anticoagulants, and ticlopidines. Treatment goals were defined according the current guidelines and included low-dose aspirin (75-325mg daily) and statins (low-intermediate risk patients: target LDL level <100 mg/dL, high-risk patients <70 mg/dL) for patients with PAD, and if necessary combined with antihypertensive drugs to receive a target blood pressure below 140/90 mmHg.[7] Additionally, PAD patients with diabetes should receive

ACE-inhibitors to a target blood pressure less than 130/80 mmHg.[7] Patients with CAD should be treated with aspirin, statins (target LDL <100 mg/dL) and ß-blockers, and additionally with ACE-inhibitors or Angiontensin receptor blockers in case of diabetes mellitus and/or heart failure.[11]

Risk factors

All cardiac risk factors were determined at baseline, including age, gender, body mass index, smoking status, hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg in non-diabetics, systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg in diabetics or the use of antihypertensive medication), diabetes mellitus (fasting blood glucose ≥7.0 mmol/l or requirement for insulin and/or oral anti-diabetic medication), hypercholesterolemia (LDL cholesterol > 135 mg/dL and/or the requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseaseas (GOLD)-classification[12]) and chronic renal insufficiency (serum creatinine >2,0 mg/dL). The cardiac risk score was calculated according the adapted Lee cardiac index which assigns 1 point for each of the following characteristics: high-risk surgery, ischemic heart disease, heart failure, cerebrovascular disease, chronic renal insufficiency, and diabetes mellitus.[13]

Follow-up and endpoints

The median follow-up of all patients was 6 years (interquartile range 2 to 9). Primary study endpoint was the occurrence of all-cause mortality. Survival status was assessed by reviewing the municipal civil registries. Cause of death was ascertained by examining death certificates, and otherwise by reviewing medical records. Cause of death was further classified as either cardiovascular or noncardiovascular death. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and includes death following MI, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular event or transient ischemic attack), and surgery related bleeding complications (only a post-operative cause of death). Sudden unexpected death was classified as a cardiovascular death.

Statistics

Continuous data were compared using analysis of variance, and are expressed as mean ± SD. Categorical data are presented as percentage frequencies and compared using x^2 tests. Analyses for trends in all baseline characteristics

(including age) between the number AVB were performed with linear-by-linear association. Logistic regression analysis was used to determine the association between polyvascular disease (2 and 3-AVB compared with 1-AVB) and short-term mortality (30 days). Cumulative survival of patients with 1, 2, or 3-AVB was determined by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox regression models were used to investigate the association between AVB (patients with 1-AVB as reference group) and mortality during long-term follow-up. All multivariate analyses were primarily adjusted for demographics (age and gender) and cardiovascular risk factors (smoking, hypertension, diabetes mellitus, hypercholesterolemia, renal dysfunction, heart failure and COPD). Secondary adjustments were made for medications usage recommended by the ESC/ACC guidelines in patients with PAD, including aspirin, statins, ß-blockers in case of prior myocardial infarction and angiotensin-converting enzyme (ACE) inhibitors in case of heart failure.[7] Finally, adjustment was made for preoperative hemoglobin levels. To evaluate the effect of medication use (aspirin, statins, ß-blockers and ACE-inhibitors) on long-term outcome, multivariate Cox regression analyses were performed with propensity score adjustment for each medication. Separate propensity scores were developed with logistic regression analyses for each type of medication. Variables included in the propensity score model were demographics (age and gender), cardiovascular risk factors (smoking, hypertension, diabetes mellitus, hypercholesterolemia, renal dysfunction, heart failure and COPD), medication use and hemoglobin. Statistical analyses were performed using SPSS software (SPSS version 15.0; SPSS, Inc., Chicago, Illinois). Hazard ratios (HR) were calculated from these models along with their 95% confidence intervals (C.I.). A p value <0.05 (2-sided) was considered statistically significant.

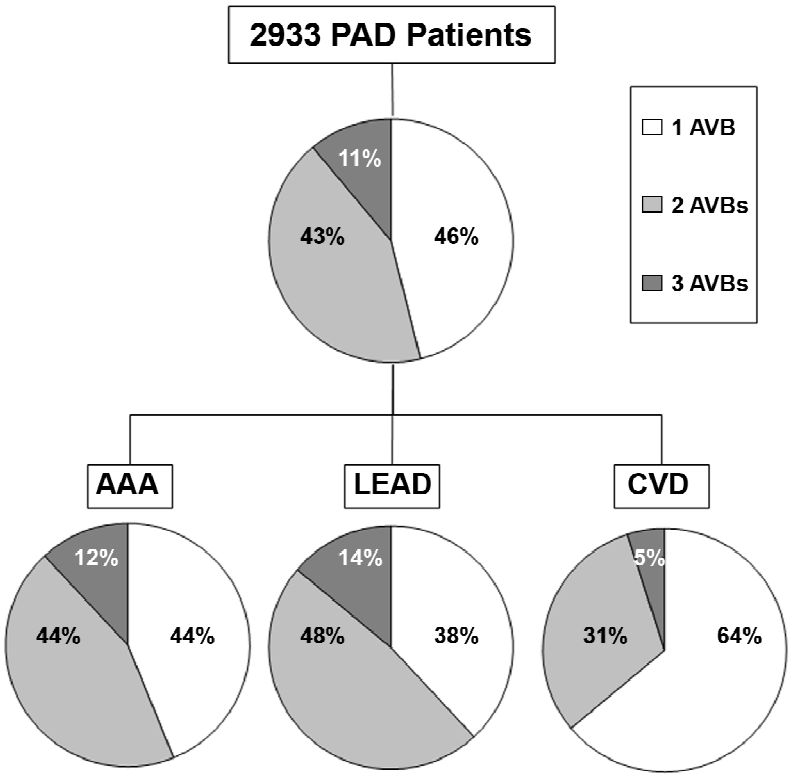
RESULTS

Description of the study population

The study population consisted of 2.933 consecutive patients with PAD referred for elective major vascular surgery. Lower extremity revascularization was performed in 1.031 (35%) patients, abdominal aortic surgery in 1.170 (40%) patients, and carotid surgery in 732 (25%) patients, respectively. Coronary artery and cerebrovascular disease were detected in 1.248 (43%) and 1.037 (35%) patients, respectively. In patients referred for lower extremity revascularization, 454 (44%) and 144 (14%) patients had concomitant documented CAD and CVD, respectively. Coronary artery disease and CVD were present in 575 (49%) and 166 (14%) of the patients referred for abdominal aortic surgery. Patients referred for carotid surgery,

219 (30%) and 79 (11%) patients had concomitant CAD and PAD. The number of affected vascular beds was determined at baseline, and one-vessel disease (1-AVB), two-vessel disease (2-AVB) and three-vessel disease (3-AVB) was detected in 1.369 (46%), 1.249 (43%) and 315 (11%) patients, respectively (*Figure 1*).

Figure 1. *Number of affected vascular beds in the total study population and subdivided for type of surgery*

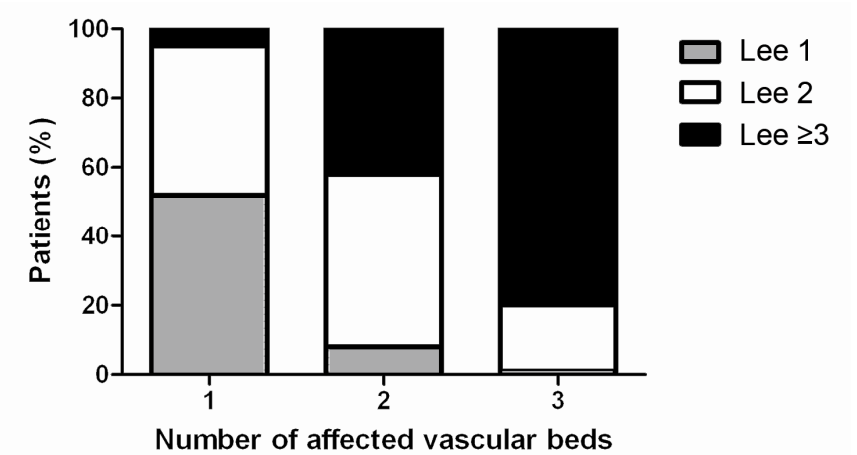


Abbreviations: PAD; peripheral arterial disease, AAA; abdominal aortic aneurysm, LEAD; lower extremity arterial disease, CVD; cerebrovascular disease, AVB; affected vascular beds

Lee cardiac index and number of affected vessels

Baseline characteristics of the study population were compared between the groups with different number of affected vascular beds and included demographic parameters and cardiovascular risk factors. A significant trend for an increased number of cardiovascular risk factors was present in patients with 2- or 3-AVB, compared with 1-AVB. Additionally, risk factor patterns were calculated following the Lee cardiac index and showed a relationship with the number of affected vessels. A Lee risk score of ≥3 was only present in 5% of patients with 1-AVB while 252 (80%) patients had a Lee risk score of ≥3 in patients with 3-AVB ($p < 0.001$, *Figure 2*).

Figure 2. *Distribution of the Lee cardiac index according to the number of affected vascular beds*



Medication use and number of affected vessels

Medication use at time of hospital discharge was registered and compared between the different patient groups (*Table 1*). Aspirin, statins, ß-blockers and ACE-inhibitors were used by 1.502 (51%), 1.131 (39%), 1.293 (44%) and 740 (25%) patients, respectively. There was a clear relationship between the year of surgery and medical treatment intensity after surgery (*Figure 3*). Importantly, aspirin was used in ≥50% of the patients from 1996, whereas statins and ß-blockers were prescribed in ≥50% of the patients from 2002. The number of AVB (1- vs. 2- vs. 3-AVB) showed a relationship with the use of statins (34 vs. 41 vs. 51%, $p < 0.001$), ß-blockers (37 vs. 48 vs. 60%, $p < 0.001$) and ACE-inhibitors (19 vs. 28 vs. 40%, $p < 0.001$). In contrast, there was no significant relationship between the number of AVB and aspirin use (53 vs. 49 vs. 53%, $p = 0.25$).

Short-term outcome

During the first 30 postoperative days, 112 (3.8%) patients died, of which 90 (80%) patients died secondary to a cardiovascular cause. Using univariate analysis, patients with 2- or 3-AVB had a significant increased mortality risk compared with patients with 1-AVB (2-AVB: OR 1.9, 95% CI: 1.22 to 2.88, 3-AVB: OR 2.5, 95% CI: 1.42 to 4.50), respectively (*Table 2*). This increased risk was present for the occurrence of cardiovascular death as well (2-AVB: OR 1.9, 95% CI: 1.16 to 3.00, 3-AVB: OR 2.2, 95% CI: 1.16 to 4.30). In multivariate analysis 2- and 3-AVB were independently associated with all-cause mortality (2-AVB: OR 1.7, 95% CI 1.03 to 2.63, 3-AVB: OR 2.5, 95% CI: 1.29 to 4.71). However, cardiovascular mortality was not longer significantly associated with polyvascular disease during short-term follow-up.

Table 1	Baseline characteristics of the study population				
	Total [N=2.933]	**1-AVB** [N=1.369]	**2-AVB** [N=1.249]	**3-AVB** [N=315]	***P*-value**
Demographics					
Age (year), mean ± SD	66 (11)	66 (12)	67 (11)	68 (10)	<0.001
Male (%)	2.189 (75)	958 (70)	984 (78)	257 (82)	<0.001
Year of surgery					0.001
< 1992	429 (15)	187 (14)	205 (16)	37 (12)	
1993-1995	653 (22)	323 (24)	270 (22)	60 (19)	
1996-1998	586 (20)	303 (22)	228 (18)	55 (18)	
1999-2001	353 (12)	177 (13)	150 (12)	26 (8)	
2002-2004	249 (9)	96 (7)	112 (9)	41 (13)	
2005-2008	663 (23)	283 (21)	285 (23)	314 (11)	
Cardiovascular risk factors					
Smoking					<0.001
No	1.139 (39)	585 (43)	456 (37)	98 (31)	
Current	1.092 (37)	490 (36)	471 (38)	131 (42)	
History	702 (24)	294 (22)	322 (26)	86 (27)	
Hypertension	1.514 (52)	594 (43)	706 (57)	214 (68)	<0.001
Hypercholesterolaemia	798 (27)	289 (21)	392 (31)	117 (37)	<0.001
Renal dysfunction	297 (10)	95 (7)	146 (10)	56 (18)	<0.001
Chronic heart failure	206 (7)	24 (2)	126 (10)	56 (18)	<0.001
COPD	557 (19)	201 (15)	271 (22)	85 (27)	<0.001
Medication at discharge					
Aspirin	1.502 (51)	726 (53)	610 (49)	166 (53)	0.25
Statin	1.131 (39)	463 (34)	506 (41)	162 (51)	<0.001
B-blocking agents	1.293 (44)	506 (37)	599 (48)	188 (60)	<0.001
Diuretics	696 (24)	244 (18)	340 (27)	112 (36)	<0.001
ACE inhibitors	740 (25)	260 (19)	335 (28)	125 (40)	<0.001
Calcium Antagonists	711 (24)	265 (19)	360 (29)	86 (27)	<0.001
AT-II antagonists	157 (5)	61 (5)	71 (6)	25 (8)	0.01
Oral anticoagulants	1.108 (38)	463 (34)	505 (40)	140 (44)	<0.001
Ticlopidines	132 (5)	45 (3)	60 (5)	27 (9)	<0.001

Abbreviations: AVB: affected vascular beds, COPD: chronic obstructive pulmonary disease, ACE-inhibitors: angiotensin converting enzyme-inhibitors, AT-II antagonists: angiotensin II antagonists.

Long-term outcome

After one-year follow-up, 308 (11%) patients died, of which 227 (74%) and 71 (26%) secondary to a cardiovascular or non-cardiovascular cause, respectively. Patients with 2- or 3-AVB had an increased risk for the occurrence of 1-year all-cause mortality (2-AVB: HR 1.3, 95% CI: 1.03 to 1.7; 3-AVB: 1.6, 95% CI: 1.1 to 2.3) and cardiovascular mortality (2-AVB: HR 1.7, 95% CI: 1.2 to 2.2; 3-AVB: 1.7, 95% CI: 1.1 to 2.6), compared with patients with 1-AVB, respectively. During long-term follow-up, 1.389 (47%) patients reached the primary endpoint of all-cause mortality. A cardiovascular or non-cardiovascular cause of death was detected in 849 (61%) and 434 (31%) patients, respectively.

Figure 3. *Post-operative prescription of aspirin, statins, ß-blockers, and ACE-inhibitors stratified according to the year of surgery*

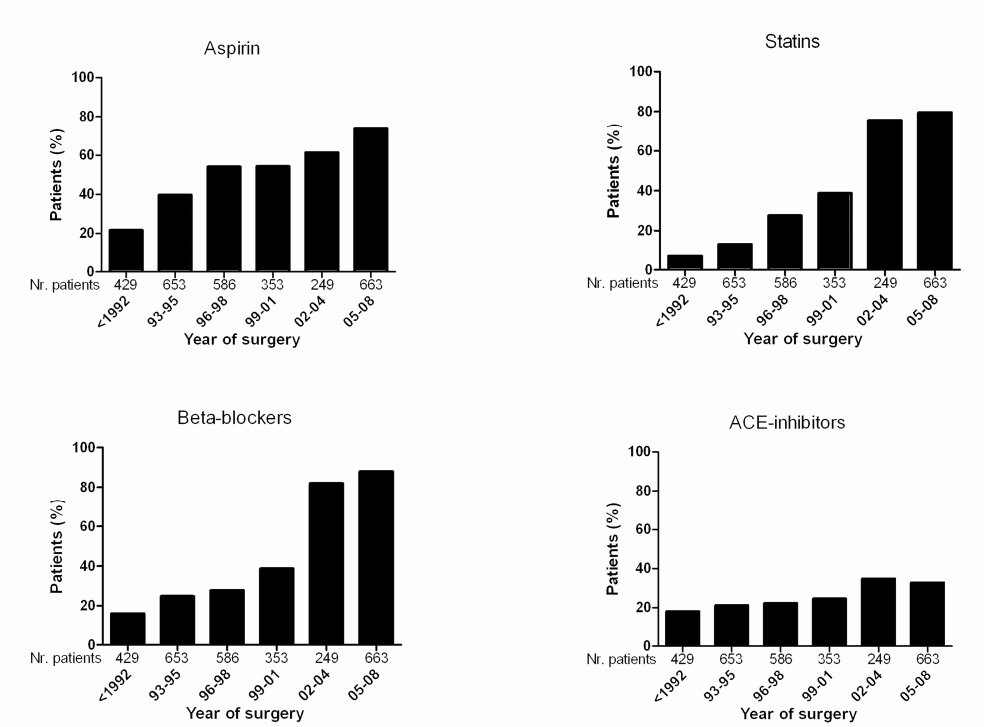
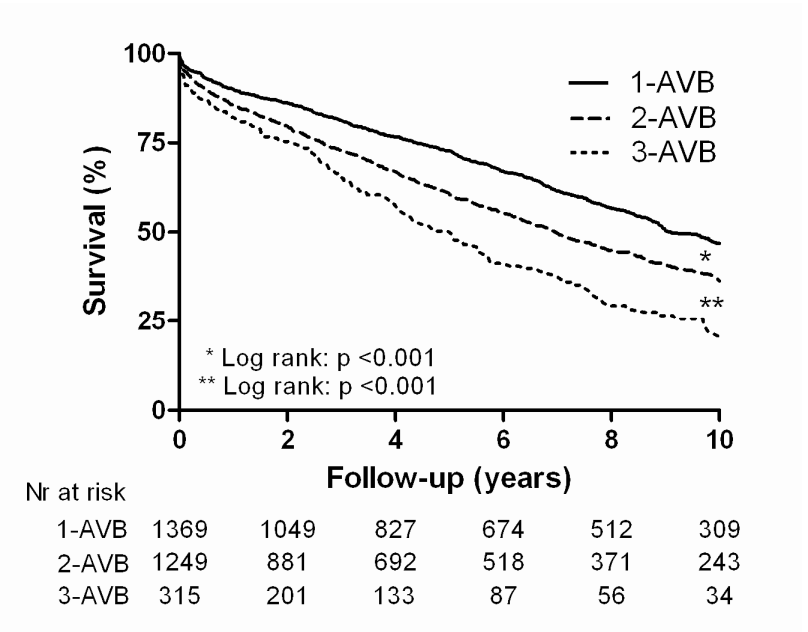


Table 2 **Short-term (30 days) survival**

	Events	Univariate		Multivariate (1)		Multivariate (2)	
	N (%)	OR	95% CI	OR	95% CI	OR	95% CI
All cause mortality							
1-AVB(N=1.369)	36 (3)	Ref.		Ref.		Ref.	
2-AVB (N=1.249)	57 (5)	1.87	1.22-2.88	1.59	1.01-2.50	1.65	1.03-2.63
3-AVB (N=315)	19 (6)	2.53	1.42-4.50	1.76	0.95-3.27	2.46	1.29-4.71
Cardiovascular mortality							
1-AVB(N=1.369)	29 (3)	Ref.		Ref.		Ref.	
2-AVB (N=1.249)	47 (5)	1.87	1.16-3.00	1.52	0.93-2.50	1.56	0.94-2.60
3-AVB (N=315)	14 (7)	2.23	1.16-4.30	1.44	0.72-2.89	1.94	0.94-4.02

Multivariate (1): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, haemoglobin. Multivariate (2): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, haemoglobin + medication use, including: aspirin, statins, ß-blockers, and ACE-inhibitors.

Figure 4. *Kaplan-Meier estimates for long-term all-cause mortality, stratified according to the number of affected vascular beds*



In the remaining 106 (8%) patients, no specific cause of death could be determined. The occurrence of all-cause mortality showed a significant relationship with the number of affected vascular beds (1-AVB 43, 2-AVB 50, 3-AVB 54%, $p < 0.001$). Kaplan-Meier estimates for long-term mortality stratified according the number of AVB showed that patients with 2- or 3-AVB had lower survival compared with patients with 1-AVB (*Figure 4*).

At 1-year follow-up, survival rates in patients with 1-, 2-, and 3-AVB were 91.4, 87.9 and 83.6, respectively. Furthermore, at 10-year follow-up, survival rates in 1-, 2- and 3-AVB were 48.0, 40.6, 29.2, respectively. Log rank rest compared cumulative survival between 1- and 2-AVB and 2- and 3-AVB and showed a significant difference in survival between both comparisons ($p < 0.001$). After multivariate regression analysis, adjusted for baseline demographic and risk factors, a strong relationship between the number of AVB and the risk of all-cause and cardiovascular mortality was detected at both 1 and 10 years of follow-up (*Table 3*). During long-term follow-up, patients with 2 or 3-AVB had an increased risk for the occurrence of all-cause mortality (2-AVB: HR 1.3, 95% CI: 1.15 to 1.45; 3-AVB: HR 1.8, 95% CI: 1.50 to 2.15), and also for the occurrence of cardiovascular mortality (2-AVB: HR 1.5, 95% CI: 1.24 to 1.68; 3-AVB: HR 2.0, 95% CI 1.60 to 2.51), compared with patients with 1-AVB, respectively.

Optimal medical therapy according the ESC/ACC guidelines was 57% in the patient group that underwent surgery between 2002 and 2008. During this period, aspirin (HR 0.52, 95% CI: 0.37 to 0.72), statins (HR 0.38, 95% CI 0.27 to 0.53) and ACE-inhibitors (HR 0.32, 95% CI 0.11 to 0.94) were significantly associated with lower mortality rates in propensity adjusted analysis. Of note, over 90% of the patients who underwent surgery after 2002 were on perioperative ß-blocker therapy.

Table 3 **Long-term survival**

	Events	**Univariate**		**Multivariate (1)**		**Multivariate (2)**	
	N (%)	OR	95% CI	OR	95% CI	OR	95% CI
All cause mortality							
1-AVB(N=1.369)	558 (43)	Ref.		Ref.		Ref.	
2-AVB (N=1.249)	630 (50)	1.32	1.18-1.48	1.27	1.13-1.43	1.29	1.15-1.45
3-AVB (N=315)	171 (54)	1.87	1.57-2.22	1.62	1.36-1.94	1.79	1.50-2.15
Cardiovascular mortality							
1-AVB(N=1.369)	334 (24)	Ref.		Ref.		Ref.	
2-AVB (N=1.249)	401 (32)	1.50	1.29-1.73	1.42	1.22-1.65	1.45	1.24-1.68
3-AVB (N=315)	114 (36)	2.14	1.73-2.65	1.81	1.45-2.27	2.00	1.60-2.51

Multivariate (1): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, haemoglobin. Multivariate (2): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, haemoglobin + medication use, including: aspirin, statins, ß-blockers, and ACE-inhibitors.

DISCUSSION

To our knowledge, the current study is the first to show a strong relationship between the number of affected vessel beds and long-term prognosis in patients with known symptomatic PAD. Compared with 1-AVB, patients with 2- or 3-AVB had significantly higher rates of all-cause and cardiovascular mortality during long-term follow-up after major vascular surgery. The process of atherosclerotic vascular disease is a diffuse progressive condition that usually affects multiple vascular territories concomitantly. All manifestations of arterial diseases are preceded by atherosclerotic plaques formation in the arterial wall. The presence of risk factors like hypertension, diabetes mellitus, smoking and hypercholesterolemia make patients prone for the development of atherosclerotic plaques. Therefore, lifestyle modification and medical treatment are strongly recommended for patients with atherosclerotic disease.[7,8]

Until now, most data regarding the prevalence and long-term prognosis of patients with polyvascular disease included determination of polyvascular disease in the primary care setting, while follow-up was generally limited to 1-year.[4,14] In most studies and registries, data on the prevalence of polyvascular disease were mainly on the presence of risk factors, symptoms and medical treatment. Hirsch *et al.* found a prevalence of polyvascular disease (PAD and CVD) of 16% in the primary care setting, which was observed by the REACH registry as well.[1,15] Recent data from the CRUSCADE investigators in patients presenting with non-ST-segment elevation acute coronary syndrome, reported a prevalence of 12% established PAD, 10% documented CVD, and 43% prior CAD.[16] Objective determination of polyvascular disease by screening and/or additional testing was performed primary by Hertzer *et al.* who observed a prevalence of CAD in 44, 30 and 33% of the PAD patients, respectively.[17] Analysis of the REACH registry showed that 2- or 3-AVB is present in 48 or 14% of PAD patients, respectively.[4] We demonstrated in the current study of patients with known PAD, a documented prevalence of 2- and 3-AVB of 43 and 11%, respectively. The slightly higher prevalence of polyvascular disease in the PAD subset of REACH patients is likely due to the inclusion of patients with ≥3 atherothrombotic risk factors without symptomatic vascular disease, in the REACH registry.

The current study showed a significant association between the presence of multiple risk factors and the presence of polyvascular disease, which was in line with previous studies that focused on the prevalence of risk factors in several atherosclerotic populations.[14,15,18] Atherothrombotic risk factor reduction is universally recommended for patients with PAD to reduce their high incidence of heart disease and stroke.[7,8,19-21] Although we found that patients with 2- or 3-AVB received better medical treatment compared with patients with lone PAD, there was still a underutilization of medication. In this study, aspirin use was observed in more than 50% of the patients included after 1996 and was associated with increased survival rates, which is in line with a recent meta-analyses.[22] The underutilization of optimal medical therapy is strongly related to the implementation of the guidelines on PAD after 2003, as before the implementation of guidelines only a minority of patients received a combination of aspirin, statins, ACE-inhibitors and in cases of ischemic heart disease additional ß-blockers was used.[7] Thereafter, the use of statins and ß-blockers has strongly increased, and 57% of the patients included in this cohort received optimal medical therapy. As reported by others, aspirin, statins and ACE-inhibitor use were all significantly associated with increased survival rates.[22] The gap between guideline recommendations and clinical practice in PAD patients remains a concerning and significant problem. Potential reasons for this under treatment could be related to

(i) low perception of the risk associated with PAD compared with CAD and CVD, and (ii) the absence of healthcare campaigns directed at providing information to individuals with PAD, especially during the previous decade.

Data regarding the perioperative outcome in the polyvascular patient population are scarce, as most studies are directed at one-year mortality rates. Our study showed that patients with 2- or 3-AVB had higher perioperative mortality rates compared with patients with 1-AVB (5 and 6 vs. 3% $p < 0.001$, respectively). Cardiovascular mortality was present in 75% of the patients that died within the first 30-days after major vascular surgery. In multivariate analyses polyvascular disease was significantly associated with increased all-cause mortality rates. Our data are in keeping with others reporting 30-day mortality rates up to 6%, of which 76% are due to cardiovascular cause in major vascular surgery patients.[18] Bhatt *et al.* reported a 30-day all-cause mortality rate of 7.3% in patients presenting with non-ST-elevation acute coronary syndrome and concomitant 3-AVB. In this study, only 3-AVB was significantly associated with increased all-cause mortality (OR 1.25, 95% CI: 1.02 to 1.54) in multivariate analysis.[16]

After one year follow-up, 11% of the patients died of which 74% secondary to a cardiovascular cause. A significant association between the number of AVB and the occurrence of all-cause and cardiovascular mortality was observed. Mortality rates increased from 8 in 1-AVB to 16% in 3-AVB. These findings are in keeping with others, as in the REACH registry one-year all-cause and cardiovascular mortality rates were approximately doubled in patients with polyvascular disease, compared with single arterial disease.[14] Furthermore, the Polyvascular Atherothrombosis Observational Survey (PATHOS) found that patients with acute myocardial infarction or stroke and concomitant PAD had an increased mortality risk (OR 2.05, 95% CI: 1.31 to 3.22) compared with patients without PAD.[23] These findings support the need for increased awareness of the cross-risk that is related to the overlap between the various arterial locations of atherothrombosis.

No prior large studies investigated the long-term prognosis of patients with polyvascular atherosclerotic disease up to 10 years. The current study found that after a follow-up period of 5 years, 50% of the patients with 3-AVB had already died, pointing at the grave prognosis of polyvascular disease. Criqui *et al.* performed the first long-term outcome study in 565 patients with large-vessel PAD and detected an increased relative risk for cardiovascular mortality (RR 5.9, 95% CI: 3.0 to 11.4) after 10-years follow-up, compared with patients without PAD.[5] Eagle *et al.* and Sutton *et al.* observed that during 10-year follow-up, CAD patients

with concomitant PAD had a 25% greater likelihood of mortality compared with CAD patients without PAD at any point in time.[24,25] Recently, Welten *et al.* performed a propensity-matched study in PAD and CAD patients, showing that during a mean follow-up of 6 ± 4 years, patients with PAD had a significantly worse long-term prognosis compared with patients with CAD (unadjusted HR 2.4, 95% CI: 2.18 to 2.65).[18] Hence, patients with combined PAD, CAD and/or CVD have the worst prognosis. Therefore, early objective detection and treatment of asymptomatic concomitant cardiovascular risk factors in patients with PAD is recommended and strongly emphasized by the current guidelines.[7,8]

Limitations

Potential limitations of the current study merit consideration. First, this study has the disadvantage of a retrospective design. Second, the standardized protocol for preoperative screening did not include echocardiography before 2002; therefore there could be an underestimation of subclinical atherosclerosis in patients undergoing surgery before this date. In addition, diagnostic methods and accuracy have changed over time, which could have influenced the criteria for the presence of documented CAD or CVD. Third, a specific cause of death could not be established in 3.6% of the patients that died during the follow-up period. One year after the last patient had been included, mortality rates were verified according the civil registries; however, reviewing the death certificates or contacting the treating general practioner could not establish cause of death. Therefore, we performed two additional analyses in which patients for whom cause of death was unknown were regarded either as cardiovascular or noncardiovascular deaths. These analyses found similar results with no influence on the significance of the outcome parameters. Finally, although this study detected significant associations between medical treatment and increased survival rates, these results need to be interpreted with some caution as this study only included medical treatment at discharge and no evaluation of treatment adherence during follow-up was available.

Conclusion

Polyvascular atherosclerotic disease in PAD patients scheduled for elective major vascular surgery is independently associated with an increased risk for all-cause and cardiovascular mortality during long-term follow-up. Peripheral arterial disease patients with polyvascular disease have more atherosclerotic risk factors and receive extended medical treatment, mainly as a result of the implementation of guidelines. However, as PAD patients with polyvascular disease still receive sub-optimal cardioprotective medication; more attention should be given to optimization of life style modification and treatment.

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Chapter 6

The influence of polyvascular disease on the obesity paradox in vascular surgery patients

Jan-Peter van Kuijk
Willem-Jan Flu
Wael Galal
Michel Chonchol
Hence J.M.Verhagen
Jeroen J. Bax
Don Poldermans

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Chapter 7

Prognostic implications of asymptomatic left-ventricular dysfunction in patients undergoing vascular surgery

Willem-Jan Flu
Jan-Peter van Kuijk
Sanne E Hoeks
Ruud J. Kuiper
Olaf Schouten
Dustin Goei
Abdou Elhendy
Hence J.M. Verhagen
Ian R Thomson
Jeroen J. Bax
Lee A Fleisher
Don Poldermans

Anesthesiology, 2010;112(6):1316-1324

ABSTRACT

Background: The prognostic value of heart failure symptoms on postoperative outcome is well acknowledged in the American College of Cardiology/American Heart Association and European Society of Cardiology perioperative guidelines. However, the prognostic value of asymptomatic left ventricular (LV) dysfunction remains unknown. This study evaluated the prognostic implications of asymptomatic LV dysfunction, assessed with routine preoperative echocardiography, in high-risk vascular surgery patients.

Methods: Echocardiography was performed preoperatively in 1.005 consecutive vascular surgery patients. Systolic LV dysfunction was defined as LV ejection fraction <50%. Isolated diastolic LV dysfunction was diagnosed based on the ratio of mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A), pulmonary vein flow and deceleration time. Troponin-T measurements and electrocardiograms were performed routinely before and after surgery. Study endpoints were 30-day cardiovascular events and long-term cardiovascular mortality. Multivariate regression analyses evaluated the relation between LV function and cardiovascular outcome.

Results: Left ventricular dysfunction was diagnosed in 506 (50%) patients, of which 80% were asymptomatic. In open vascular surgery (N=649), both asymptomatic systolic and isolated diastolic LV dysfunction were associated with 30-day cardiovascular events (OR 2.3, 95% CI: 1.4 to 3.6 and OR 1.8, 95% CI: 1.1 to 2.9) and long-term cardiovascular mortality (HR 4.6, 95% CI: 2.4 to 8.5 and HR 3.0, 95% CI: 1.5 to 6.0). In endovascular surgery (N=356), only symptomatic heart failure was associated with 30-day cardiovascular events (OR 1.8, 95% CI: 1.1 to 2.9) and long-term cardiovascular mortality (HR 10.3, 95% CI: 5.4 to 19.3).

Conclusions: This study demonstrated that asymptomatic LV dysfunction is predictive for 30-day and long-term cardiovascular outcome in open vascular surgery patients. These data suggest that preoperative risk stratification should not solely include heart failure symptoms, but routine preoperative echocardiography might be considered for risk stratification of patients undergoing open vascular surgery.

INTRODUCTION

Worldwide, about 100 million adults undergo noncardiac surgery every year,[1] and by the year 2020 this number will increase by 25%.[2] The risk of adverse perioperative cardiovascular events after vascular surgery is particularly high as compared with other noncardiac surgeries.[3] Although ischemic heart disease is acknowledged to be the most important risk factor for cardiovascular events after noncardiac surgery, several studies indicate that symptomatic heart failure is equally important.[4-6] In the general population the prevalence of symptomatic heart failure is estimated to be around 2 to 3% and increases with age, with a prevalence estimated between 10 to 20% in septo- and octogenarians.[7] Whereas the term heart failure describes a clinical syndrome, LV dysfunction describes the impaired mechanical properties of the left-ventricle. Asymptomatic LV dysfunction is considered a precursor of symptomatic heart failure, associated with high mortality.[7] The prevalence of patients with asymptomatic LV dysfunction and symptomatic heart failure is assumed to be similar.[8]

In the most recent American College of Cardiology/American Heart Association (AHA) and European Society of Cardiology (ESC) perioperative guidelines,[3,9] the prognostic value of symptomatic heart failure on postoperative outcome is well acknowledged. However, the prognostic implications of asymptomatic LV dysfunction remains unknown. Routine perioperative evaluation of LV function is not recommended in ACC/AHA perioperative guidelines (Class III, Level of Evidence: C).[9] Additionally, LV assessment with rest echocardiography is not recommended in ESC perioperative guidelines (Class III, Level of Evidence: C) for asymptomatic patients.[3] We conducted the present study to evaluate the impact of asymptomatic isolated diastolic and asymptomatic systolic LV dysfunction, evaluated with routine preoperative echocardiography, on postoperative outcome of patients undergoing open or endovascular surgery.

MATERIAL AND METHODS

Study population

The study population has been previously described and consisted of 1.005 consecutive vascular surgery patients undergoing elective (open or endovascular) lower extremity artery, carotid artery or abdominal aorta repair.[10] This prospective cohort study was performed at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period of 2002 to 2008. The study was approved by the hospital's ethics committee and performed with informed consent of all patients.

Baseline characteristics

Prior to surgery, a detailed history was obtained from every patient. Cardiac history was assessed and ischemic heart disease was defined as a history of angina pectoris, coronary revascularization or myocardial infarction. Additional clinical data included age, gender, blood pressure, heart rate, cerebrovascular disease (history of ischemic or hemorrhagic stroke), renal dysfunction (serum creatinine >2 mg/dL), diabetes mellitus (fasting blood glucose ≥126 mg/dL or requirement of anti-diabetic medication), hypertension (blood pressure ≥140/90 mmHg in non-diabetics and ≥130/80 mmHg in diabetics,[11] or requirement of antihypertensive medication), hypercholesterolemia (low density lipoprotein cholesterol ≥135 mg/dL or requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification) and smoking status. Finally, the use of β-blockers, statins, aspirin, oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics and nitrates was recorded.

Echocardiography

Preoperatively, transthoracic echocardiography was performed in all patients using a portable Acuson Cypress Ultrasound System (Acuson, A Siemens Company, Mountain View, CA) with a 3V2C transducer (3.0/3.5/2.5/2.0 MHz) for adult cardiac evaluation. Standard parasternal and apical 2- and 4-chamber views were obtained during rest with the patient in the left lateral decubitus position as recommended.[12] Left-ventricular end-systolic and end-diastolic volumes were determined and LV ejection fraction was calculated using the biplane Simpson's technique,[13] with an inter- and intra-observer variability of 9 to 12 and 6%, respectively.[14] Systolic (S) and diastolic (D) pulmonary vein flow, deceleration time and ratio of mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A) were determined in apical 4-chamber. Echocardiographic data were for research purposes and were not used for clinical management.

Definition of LV dysfunction

Left-ventricular ejection fraction <50%, both with and without accompanying diastolic dysfunction, defined systolic LV dysfunction.[7] Diastolic LV dysfunction was confirmed in patients with E/A-ratio <0.8 (impaired relaxation) or >2 (restrictive relaxation).[15] Abnormal pulmonary vein flow (S/D <1) was used to distinguish normal and pseudo-normal diastolic LV function in patients with E/A-ratio between 0.8 to 2.[16] Deceleration time >220 ms (impaired relaxation) or <140 ms (restrictive relaxation) defined diastolic LV dysfunction in patients with atrial fibrillation.[16] Diastolic LV dysfunction, in the presence of a LV ejection fraction ≥50%, defined asymptomatic isolated diastolic dysfunction. The presence of LV

dysfunction in combination with heart failure symptoms (shortness of breath, fatigue, exercise intolerance, signs of fluid retention) defined symptomatic heart failure.[7] Two experienced investigators performed off-line assessments of the obtained ultrasound images. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessment and a majority decision was reached.

Study outcomes

Serial electrocardiograms and troponin-T measurements were obtained from all patients prior to surgery, postoperatively on day 1, 3, 7 and before discharge. Study endpoints were 30-day cardiovascular events (CV), defined as myocardial ischemia, myocardial infarction and CV mortality, and long-term CV mortality. Myocardial ischemia was present in patients with normal preoperative and elevated (>0.03 ng/mL) troponin-T levels postoperatively.[17] Elevated troponin-T levels in combination with electrocardiographic changes (new onset ST-T changes and pathological Q waves) defined myocardial infarction.[18] Troponin T level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany). Patients with elevated troponin-T levels before surgery were not included in the study. Patients were subjected to a follow up visit with one of the study investigators 30-day post surgery and for those patients who did not attend, we approached the referring physicians. In patients still admitted or re-admitted at the Erasmus MC, 30-day follow up was completed using the Erasmus MC medical records. Long-term mortality was assessed by approaching the municipal civil registries. Cause of death was ascertained by examining death certificates, and otherwise by reviewing medical records. Cause of death was classified as either cardiovascular or noncardiovascular death. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and includes death following myocardial infarction, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular event or transient ischemic attack), and surgery related bleeding complications (only a postoperative cause of death). Sudden unexpected death was classified as a cardiovascular death. Cause of death was separately assessed by two authors. In the absence of consensus, a third investigator assessed the cause of death and a majority decision was reached. Follow-up was completed in all patients.

Statistical analysis

Continuous variables are described as means ± standard deviation (SD) and dichotomous data as numbers and percentages. Continuous data were compared

using ANOVA for trend and categorical data using the linear by linear association. The prognostic value of LV dysfunction towards 30-day and long-term follow up was evaluated with logistic and Cox regression analysis, respectively. Multivariate analysis were primarily adjusted for covariates (age and sex, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease and smoking status) prospectively locked into the model based on the clinical knowledge and belief that these factors might (i) contribute to the study outcomes and (ii) confound the association between the primary echo predictors and the study outcomes. Secondary adjustments were done in a step-wise fashion and these analyses were adjusted for medication use (β-blockers, statins, aspirin, oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics and nitrates) on top of the covariates used in the primary regression model We report (crude and adjusted) odds and hazard ratios with their 95% confidence interval (95%-CI). For all tests, a *p*-value <0.05 (two-sided) was considered significant. Cumulative long-term survival was determined by the Kaplan-Meier method. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient population

A total of 1.005 patients undergoing open vascular (N=649 or 65%) or endovascular (N=356 or 35%) surgery were included in the study. Of the open vascular surgery patients; 148 patients (23%) underwent carotid artery repair, 249 patients (38%) underwent abdominal aorta repair, and 252 patients (39%) underwent lower extremity artery repair. In comparison, of the endovascular patients; 90 patients (25%) underwent carotid artery repair, 162 patients (46%) underwent abdominal aorta repair, and 104 patients (29%) underwent lower extremity artery repair. All patients undergoing open vascular surgery had general anesthesia and 56 (35%) of the patients undergoing endovascular aortic repair had general anesthesia. General anesthesia was not provided for the percutaneous procedures.

The majority of patients were men (77%) and the mean age was 67 ± 10 years. Mean follow-up was 2.2 ± 1.8 years (range 3 to 79 months). Left-ventricular dysfunction was diagnosed in 506 (50%) patients. Of the patients with LV dysfunction, 403 (80%) patients had asymptomatic LV dysfunction and 103 (20%) had symptomatic heart failure. Of the patients with asymptomatic LV dysfunction, 209 (52%) had asymptomatic isolated diastolic LV dysfunction and 194 (48%) had

asymptomatic systolic LV dysfunction. Of the 103 patients with symptomatic heart failure, 72/70% patients had New York Heart Association Class II, 28/27% patients had New York Heart Association Class III (12 patients had signs of fluid retention objectified as peripheral oedema) and 3/3% patients had New York Heart Association Class IV, with signs of pulmonary oedema objectified with physical examination.

Table 1 **Baseline characteristics according to left-ventricular function**

	Normal LV function [N=499]	**Asymptomatic diastolic LV dysfunction** [N=209]	**Asymptomatic systolic LV dysfunction** [N=194]	**Symptomatic heart failure** [N=103]	***P* for trend**
Demographics (mean ± SD)					
Age	65 (11)	70 (10)	70 (8)	70 (10)	<0.001
Male (%)	363 (73)	154 (74)	168 (87)	84 (82)	0.001
Systolic blood pressure	141 (24)	142 (24)	141 (26)	135 (23)	0.111
Diastolic blood pressure	79 (12)	80 (12)	79 (12)	77 (12)	0.199
Heart rate	70 (13)	73 (13)	73 (15)	72 (15)	0.012
Medical history (%)					
Ischemic heart disease	165 (33)	83 (40)	102 (53)	80 (78)	<0.001
Cerebrovascular disease	169 (34)	83 (40)	76 (39)	25 (24)	()0.603
Renal dysfunction	62 (12)	34 (16)	41 (21)	42 (41)	<0.001
Diabetes mellitus	141 (28)	62 (30)	64 (33)	30 (29)	0.698
Hypertension	294 (59)	153 (73)	135 (70)	76 (74)	<0.001
Hypercholesterolemia	303 (65)	131 (65)	114 (60)	61 (63)	0.729
COPD	100 (20)	49 (23)	50 (26)	32 (31)	<0.001
Smoker, current	225 (45)	85 (41)	69 (36)	41 (40)	0.046
Surgery type (%)					
Open	320 (64)	129 (62)	118 (61)	82 (80)	0.102
LEAD	131 (26)	42 (21)	43 (22)	36 (35)	0.926
Abdominal aorta repair	110 (22)	51 (24)	48 (25)	40 (39)	0.100
Carotid artery repair	79 (16)	36 (17)	27 (14)	6 (6)	0.062
Endovascular	179 (36)	80 (38)	76 (39)	21 (20)	0.102
LEAD	61 (12)	22 (10)	16 (8)	5 (5)	0.179
Abdominal aorta repair	71 (14)	40 (19)	37 (19)	14 (14)	0.065
Carotid artery repair	47 (10)	18 (9)	23 (12)	2 (1)	0.633
Medication (%)					
β-blockers	368 (74)	161 (77)	162 (84)	87 (84)	0.001
Statins	352 (71)	145 (70)	149 (77)	72 (70)	0.433
Aspirin	303 (61)	110 (53)	114 (60)	61 (59)	0.578
Oral anticoagulants	61 (12)	35 (17)	41 (21)	27 (26)	<0.001
ACE inhibitors	129 (26)	65 (31)	63 (33)	53 (52)	<0.001
ARB	49 (13)	29 (14)	36 (19)	23 (22)	0.011
Diuretics	95 (19)	54 (26)	56 (29)	49 (48)	<0.001
Nitrates	32 (6)	19 (9)	20 (10)	30 (29)	<0.001

Angiotensin-converting enzyme (ACE), chronic obstructive pulmonary disease (COPD), left-ventricular (LV), standard deviation (SD), lower extremity arterial disease (LEAD), angiotensin receptor blocker (ARB)

Baseline characteristics

Clinical parameters are shown in *Table 1*. Patients with LV dysfunction were older and had higher incidence of ischemic heart disease, renal dysfunction, hypertension, chronic obstructive pulmonary disease and had higher resting heart rate compared to patients with normal LV function. In addition, patients with LV dysfunction more often received β-blockers, oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics and nitrates. Patients with asymptomatic systolic LV dysfunction or symptomatic heart failure were more often male. A higher number of patients with symptomatic heart failure underwent open surgery compared to the other groups.

Table 2 **Left-ventricular function and postoperative outcome**

	Normal LV function [N=499]		Asymptomatic diastolic LV dysfunction [N=209]		Asymptomatic Systolic LV dysfunction [N=194]		Symptomatic heart failure [N=103]		*P*-value
30-day (%)									
Cardiovascular	5	(10)	38	(18)	44	(23)	50	(49)	<0.001
Myocardial	5	(10)	36	(17)	41	(21)	45	(44)	<0.001
Cardiovascular	2	(0)	4	(2)	7	(4)	11	(11)	<0.001
All cause mortality	6	(1)	5	(2)	7	(4)	11	(11)	<0.001
Long-term (%)									
Cardiovascular	1	(3)	21	(10)	31	(16)	40	(39)	<0.001
All cause mortality	5	(11)	31	(15)	38	(20)	41	(40)	<0.001

Left-ventricular (LV)

Thirty-day outcome

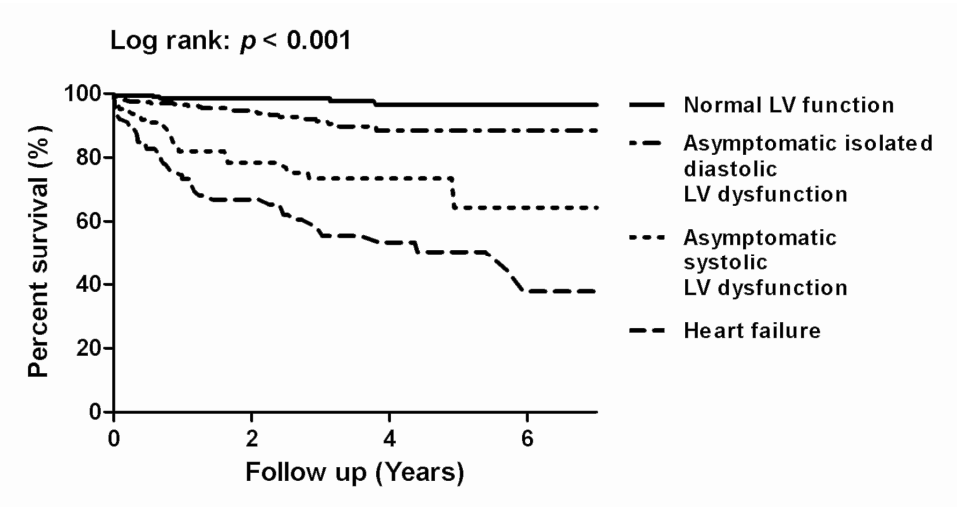
During 30-day follow-up 172 (17%) patients had a non-fatal myocardial event of which 131 (76%) patients had myocardial ischemia and 41 (24%) patients had myocardial infarction. In total, 51 (10%) patients with normal LV function had a 30-day CV event, compared to 38 (18%) patients with asymptomatic isolated diastolic LV dysfunction, 44 (23%) patients with asymptomatic systolic LV dysfunction and 50 (49%) patients with symptomatic heart failure ($p < 0.001$, *Table 2*). Multivariate analyses, in patients undergoing open surgery, demonstrated that asymptomatic isolated diastolic LV dysfunction, asymptomatic systolic LV dysfunction and symptomatic heart failure were all associated with 30-day CV events with odds ratio's of 1.8 (95% CI: 1.1 to 2.9), 2.3 (95% CI: 1.4 to 3.6) and 6.8 (95% CI: 4.0 to 11.6), respectively (*Table 3*). Other risk factors associated with 30-day CV events were age, ischemic heart disease, renal dysfunction and chronic obstructive pulmonary disease with odds ratios of 1.8 (95% CI: 1.0 to 1.1), 1.7 (95% CI: 1.1 to 2.6), 3.9 (95% CI: 2.2 to 7.1) and 1.8 (95% CI: 1.2 to 2.6), respectively. Multivariate analyses, in patients undergoing endovascular surgery, demonstrated that symptomatic heart failure was associated with 30-day CV events with an odds

ratio of 9.3 (95% CI: 2.3 to 37.7) (*Table 4*). For both types of surgical procedures, additional adjustment for medication use (β-blockers, statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers and diuretics) did not change the prognostic value of LV dysfunction towards 30-day outcome.

Long-term outcome

During long-term follow-up 164 (16%) patients died. The study endpoint long-term CV mortality was reached in 107 (11%) patients. In total, 15 (3%) patients with normal LV function died due to CV causes, compared to 21 (10%) patients with asymptomatic isolated diastolic LV dysfunction, 31 (16%) patients with asymptomatic systolic LV dysfunction and 40 (39%) patients with symptomatic heart failure ($p < 0.001$, *Table 2*).

Figure 1. *Left-ventricular (LV) function and long-term survival after vascular surgery*



Cumulative survival for all patients is shown in *Figure 1* (log rank $p < 0.001$). Of the patients with LV dysfunction who reached the study endpoint long-term CV mortality, 48 patients (52%) demonstrated myocardial ischemia or infarction during 30-day follow-up.

Multivariate analyses, in patients undergoing open surgery, demonstrated that asymptomatic isolated diastolic LV dysfunction, asymptomatic systolic LV dysfunction and symptomatic heart failure were all associated with long-term CV mortality with hazard ratio's of 3.0 (95% CI: 1.5 to 6.0), 4.6 (95% CI: 2.4 to 8.5) and 10.3 (95% CI: 5.4 to 19.3), respectively (*Table 3*).

Table 3 **Association between left-ventricular function and postoperative outcome: Open vascular surgery**

	N	(%)	Univariate		Multivariate	
30-day CV events			**OR**	**[95% CI]**	**OR**	**[95% CI]**
Normal LV function	44/320	(14)	1.0		1.0	
Isolated diastolic LV dysfunction	30/129	(23)	2.0	1.2-3.1	1.8	1.1-2.9
Systolic LV dysfunction	36/118	(31)	2.6	1.7-4.0	2.3	1.4-3.6
Symptomatic heart failure	44/82	(54)	8.3	5.1-13.4	6.8	4.0-11.6
Long-term CV mortality			**HR**	**[95% CI]**	**HR**	**[95% CI]**
Normal LV function	8/320	(3)	1.0		1.0	
Isolated diastolic LV dysfunction	14/129	(11)	3.5	1.8-6.8	3.0	1.5-6.0
Systolic LV dysfunction	23/118	(20)	5.2	2.8-9.7	4.6	2.4-8.5
Symptomatic heart failure	31/82	(38)	13.6	7.5-24.6	10.3	5.4-19.3
Long-term all cause mortality			**HR**	**[95% CI]**	**HR**	**[95% CI]**
Normal LV function	37/320	(12)	1.0		1.0	
Isolated diastolic LV dysfunction	20/129	(16)	1.5	0.9-2.3	1.4	0.9-2.1
Systolic LV dysfunction	28/118	(24)	1.8	1.2-2.7	1.7	1.1-2.5
Symptomatic heart failure	32/82	(39)	3.9	2.6-5.8	3.1	2.0-4.8

Multivariate analysis adjusted for: age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease and smoking. Cardiovascular (CV), confidence interval (CI), hazard ratio (HR), left-ventricular (LV)

Table 4 **Association between left-ventricular function and postoperative outcome: Endovascular surgery**

	N	(%)	Univariate		Multivariate	
30-day CV events			**OR**	**[95% CI]**	**OR**	**[95% CI]**
Normal LV function	7/179	(4)	1.0		1.0	
Isolated diastolic LV dysfunction	8/80	(10)	2.7	0.9-7.8	2.2	0.7-6.9
Systolic LV dysfunction	8/76	(11)	2.9	1.0-8.6	2.5	0.8-7.8
Symptomatic heart failure	6/21	(29)	9.8	2.9-33.0	9.3	2.3-37.7
Long-term CV mortality			**HR**	**[95% CI]**	**HR**	**[95% CI]**
Normal LV function	7/179	(4)	1.0		1.0	
Isolated diastolic LV dysfunction	7/80	(9)	2.2	0.8-6.4	1.7	0.5-5.3
Systolic LV dysfunction	8/76	(11)	2.4	0.8-6.5	2.2	0.8-6.6
Symptomatic heart failure	9/21	(43)	14.5	5.4-39.1	11.4	3.7-35.6
Long-term all cause mortality			**HR**	**[95% CI]**	**HR**	**[95% CI]**
Normal LV function	17/179	(10)	1.0		1.0	
Isolated diastolic LV dysfunction	11/80	(14)	1.5	0.7-3.2	1.2	0.5-2.7
Systolic LV dysfunction	10/76	(13)	1.3	0.6-2.9	1.2	0.5-2.9
Symptomatic heart failure	9/21	(43)	6.1	2.7-13.8	5.1	1.9-13.3

Multivariate analysis adjusted for: age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease and smoking. Cardiovascular (CV), confidence interval (CI), hazard ratio (HR), left-ventricular (LV)

Other risk factors associated with long-term CV mortality were age, ischemic heart disease, renal dysfunction and smoking with hazard ratios of 1.1 (95% CI: 1.1 to 1.2), 1.6 (95% CI: 1.1 to 2.8), 2.5 (95% CI: 1.3 to 5.1) and 2.0 (95% CI: 1.2 to 3.1), respectively. Multivariate analyses, in patients undergoing

endovascular surgery, demonstrated that symptomatic heart failure was associated with long-term CV mortality with a hazard ratio of 11.4 (95% CI: 3.7 to 35.6) (*Table 4*). For both types of surgical procedures, additional adjustment for medication use did not change the prognostic value of LV dysfunction towards long-term outcome.

DISCUSSION

The present study demonstrated that open vascular surgery patients with asymptomatic isolated diastolic- or systolic LV dysfunction, were at increased risk for 30-day CV events and long-term CV mortality. In endovascular surgery patients, only symptomatic heart failure was associated with an increased risk for 30-day CV events and long-term CV mortality. In ACC/AHA and ESC guidelines, symptoms of heart failure are acknowledged to be an important predictor of postoperative outcome. However, our data suggest asymptomatic LV dysfunction should be imbedded in preoperative risk stratification of vascular surgery patients, as well.

Left-ventricular dysfunction is caused by neuro-hormonal responses activated by cardiac injury or an increased hemodynamic load. These responses are known to induce (i) sympathetic stimulation, (ii) salt and water retention, and (iii) vasoconstriction.[19,20] Although these responses are initially adaptive, they become maladaptive over time, due to a process called LV remodelling. This process leads to (i) LV hypertrophy (concentric remodelling) associated with diastolic LV dysfunction, or (ii) LV dilatation (eccentric remodelling) associated with systolic LV dysfunction.[21] During surgery, high catecholamine production is responsible for vasoconstriction and hemodynamic stress.[2] Surgical stress and perioperative fluid administration increases ventricular pre- and afterload, making patients with systolic LV dysfunction susceptible for perioperative myocardial damage.[22] During surgery there is an increased oxygen demand and patients with coronary artery stenosis are at increased risk for perioperative myocardial damage, due to an oxygen supply–demand mismatch.[3,23] Patients with diastolic LV dysfunction have a reduced coronary flow reserve making them susceptible to perioperative myocardial damage as well.[21] In addition, concentric remodelling causes a reduction of LV compliance, making LV filling dependent upon blood volume contributed by ventricular preload. Perioperative LV preload reductions can result in tachycardia with concomitant reduction of coronary perfusion, leading to myocardial damage.[24]

Episodes of perioperative myocardial damage are most often silent and therefore patients often remain untreated, which might contribute to an increased

risk of long-term CV mortality.[25,26] We have found that approximately three out of four patients with perioperative damage, had LV dysfunction. In line with previous studies, we have found that endovascular surgery was associated with a reduced incidence of perioperative myocardial damage, compared with open surgery, possibly explained by reduced myocardial stress and the need for lower fluid administration during endovascular procedures.[27,28] In addition, one should keep in mind that carotid surgery is associated with lower cardiac risk compared with abdominal aneurysm repair and lower extremity revascularization.

Myocardial perfusion scintigraphy and pharmacological stress echocardiography are known to accurately stratify patients at risk for perioperative myocardial damage.[29-31] In addition, the presence of wall motion abnormalities at rest has predictive value for the development of perioperative cardiac events as well.[31] Until now, studies addressing the impact of heart failure in surgical patients, mainly focused on symptomatic patients with a reduced LV ejection fraction.[5,23,32,33] A retrospective study conducted by Xu-Cai *et al.* evaluated the impact of symptomatic heart failure with a preserved LV ejection fraction, demonstrating an increased risk for long-term mortality. However no increased risk for perioperative mortality was observed.[34] Recently, Maytal *et al.* studied 313 vascular surgery patients and found diastolic LV dysfunction to be a predictor of adverse CV outcome, however systolic LV dysfunction was not.[35] Several differences between the study conducted by Maytal *et al.* and the present study that might explain the different outcome regarding the impact of systolic LV dysfunction on CV outcome, such as: (i) subanalysing open vs. endovascular surgery, (ii) troponin T measurements obtained routinely or when clinically indicated, (iii) definition of the LV function groups, and (iv) follow-up duration. To our knowledge, the present study is first to demonstrate that asymptomatic LV dysfunction (diastolic and systolic) is associated with an increased risk for in open vascular surgery patients.

In the most recent ACC/AHA and ESC perioperative guidelines,[3,9] the prognostic value of symptoms of heart failure on postoperative outcome is well acknowledged and incorporated into the decision process with regard to proceeding directly to surgery. In addition, preoperative cardiac risk indices incorporate symptomatic heart failure as an important risk factor.[4,6,36] To define surgical patients at 'high risk' for developing adverse CV events, one point should be assigned to patients with (a medical history of) current symptoms of heart failure, next to other risk factors such as ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus or high-risk surgery. To prevent an underestimation of the 'cardiac risk burden' of vascular surgery patients, our data

suggest that asymptomatic LV dysfunction should be imbedded in these risk indices as well.

Our results indicate that asymptomatic LV dysfunction is not associated with increased risk for 30-day CV events and long-term CV mortality in endovascular surgery patients. An explanation of this finding could lie in the fact that endovascular surgery is associated with reduced myocardial stress compared to open vascular surgery.[27,28] The detection of asymptomatic LV dysfunction with routine preoperative echocardiography could, therefore, add valuable information in the decision making between open and endovascular surgery.

Biochemical markers, such as N-terminal pro-B-type natriuretic peptide, are increasingly used in the detection and exclusion of heart failure,[37] and have proven to predict poor outcome after vascular surgery.[38] Standard measurements of this biochemical marker may play an important role to detect asymptomatic LV dysfunction in vascular surgery patients, regardless of the presence of heart failure symptoms. However, the diagnostic value of natriuretic peptides in asymptomatic patients at risk for diastolic or systolic LV dysfunction is controversial. In a recent study conducted by Luers *et al.*, plasma levels of natriuretic peptides significantly increased with a decreasing ejection fraction and with a severe degree of diastolic dysfunction.[39] Therefore, the authors suggest that high-risk individuals may be screened most efficiently by using a score system, incorporating clinical data and N-terminal pro-B-type natriuretic peptide. In vascular surgery patients, future studies are needed to evaluate the value of B-type natriuretic peptides vs. echocardiography to detect LV dysfunction in patients with or without heart failure symptoms. In 2003 Grayburn *et al.* proposed to shift the paradigm from preoperative noninvasive risk stratification to therapy.[40] Routine preoperative evaluation of LV function could reveal patients with asymptomatic LV dysfunction eligible for pharmacological treatment. Before surgery, low-dose β-blockade could be considered, titrated to obtain a heart rate between 60-70 beats per minute.[41] In addition, initiation of angiotensin blockers could be considered after surgery.[42]

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent the general vascular surgery population scheduled. Second, although two experienced investigators performed an off-line assessment of ultrasound images, we cannot rule out inter-observer variability to have had a minor influence on our results. Third, the evaluation of diastolic LV function with conventional Doppler, ratio of mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A) and pulmonary vein filling patterns was limited due to

preload dependency and not including Valsalva maneuver, ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E'), isovolumetric relaxation time or Tissue Doppler Imaging.

In conclusion, this study demonstrated that asymptomatic LV dysfunction is a predictor of CV outcome in open vascular surgery patients. These data suggest that preoperative risk stratification should not solely include symptomatic heart failure, already acknowledged in ACC/AHA and ESC perioperative guidelines; however asymptomatic LV dysfunction should be imbedded as well. Standard preoperative evaluation of LV function could be argued based on our results, suggesting a move towards more routine use of cardiac echo in open vascular surgery patients.

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Chapter 8

Comparing open and endovascular repair of abdominal aortic aneurysm: Do not forget the importance of perioperative ischemia

Jan-Peter van Kuijk
Willem-Jan Flu
Don Poldermans

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To the editor: Dr Lederle and colleagues conducted a randomized trial to compare endovascular (EVAR) vs open repair of abdominal aortic aneurysm (AAA), showing lower perioperative mortality for endovascular than open repair.[1] Importantly, the early advantage of endovascular repair was not offset by increased mortality in the first 2 years after repair.

The atherosclerotic process is often not limited to a single arterial location, giving it a character of a systemic and generalized disease. More than 25 years ago, Hertzer and colleagues already demonstrated that only 6% of the patients with an AAA have a healthy coronary tree.[2] Feringa and colleagues studied a group of vascular surgery patients who underwent preoperative cardiac testing, and observed an asymptomatic ejection fraction <40% or silent ischemia (new wall motion abnormalities) was present in 14% and 41% of the patients, respectively.[3]

In the vast majority of the patients, the atherosclerotic process remains asymptomatic. However, surgical stress elucidates a rapid progression of the atherosclerotic disease. This progression is reflected by asymptomatic perioperative troponin T release, an important marker of underlying coronary artery disease. Studies have demonstrated prevalence's of 10% and 30% of troponin T release after endovascular and open repair, respectively.[4] Importantly, up to 90% of the troponin T elevations were asymptomatic. The occurrence of asymptomatic perioperative myocardial damage, assessed with troponin T measurements and continuous electrocardiographic monitoring for 72 hours, was associated with a 2.3 fold increased risk for long-term mortality in vascular surgery patients.[4, 5]

In conclusion, EVAR has a reduced perioperative stress response compared to open repair, which is very likely to explain the reduced short-term mortality rates. The disappearance of the early advantage of endovascular repair after 2 years could be explained by the high incidence of asymptomatic coronary artery disease, with an accelerated subclinical progression due to surgical stress. This results in asymptomatic perioperative cardiac damage and reduced survival rates during long-term follow-up. Routine perioperative troponin T evaluation should be recommended to detect early postoperative cardiac damage and identify patients who will benefit from aggressive follow-up and medical treatment after AAA repair.

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Chapter 9

Asymptomatic perioperative cardiac damage: long-term prognosis

Jan-Peter van Kuijk
Willem-Jan Flu
Michiel T Voûte
Olaf Schouten
Don Poldermans

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PERIOPERATIVE CARDIAC DAMAGE

Worldwide more than 230 million major surgeries are performed annually, and this number continues to grow.[1] The estimated post-operative myocardial infarction (MI) rate is 1% (approximately 2.300.000 patients) and the cardiovascular mortality rate is approximately 0.3% (690.000 patients).[1] The incidence of asymptomatic perioperative cardiac damage is not well known but can be as high as 20% in patients undergoing high-risk surgery, such as vascular surgery.[2,3]

Despite improved medical treatment strategies, perioperative cardiac complications remain a significant problem. With aging of the population, more high-risk cardiac patients will undergo surgery, possibly resulting in an increased incidence of perioperative MI. According to current guidelines, MI is characterized by ECG criteria and cardiac enzymes including creatine kinase (MB) and cardiac troponins.[4] However, in the perioperative period symptoms of cardiac complications might be masked by residual anesthetic effects and postoperative conditions such as incisional pain. Consequently, as most cardiac events are asymptomatic or concealed by other postoperative symptoms, while ECG changes are often transient, cardiac damage might not be detected until it develops into complete MI. In fact, it is estimated that up to 75% of postoperative cardiac complications remains unnoticed.

The pathophysiology of perioperative cardiac events is described by two distinct mechanisms that have been described as type 1 and type 2 by the universal definition of MI.[4] Type 1 MI was defined as an acute coronary syndrome (ACS) that occurs when a coronary plaque ruptures, leading to thrombus formation and subsequent acute coronary thrombosis, ischemia and infarction. This type of MI is elucidated by the perioperative surgical stress response that includes a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation and consequent hypercoagulability.[5] In patients with significant coronary artery disease, MI may also be caused by a sustained myocardial supply-demand imbalance (type 2 MI) due to tachycardia and increased myocardial contractility.[5] The presence of silent, heart rate-related ST-segment depression in high-cardiac-risk patients undergoing major surgery have been described in up to 41% of the patients during the post-operative period and has been demonstrated to be associated with short- and long-term morbidity and mortality.[6] In addition, several studies have correlated continuous 12-lead ST-segment analysis with serial cardiac troponin measurements after major vascular surgery.[7] Troponin elevations occurred after prolonged, transient, postoperative ST-

segment depression, and peak troponin elevations correlated with the duration of ST depression.[8]

Detection of asymptomatic perioperative cardiac damage

The detection of asymptomatic cardiac damage in surgical patients is challenging and requires standard assessment of cardiac troponin levels in the perioperative period with short time intervals, for example, on day 1, 2, and 3 after surgery. Importantly, recent studies using highly sensitive troponin essays have demonstrated that low-level troponin elevations (>0.03 ng/mL) are common in high-cardiac-risk patients postoperatively, even with little but most often with no evidence of ECG ischemia.[9] In this respect, it has to be recognized that the majority of perioperative cardiac events occur within the first 3 days after surgery.[10] Preferably, continuous ECG monitoring is applied for the first days after surgery in studies reporting on the incidence and consequences of perioperative cardiac events. This time consuming approach might explain why there are only few studies published so far exploring the effects of asymptomatic perioperative cardiac damage. The prognostic implication of asymptomatic perioperative cardiac damage, in particular low-level troponin elevations, is ill defined.

Prognostic implications of asymptomatic perioperative cardiac damage

Perioperative ST-segment depression and postoperative troponin elevations have both been related to adverse short-, mid- and long-term cardiac morbidity and mortality.[11-13] Early mortality after perioperative MI ranges between 3.5 to 25% and is higher in patients with major troponin elevation compared to patients with minor troponin elevation.[8,13,14] Lopez-Jimenez *et al.* and Kim *et al.* demonstrated that asymptomatic abnormal levels of troponin T in patients scheduled for noncardiac surgery were associated with a more than four to six-fold increased risk of cardiac events during a six months follow-up period.[11] The long-term prognostic value of postoperative troponin release has especially been studied in major vascular surgery patients. Landesberg *et al.* and Kertai *et al.* studied the prognostic value of low-level and conventional troponin elevations on long-term mortality after major vascular surgery, and observed that postoperative troponin elevations even at low cut-off levels are independent and complementary predictors of long-term mortality.[8,12]

Recently Winkel *et al.* demonstrated that asymptomatic perioperative cardiac damage, defined as cardiac troponin T elevations without ischemic symptoms or ECG abnormalities, was associated with an increase for mortality during a follow-up of 2.9 years in 220 patients who underwent endovascular abdominal aortic aneurysm repair.[15] Patients with asymptomatic cardiac damage

had a mortality rate of 49 versus 15% for patients without perioperative cardiac damage ($p < 0.001$). Also after adjustment for clinical risk factors and medication use applying multivariate Cox regression analysis, asymptomatic cardiac damage was associated with a 2.3-fold increased risk for death (hazard ratio 2.30, 95% confidence interval 1.1 to 5.1).

Management of patients with asymptomatic cardiac damage

The strong association between high-risk patients, perioperative ischemia characterized by troponin release, and its influence on short- and long-term outcome has emerged the need for prevention and treatment. The unpredictable progression of an instable coronary plaque during surgical stress is the most important target for systemic therapy. Medical treatment aimed at plaque stabilization has shown promising results for perioperative as well as long-term risk reduction. Prophylactic ß-blockade is advised for patients already on ß-blocker therapy, those with preoperative stress-inducible myocardial ischemia and to treat angina, symptomatic arrhythmias, heart failure or hypertension.[16] In our center all patients scheduled for major vascular surgery are prescribed a low dose ß-blocker (e.g. bisoprolol 2.5 mg) started as early as possible, preferably 30 days prior to surgery. This allows safe dose titration to achieve a target heart rate of approximately 65 beats per minute. Furthermore, we promote the idea of prolonged treatment after surgery. In addition to ß-blocker therapy, high-risk patients should also receive statins in the perioperative period. Several recent retrospective studies have shown a beneficial effect of statins on perioperative cardiac outcome with adjusted Hazard ratio's ranging from 0.20 to 0.62.[17] Importantly, Kertai *et al.* also found the effect of statins to be independent of β-blocker use. Recently, the results of the randomized, double-blind, placebo controlled Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE) III trial became available confirming the efficacy and safety of perioperative statin therapy for the prevention of perioperative cardiovascular events.

FUTURE PERSPECTIVES

The perioperative surgical stress results in a hypercoagulable state, which is in combination with atherosclerotic plaques the perfect substrate for the development of perioperative cardiac damage. Although aspirin reduces the risk of plaque rupture and subsequent cardiovascular events, there remains a substantial risk for such events during follow-up. The thienopyridine derivate clopidogrel is an antiplatelet agent that inhibits the platelet aggregation induced by adenosine diphosphate. The efficacy and safety of combining clopidogrel and aspirin (dual antiplatelet therapy) compared to aspirin alone, has recently been proven in a

meta-anlyses of studies including patients with acute coronary syndromes (34% risk reduction of nonfatal MI).[18] Nowadays, asymptomatic perioperative cardiac damage is not treated with clopidogrel, although late outcome hereafter is severely compromised. Randomized controlled studies are needed to investigate the role of clopidogrel as a preventive treatment in patients with asymptomatic cardiac damage.

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PART II

DIABETES MELLITUS

Chapter 10

Perioperative blood glucose monitoring and control in major vascular surgery patients

Jan-Peter van Kuijk
Olaf Schouten
Willem-Jan Flu
Corstiaan A. den Uil
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Diabetes Mellitus (DM) is an independent predictor for morbidity and mortality in the general population, which is even more apparent in patients with concomitant cardiovascular risk factors. As the prevalence of DM is increasing, with an ageing general population, it is expected that the number of diabetic patients requiring surgical interventions will increase. Perioperative hyperglycaemia, without known DM, has been identified as a predictor for morbidity and mortality in patients undergoing surgery. Moreover, early studies showed that intensive blood-glucose-lowering therapy reduced both morbidity and mortality among patients admitted to the postoperative intensive care unit (ICU). However, later studies have doubted the benefit of intensive glucose control in medical-surgical ICU patients. This article aims to comprehensively review the evidence on the use of perioperative intensive glucose control, and to provide recommendations for current clinical practice. A systematic review was performed of the literature on perioperative intensive glucose control. Based on this literature review, we observed that intensive glucose control in the perioperative period has no clear benefit on short-term mortality. Intensive glucose control may even have a net harmful effect in selected patients. In addition, concerns on the external validity of some studies are important barriers for widespread recommendation of intensive glucose control in the perioperative setting. We propose that guidelines recommending intensive glucose control should be re-evaluated. In addition, moderate tight glucose control should currently be regarded as the safest and most efficient approach to patients undergoing major vascular surgery.

INTRODUCTION

Diabetes Mellitus (DM) is currently affecting over 40 million people in the European Union alone. Importantly, the prevalence of DM is strongly related to age; over 20% of the population aged above 60 years is diabetic.[1] With an ageing Western population, the impact of diabetes is a major health burden and will increase dramatically within the next 20 years.[2]

Simultaneously, aging of the population will also cause an increase of patients with peripheral arterial disease (PAD). The combination of an increasing incidence of diabetes and PAD will result in an increasing number of pre-diabetic patients requiring vascular surgical procedures. Patients with diabetes or an impaired glucose tolerance (IGT) are more prone to dysregulation of glucose haemostasis, especially during surgical stress or critical illness. This condition develops independently of previous diagnosed diabetes and is also called stress diabetes or diabetes of injury.[3,4] These hyperglycaemic conditions have been identified as an important risk factor (Relative Risk 3.9) for morbidity and mortality in patients undergoing surgery.[5]

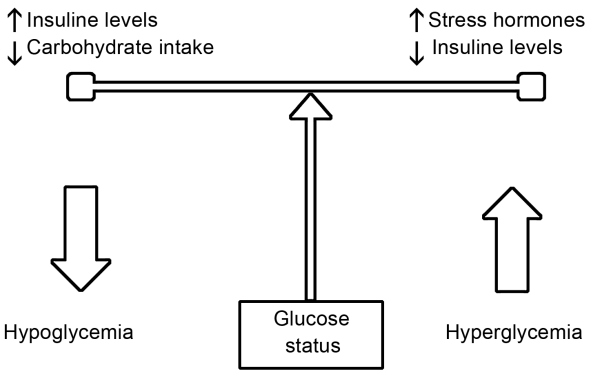
Since glucose dysregulation has such an impact on postoperative and long-term outcome in these patients, adequate preoperative screening as well as perioperative and postoperative glucose management are of critical importance. Therefore, the aim of the current systematic review is to (i) provide an overview of recent evidence on preoperative screening of vascular surgery patients with respect to diabetes and glucose tolerance, and (ii) to provide an overview of recent evidence on monitoring and treatment strategies for adequate glucose regulation in the perioperative period during vascular surgical procedures.

PATHOPHYSIOLOGY OF GLUCOSE REGULATION DISORDERS

In patients with pre-diabetes, many factors are involved in determining the glycemic response, both during a stable homeostatic phase and during stressing moments like surgery or critical illness. During normal daily activities, there is a relative balance between glucose metabolism and insulin secretion, resulting in slightly elevated blood glucose levels. These elevated glucose levels do not result in classical diabetic symptoms. However, the abundance of glucose molecules in the blood result in microvascular damage of the kidneys, retina and peripheral nerves.[6] The glucose balance can be easily disturbed by stress and fasting associated with surgery. During the time between the preoperative period and the postoperative

recovery the following factors may change radically: (i) insulin secretory capability, (ii) insulin sensitivity, (iii) overall metabolism, and (iv) nutritional intake.[7] There is an imbalance in blood glucose lowering and stimulating agents, leading to hyperglycaemia and excess circulating free fatty acids.[7] These free fatty acids require aerobic metabolism, and result in increased oxygen consumption with major consequences, especially in the presence of concomitant myocardial ischemia. Free fatty acids also inhibit myocardial glucose use, decrease contractility, predispose to develop arrhythmias, and increase accumulation of free radicals.[8] In addition to this, hyperglycaemia also causes fluid shifts (glycosuria and dehydration), promotes the inflammatory response leading to endothelial dysfunction, enhances platelet aggregation, and reduces immune function by impaired complement activity.[4] In summary, hypoglycaemia results from predominance of the glycemic effects of a decrease in carbohydrate intake and an increase in circulating insulin. Hyperglycaemia is characterized by a predominance of the glycemic effects of an increase in stress hormones and a decrease of circulating insulin levels (*Figure 1*).

Figure 1. *Schematic representation for the balance of perioperative blood glucose status*

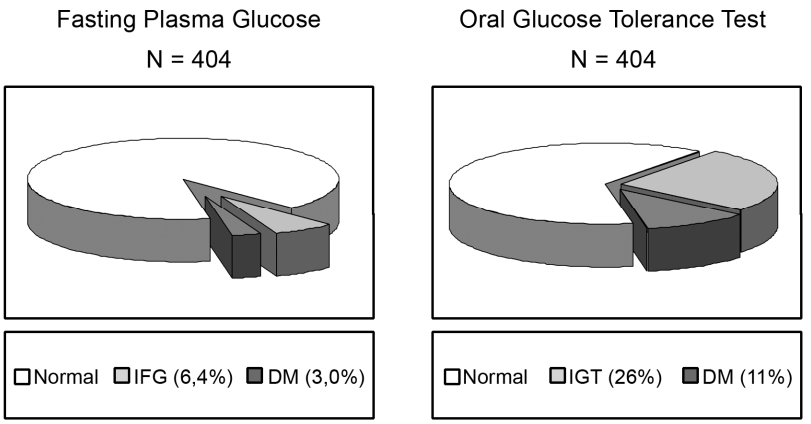


PREOPERATIVE TESTING FOR DIABETES

In pre-diabetic patients, elevated glucose levels are usually present for 7 to 10 years before the diagnosis of DM is made.[9] Screening for glucose regulation disorders can be performed by either fasting plasma glucose (FPG) measurement or oral glucose tolerance testing (OGTT). Fasting plasma glucose measurement includes a blood glucose measurement in the morning after overnight fasting. Oral glucose tolerance testing included a fasting glucose measurement and an additional blood glucose sample 2 hours after the ingestion of 75-gram oral glucose

load. Impaired fasting glucose is defined as plasma glucose of 100 to 125 mg/dl (5.6 to 6.9 mmol/l), and IGT as plasma glucose of 140 to 199 mg/dl (7.8 to 11.1 mmol/l). According to the American Diabetes Association guidelines, DM was defined as FPG ≥126 mg/dl (7.0 mmol/l) and/or plasma glucose ≥200 mg/dl (11.1 mmol/l).[2] Several prospective studies in nondiabetic adults demonstrated a significant additional value of OGTT to FPG, with respect to the relationship between hyperglycemia and risk of cardiovascular disease. The "Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe"(DECODE) Study group showed that the addition of OGTT to FPG significantly improved the prediction of all-cause mortality (HR 1.73, 95% CI: 1.5 to 2.1), cardiovascular disease (HR 1.42, 95% CI: 1.02 to 1.9) and coronary heart disease (HR 1.56, 95% CI: 1.03 to 2.4).[9] These results were confirmed by The Cardiovascular Health Study that showed an association between FPG levels >6.3 mmol/L and increased cardiovascular risk (HR 1.66, 95% CI: 1.4 to 2.0).[10] Furthermore, this population-based study showed the additional value of the OGTT to fasting plasma glucose measurement, as two-hour glucose loading level was associated with a linear increased cardiovascular risk (HR 1.02, 95% CI: 1.00 to 1.04) per 0.6 mmol/L increase in blood glucose level 2 hours after glucose loading.

Figure 2. *Additional value of Oral Glucose Tolerance Testing over Fasting Plasma Glucose measurement. Figure reproduced from reference 11, with permission of the publisher*



In a recent study, van Kuijk *et al.* (*Figure 2*) studied the additional effect of OGTT to FPG for the detection of IGT and DM in patients scheduled for major vascular surgery as well.[11] A strong additional effect on diagnosing IGT and DM by oral glucose tolerance testing was shown. Seventy-five percent of the patients with IGT and 72% of the patients with DM would have been missed, if only the fasting glucose levels were measured. Importantly, as DM is one of the cardiovascular risk

factors of the adapted Lee Risk index, detection of new DM in patients scheduled for major vascular surgery, results in an increased risk score.[12] In patients with other concomitant cardiovascular risk factors, addition of DM will result in a need for more extended pre-operative testing and subsequent treatment. However, preoperative testing for glucose regulation disorders is not routinely performed in vascular surgery patients.

Currently, the use of pre-operative FPG or OGTT is only recommended by the European Society of Cardiology / European Association for the Study of Diabetes in patients undergoing surgery with ≥2 clinical cardiovascular risk factors.[13] The American College of Cardiology / American Heart Association (ACC/AHA) guidelines for preoperative management in patients with PAD undergoing non-cardiac surgery, recommend a fasting plasma glucose measurement, but not a pre-operative glucose-loading test.[6]

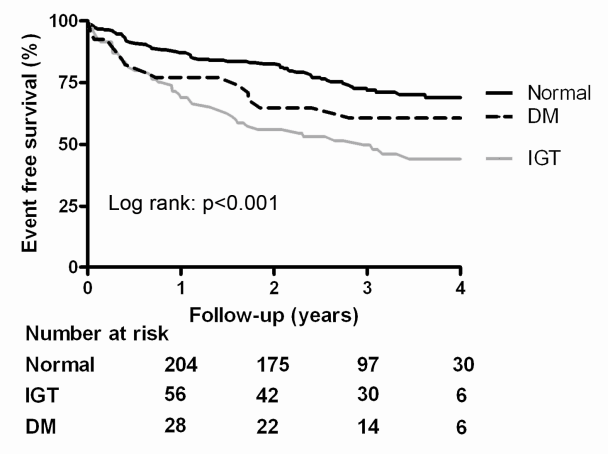
OUTCOME AFTER VASCULAR SURGERY IN PRE-DIABETIC PATIENTS

In vascular surgery patients, pre-operative elevated glycated hemoglobin and pre-operative impaired fasting glucose have been related to an increase in cardiovascular events and/or all cause mortality during follow-up.[14,15] O'Sullivan *et al.* showed that patients scheduled for vascular surgery without DM but with suboptimal glycated hemoglobin levels (6 to 7%) had a significantly higher incidence of overall 30-day mortality compared to patients with glycated hemoglobin levels <6% (56.5 vs 15.7% $p < 0.001$).[14] This was confirmed by Feringa *et al.* in vascular surgery patients with IGT and/or DM detected by OGTT, which had an 2.2-fold increased risk for ischemia, 3.8-fold for troponin T release, 4.3-fold for 30-day cardiac events, and 2.7-fold for long-term cardiovascular events.[15]

The presence of DM is an established and risk factor for atherosclerotic coronary disease and PAD, independent of other atherogenic risk factors, with a relative risk averaging two fold for men and three fold for women.[16] Patients with DM can have two types of vascular disease: (i) a non-occlusive microcirculatory dysfunction involving the kidneys, retina and peripheral nerves, and (ii) a macroangiopathy characterized by atherosclerotic lesions of the coronary and peripheral arterial circulation.[17] Based on these pathogenic mechanisms it could be assumed that patients scheduled for vascular surgery and concomitant DM would have an increased risk of morbidity and mortality due to atherosclerotic disease. However, several studies have shown conflicting results regarding the association between DM and the risk of cardiovascular morbidity and mortality in vascular

surgery patients. Malmstedt *et al.* studied a group of diabetic patients who underwent infrainguinal bypass surgery.[18] They observed an increased risk of renal insufficiency and infected foot ulcer in patients with perioperative hyperglycemia. This was confirmed by Ramos *et al.* who demonstrated an increased risk of postoperative infections after vascular surgery in patients with perioperative hyperglycemia.[19] Importantly, this was independent of diabetic status. Van Kuijk *et al.* recently showed that patients with IGT or DM detected by OGTT have an increased risk for the development of cardiovascular events during follow-up (*Figure 3*).[11] However, other studies demonstrated that patients with DM do not appear to be at increased risk of death after intermediate[20] or high risk surgery.[21] Some of these studies suffered from a small number of adverse outcomes and incomplete documentation of important comorbidities. In response to this controversy, Axelrod *et al.* performed a large study in patients undergoing elective major vascular surgery. They demonstrated that in univariate analysis, patients with DM had a higher incidence rate of perioperative death (3.9 vs 2.6%, $p = 0.001$) and cardiovascular complications (3.3 vs 2.6%, $p = 0.01$) compared to patients without diabetes. After controlling for comorbid conditions, procedure type, and diabetic complications, only insulin-dependent diabetes was an independent risk factor for death or cardiovascular complications.[22] However, this study mainly included lower risk patients with known DM, while the risk of diabetes is most clear in intermediate and high-risk patients.

Figure 3. *Cardiovascular event free survival during long-term follow-up after glucose-loading test in patients undergoing major vascular surgery. Figure reproduced from reference 11 with permission from the publisher*



Recently, Protack *et al.* investigated the influence of DM as part of the metabolic syndrome in patients who underwent carotid revascularization.[23] Vascular surgery patients with metabolic syndrome and/or DM had an increased

risk of perioperative morbidity as well as stroke, myocardial infarction and major adverse events during long-term follow-up, compared to those without metabolic syndrome. Overall, vascular surgical patients with concomitant diabetes are more likely to experience perioperative and long-term cardiac events.

PERIOPERATIVE MONITORING AND TREATMENT OF BLOOD GLUCOSE LEVEL DISORDERS

Aims of perioperative management

In 2001, Van den Berghe *et al.* published the first Leuven study, a randomized controlled trial of critically ill patients, which showed that tight glucose control significantly reduced hospital morbidity and mortality.[24] Other studies have shown that tight glycemic control is associated with decreased infection rates and improved survival during cardiac surgery [25], in the setting of acute neurologic injury [26] and acute myocardial infarction.[27] Based on these studies, several professional societies, including the American Diabetes Association and the American Association of Clinical Endocrinologists, now recommend tight glucose control in all surgical or medical critically ill adults.[2,24,28] Based on the pathophysiologic mechanisms of symptomatic DM and the study by Van den Berghe *et al.*, prevention of hyperglycaemic periods has been suggested to decrease the risk of dehydration, electrolyte abnormalities, diabetic ketoacidosis but also improved wound healing.[24] Therefore, the following treatment aims are provided for known diabetic patients: (i) avoid hypoglycaemia, (ii) avoid excessive hyperglycaemia (main aim <11 mmol/L), (iii) avoid loss of electrolytes (potassium, magnesium and phosphate), and (iv) prevent lipolysis and proteolysis. [29,30]

However, patients with unknown DM or IGT are not sufficiently controlled during the perioperative period. This status of relative insulin deficiency is associated with an increased secretion of catabolic hormones during surgery, but also in critical illness and trauma. As patients undergoing surgery are routinely not extensively tested for IGT or unknown DM, hyperglycaemic episodes may have their first occurrence during surgery or critical illness.[31] Especially older patients without known DM are prone for the development of critical illness-induced or surgery-induced hyperglycaemia (blood glucose of ≥ 11 mmol/L). Treatment aims in these patients are mainly directed at avoidance of hyperglycaemia and loss of electrolytes. Hyperglycaemic periods are most often treated with short-acting insulin therapy. However, the risk of hypoglycaemia may not be underestimated and can have serious adverse effect, including seizure, coma or even death.

INFLUENCE OF PERIOPERATIVE HYPERGLYCEMIA AND TREATMENT ON OUTCOME

Post-operative outcome in patients with and without known DM has extensively been studied in intensive care unit (ICU) patients. However, data regarding the influence of glucose regulation disorders on the outcome after major vascular surgery are relatively scarce. Therefore, treatment recommendations for vascular surgery patients are based on the current knowledge in ICU patients. For the current systematic review, all studies in surgical and combined surgical-medical ICU patients were selected and reviewed to provide an overview of mortality rates and other outcome parameters (*Table 1*).

Table 1 **Study characteristics of the selected studies**

Author	Patients (N)	DM (%)	Type of surgery	Glucose target (mmol/L)	Mortality RR (95%CI)
Surgical ICU patients					
He [31]	188	18	Abdominal	4.4-6.1	Not reported
Stecher [32]	117	13	Abdominal	4.4-6.1	1.05 (0.45-2.46)
Grey [33]	61	12	General	4.4-6.6	0.53 (0.17-1.69)
Kia [34]	265	26	Abdominal	4.1-6.3	1.74 (0.86-3.51)
Total	635	20		4.1-6.6	1.12 (0.60-2.10)
Surgical-Medical ICU patients					
Mitchell [35]	70	14	Surgical 62%	4.4-6.1	3.00 (0.89-10.16)
Wang [36]	116	11	Surgical 15%	4.4-6.1	0.27 (0.13-0.57)
Brunkhorst [37]	537	30	Surgical 53%	4.4-6.1	0.95 (0.71-1.27)
Iapichino [38]	72	17	Surgical 32%	4.4-6.1	Not reported
Mackenzie [39]	240	83	Surgical 46%	4.0-5.9	0.82 (0.58-1.15)
Arabi [40]	523	40	Surgical 17%	4.4-6.1	0.84 (0.64-1.09)
Devos [41]	1101	19	Surgical 58%	4.4-6.1	1.20 (0.93-1.55)
Azevedo [#]	337	31	Surgical 40%	4.4-6.6	0.91 (0.62-1.34)
NICE-SUGAR	6104	20	Surgical 34%	4.5-6.0	1.14 (1.02-1.28)
Overall	3631	23		4.0-6.6	0.96 (0.80-1.15)

Abbreviations: DM; diabetes mellitus, RR; relative risk, ICU; intensive care unit

Intensive care unit patients

Known diabetes mellitus is present in up to 26% of the critically ill patients requiring intensive care treatment.[24,32] If a critically ill patient requires more than five days intensive care treatment, there is a 20% risk of death and substantial morbidity.[33] Intensive care patients with DM are known to have higher risk of severe infections and failure of vital organs, thereby amplifying the risk of an adverse outcome. However, not only patients with known DM have higher risk of adverse outcome after ICU treatment. New onset DM, presenting with perioperative hyperglycaemia common in critically ill patients. The occurrence of hyperglycaemia

in non-diabetics has been suggested to be associated with an increased morbidity and mortality in those patients.[34]

Randomized controlled trials

Van den Berghe *et al.* performed the first single-center randomized (but unblinded) controlled trial (RCT) to study the influence of intensive insulin therapy compared to conventional treatment in 1548 surgical ICU patients.[24] They hypothesized that hyperglycaemia or relative insulin deficiency during critical illness may confer to morbidity and mortality. Target blood glucose levels were 9.9 to 11.0 mmol/L and 4.4 to 6.1 mmol/L in the conventional and intensive group, respectively. The study showed a 34% relative risk reduction in overall in-hospital mortality in the intensive treatment group. However, this reduction was observed only in patients requiring more than 5 days of intensive care treatment. Regression analysis of these results indicated that the lowered blood glucose rather than the insulin dose was related to the reduction in mortality and morbidity.[35] Since the first study by vd Berghe *et al.* additional studies have been performed, to determine if the benefits and risks of tight glucose control are generalizable to surgical ICU patients, medical ICU patients and operating rooms.[32,36] Several studies have shown inconsistent results as some showed a positive result on mortality and other neutral or even negative results. In 2006, Van den Berghe *et al.* performed a second RCT to compare intensive insulin treatment and conventional therapy in 1200 medical ICU patients.[37] Intensive insulin treatment decreased ICU and hospital length of stay, ventilator days, and incidence of kidney injury. However, it did not reduce overall mortality in the total study population. Again in patients with longer ICU stay (≥3 days) intensive insulin treatment was associated with a decrease in mortality from 53 to 43%. In contrast, there was a trend towards higher mortality rates in the subgroup of patients with ICU stays shorter than 3 days. Additionally, the increased occurrence of hypoglycemia in the intensive treatment group (19 vs 3%) was an independent predictor of death in multivariate analysis. Recently, the European GLUCONTROL trial (mixed medical-surgical ICU patients) and the VISEP trial (medical ICU patients) were stopped early due to safety concerns given a high incidence of severe hypoglycemia and serious adverse events.[38,39]

The recent Normoglycemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial was designed to test the hypothesis that intensive glucose control reduces mortality at 90 days in medical-surgical ICU patients. Recent published results showed that patients with intensive insulin treatment had an increased risk for overall mortality within the first 90 days from ICU stay (OR 1.14, 95% CI: 1.02 to 1.28, $p = 0.02$).[40] In addition, severe hypoglycaemia was significantly more often noted in patients with tight glucose

control (6.8 vs 0.5%). Subgroup analysis of surgical vs nonsurgical ICU patients showed no significant difference for the treatment effect. These results suggest that achieving normoglycaemia in medical-surgical ICU patients does not necessarily benefit ICU patients, but may be even harmful.

Meta-analysis

Wiener *et al.* recently summarized all intensive insulin treatment studies in a meta-analysis.[41] They included 29 randomized controlled trials regarding tight glucose control in critically ill adults, totalling 8.432 patients. The included studies were subdivided according to the ICU setting (surgical, medical or combined) and to glucose goal (tight vs moderate glucose control). No significant differences in hospital mortality rates were detected, even not when mortality rates were subdivided for type of ICU setting and/or glucose target. Tight glucose control significantly reduced the risk of septicaemia in surgical ICU patients, when compared to usual glucose control. However, this was at the cost of an over fivefold increased in the risk of hypoglycaemia when the tight glucose control regimen was used (RR 5.13, 95% CI: 4.09 to 6.43). The meta-analysis had the usual limitations of pooled data and the fact that some of the included studies were relatively small. In addition to this, the analyses on hospital mortality were underpowered to detect the 1.7% difference in mortality rate that was identified. As the study by Van Den Berghe is regarded as the main basis for the present guidelines on tight glucose control in critically ill patients, it is remarkable that this study was identified as having outlying results by tests of heterogeneity in the meta-analysis by Wiener. Three important reasons for these different results are: (i) bias by an un-blinded trial design, (ii) the unusual high mortality in the conventional group may be the result of chance, and (iii) several atypical clinical practices were performed (use of early glucose infusion and high levels of parenteral nutrition, both possible inducing hyperglycaemia). This meta-analysis is a large effectiveness study. In general there is lack of agreement for standard glycemic control levels and incomplete reporting in most included trials. However, as this meta-analysis presents the effect of targeting tight glycemic control in several ICU settings with different treatment regimens, the results are more generalizable.

Conclusion intensive care unit patients

Although several RCTs, systematic reviews and a meta-analysis have led to differing conclusions, many professional organizations recommend tight glucose control for patients treated at the ICU. However, barriers to widespread adoption of tight glucose control include the risk of hypoglycaemia, concerns about the external validity of some studies, and the difficulty of achieving normoglycemia in ICU patients.

MONITORING AND TREATMENT RECOMMENDATIONS IN MAJOR VASCULAR SURGERY

Patients undergoing major vascular surgery most often die from cardiovascular co-morbidities.[42] With the growing age of the population, patients scheduled for vascular surgery more often have additional cardiovascular risk factors at time of surgery. Screening for glucose regulation disorders should be performed in all patients with ≥2 clinical risk factors. The current guidelines for patients undergoing surgery recommend strict glucose regulation during the perioperative phase and intensive care treatment.[2,28,43] These recommendations are based largely based on 1 clinical trial that showed decreased mortality in a surgical intensive care unit.[24] Several large RCT's have been provided since then, however, all of them failed to show the same mortality benefit. We performed a critical review of the available ICU studies and concluded that overall mortality in patients randomized to tight glucose regulation is not decreased compared to moderate tight glucose control. The recent NICE-SUGAR trial also observed an increased mortality risk for all types of ICU patients at 90 days from ICU stay, independent of diabetic status.

No randomized controlled trials specifically addressing the monitoring and treatment of hyperglycaemia during major vascular surgery have been performed. Therefore results of studies in comparable patient groups have to be translated for this patient population. The current guidelines for perioperative care in PAD patients recommend a target glucose level of <11 mmol/L during the perioperative phase. Based on the current available studies, moderate tight glucose control with a target blood glucose level between 6.0 and 8.3 mmol/L could be more beneficial. Additionally, there is an increased risk for hypoglycaemia in patients with tight glucose control. Therefore moderate tight glucose control could have the advantage of decreasing the risk of both hyperglycaemia and the prevention of hypoglycaemia during major vascular surgery.

CONCLUSION

A few studies regarding the influence of perioperative blood sugar monitoring and treatment in patients undergoing vascular surgery have been performed. Based on these studies and a diversity of studies in the intensive care setting, patients scheduled for vascular surgery with known DM should be treated with insulin infusion during the perioperative phase with a moderate tight glucose control regimen. Unknown diabetics should be tested pre-operatively for glucose regulation disorders if ≥2 clinical risk factors are present. Further prospective randomized

studies needs to be undertaken to establish the absolute benefits of moderate versus tight glucose control in vascular surgical patients in the perioperative period.

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Chapter 11

Preoperative oral glucose tolerance testing in vascular surgery patients; long-term cardiovascular outcome

Jan-Peter van Kuijk
Martin Dunkelgrun
Frodo Schreiner
Willem-Jan Flu
Wael Galal
Ron T. van Domburg
Sanne E. Hoeks
Yvette R.B.M. van Gestel
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Background: Diabetes Mellitus (DM) is an important risk factor in vascular surgery patients, influencing late outcome. Screening for diabetes is recommended by fasting glucose measurement. Oral glucose tolerance testing (OGTT) could enhance the detection of patients with impaired glucose tolerance (IGT) and DM. The study aim was to asses the additional value of OGTT on top of fasting glucose levels in vascular surgery patients to predict long-term cardiovascular outcome.

Methods: A total of 404 patients without signs or histories of IGT (plasma glucose 7.8 to 11.1 mmol/l) or DM (glucose ≥11.1 mmol/l) were prospectively included and subjected to OGTT. Cardiac risk factors were noted. Primary outcome was the occurrence of late cardiovascular events (composite of cardiovascular death, angina pectoris, myocardial infarction, percutaneous coronary intervention / coronary artery bypass grafting or cerebrovascular accidents / trainsient ischemic attack), and secondary outcome included all-cause and cardiovascular mortality rates, in survivors of vascular surgery. Median follow-up was 3.0 [interquartile range 2.4 to 3.8] years.

Results: Impaired glucose tolerance (N=104) and DM (N=43) were detected by fasting glucose levels in 26 (25%) and 12 (28%) patients, and by OGTT in 78 (75%) and 31 (72%) patients, respectively. During follow-up, 131 patients experienced a cardiovascular event. Using multivariate analysis, patients with IGT showed a significant increased risk for cardiovascular events (HR 2.77, 95% CI: 1.83 to 4.20) and mortality (HR 2.06, 95% CI: 1.03 to 4.12). Patients with DM showed a non-significant increased risk for cardiovascular events.

Conclusion: Vascular surgery patients with IGT or DM detected by pre-operative OGTT, have an increased risk of developing cardiovascular events and mortality during long-term follow-up. It is recommended that non-diabetic vascular surgery patients should be tested for glucose regulation disorders prior to surgery.

INTRODUCTION

Patients with known diabetes are at increased risk for developing peri-operative complications.[1] Dysregulation of glucose hemostasis, especially during (surgical) stress, is an important characteristic of the prediabetes phase. Impaired fasting glucose (IFG) has been shown to be associated with adverse cardiovascular outcome.[1,2] Therefore, the American Diabetes Association recommends pre-operative assessment of fasting glucose levels.[3] However, during the last decade, other studies showed an increased value of oral glucose tolerance testing (OGTT) compared to IFG for the prediction of cardiovascular events in various nonsurgical populations.[4-7] The DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europa) study demonstrated substantial discrepancies between the predictive values of IFG compared to OGTT.[8] In this study of non-surgical patients, the risk of death from all-cause, cardiovascular and coronary artery disease was significantly increased in subjects with impaired glucose tolerance (IGT) and newly diagnosed DM. Furthermore, the predictive value of IFG depended strongly on the OGTT. Currently, the European Society of Cardiology (ESC) / European Association for the Study of Diabetes (EASD) guidelines provide a class I recommendation for primary screening in patients with clinical cardiovascular risk factors.[9] The American College of Cardiology (ACC) / American Heart Association (AHA) guidelines for preoperative management in patients with peripheral arterial disease (PAD) undergoing non-cardiac surgery, do not recommend a pre-operative glucose-loading test.[10] Prior results of the current study showed an increase in postoperative ischemia in patients with IGT and DM during short-term follow-up. To our knowledge, no prior studies investigated the association between OGTT and long-term cardiovascular outcome after vascular surgery. As we know that glucose intolerance leads to impaired outcome in nonsurgical patients, we hypothesize that this association could be present in patients scheduled for vascular surgery as well.

METHODS

Study design and population

This prospective study consisted of 404 consecutive non-diabetic patients scheduled for elective vascular surgery in the Erasmus medical centre during the time period from November 2004 till May 2007. All patients gave informed consent. The exclusion criterion was the presence of DM, defined as a known history of DM, with or without the use of insulin or oral glucose-lowering agents.

Study protocol

Preoperatively, all patients underwent an OGTT, carried out as stated by the American Diabetes Association (ADA).[3] First blood sample was taken in the morning after overnight fasting and the second sample was obtained 2 hours after the ingestion of 75-g oral glucose load. Glucose status was scored using fasting plasma glucose (FPG) and the OGTT. Impaired fasting glucose was defined as plasma glucose of 100 to 125 mg/dl (5.6 to 6.9 mmol/l), and IGT as plasma glucose of 140 to 199 mg/dl (7.8 to 11.1 mmol/l). According to the ADA guidelines, DM was defined as FPG ≥ 126 mg/dl (7.0 mmol/l) and/or plasma glucose ≥ 200 mg/dl (11.1 mmol/l). Consequently, all patients were classified as having normal test results, IGT or DM.

Patient data

Previous medical history, clinical characteristics and medication use were obtained from the outpatient clinic visits and the patients' medical record. During hospital stay, type of surgery was recorded and classified into the following categories: carotid surgery, abdominal and thoracic aortic surgery (dilatating or occlusive), and lower extremity (dilatating or occlusive). The cardiac risk score was calculated according the adapted Lee cardiac index.[11] Ischemic heart disease was defined as a history of angina and/or myocardial infarction. Renal impairment was defined as a serum creatinine concentration of ≥2.0 mg/dl and hypertension was defined as blood pressure ≥140/90 mmHg or the use of blood pressure lowering agents. Congestive heart failure was defined according the American Heart Association (AHA) and the American College of Cardiology (ACC) guidelines.[10] Stroke was defined as a history of either a cerebral vascular accident (CVA; either ischemic or hemorrhagic) or a transient ischemic attack (TIA). Smoking status was defined as current smoking or a history of smoking.

Follow-up

The median follow-up of all patients was 3.0 years [interquartile range 2.4 - 3.8]. One year after inclusion of the last patient, mortality rates were verified according the Civil Registry. Cause of death was ascertained by examining the death certificates, and otherwise by reviewing the medical records. Secondly, for ascertainment of the occurrence of the other composites of the primary endpoint, the authors (J.P.K. and M.D.) reviewed primarily all medical records of all patients. In addition to this the survivors were sent the questionnaire. A response rate of 82% was achieved within the group of survivors. There was a close agreement between the medical record review data and the data collected from the questionnaires. The survivors were sent a questionnaire for the registration of

major adverse cardiovascular events during the post-operative period. Furthermore, current medication use was assessed with the questionnaire as well.

Endpoints

The primary endpoint was the occurrence of cardiovascular events during long-term follow-up, with a minimum of at least one year. Cardiovascular events were defined as the composite of cardiovascular death, angina pectoris, myocardial infarction, percutaneous coronary intervention / Coronary Artery bypass grafting or CVA/TIA. Secondary endpoints included all-cause and cardiovascular mortality. All-cause mortality was defined as death due to any cause. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and includes death following MI, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular event or transient ischemic attack), surgery related bleeding complications (only a post-operative cause of death), and others. Sudden unexpected death was classified as a CV death.

Statistics

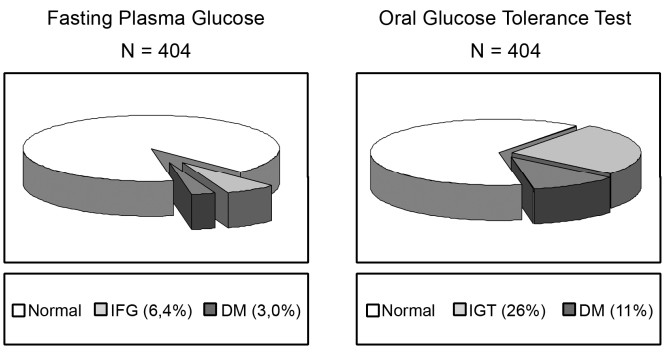
Continuous data were compared using analysis of variance, and are expressed as mean ± SD. Categorical data are presented as percentage frequencies, and differences between proportions were compared using x^2 test. Logistic regression analysis was used to determine the association between IGT, DM and short-term cardiac ischemia. Cumulative survival between patients with normal test results, IGT and DM was determined by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox regression models (using SPSS version 15.0; SPSS, Inc., Chicago, Illinois) were used to investigate the association between IGT, DM (patients with normal test results as reference group) and postoperative cardiovascular events and mortality. In addition, Cox regression analysis was used to assess the relationship between Lee risk index and both endpoints. Adjustments were made for age, gender, history of myocardial infarction, angina pectoris, percutaneous coronary intervention / coronary artery bypass grafting, congestive heart failure, CVA/TIA, renal insufficiency, smoking, COPD, hypertension, hypercholesterolemia and type of surgery. Hazard ratios (HR) were calculated from these models along with their 95% confidence intervals (CI). A p-value < 0.05 was considered statistically significant. The authors are solely responsible for the design and conduct of this study; all study analysis, the drafting and editing of the paper and its final contents.

RESULTS

Description of the study population

Elective vascular surgery was performed in 404 patients, who underwent a preoperative FPG and OGTT measurement. Baseline characteristics of the patients with normal test results, IGT and DM are listed in Table 1. Mean age of the study population was 66 ± 13 years, and 74% of the patients were male. At baseline, no significant differences between the groups were detected in previous history. However, patients with DM had more often hypertension and hypercholesterolemia. Renal function, estimated by serum creatinine and Modification of Diet in Renal Disease formula, in patients with IGT and DM was significantly worse than in patients with a normal test. In patients with IGT, there was less use of statins and β-blocking agents during the follow-up period, compared to patients with DM. Normal glucose levels were observed in 257 (63%) patients after both tests. Impaired glucose tolerance was detected in 104 (26%) patients, of which 26 (25%) patients presented with impaired fasting glucose (IFG). In the remaining 78 (75%) patients, IGT was only detected after the OGTT. Forty-three (11%) patients were diagnosed as having DM, of which 12 (28%) patients presented with diabetic fasting glucose levels. In the remaining 31 (72%) patients, diabetic fasting glucose levels were only detected after glucose loading (*Figure 1*).

Figure 1. *Additional value of the oral glucose loading test compared to fasting plasma glucose measurement for the detection of diabetes mellitus*



Cardiovascular events and mortality

During a median follow-up period of 3.0 years [interquartile range 2.4 - 3.8], 131 patients experienced a cardiovascular event (*Figure 2 and Table 2*). Patients with IGT showed a significant increased risk in cardiovascular events during long-term follow-up in both univariate (HR 2.41, 95% CI: 1.65 to 3.53) and multivariate analysis (HR 2.68, 95% CI: 1.80 to 3.98) (*Table 2*). In patients with DM, a

borderline unadjusted increased risk in cardiovascular events was seen (HR 1.68, 95% CI: 0.96 to 2.95). After adjustment for baseline characteristics a slight trend was observed as well, though it did not achieve statistical significance (HR 1.59, 95% CI: 0.89 to 2.82).

Table 1 **Baseline characteristics**

	Total [N=550]	**Normal** [N=257]	**IGT** [N=104]	**DM** [N=43]	***P*-value**
Demograhics					
Age (yrs), mean ± SD	66±13	65 ±14	66±12	77±11	0.68
Male	74	72	76	81	
Medical history					
Myocardial infarction (%)	25	22.8	30.0	28.6	0.33
Angina Pectoris (%)	26	26	24	29	0.84
PCI/CABG (%)	16	14	22	13	0.15
Ischemic heart disease (%)	26	26	28	22	0.78
Chronic heart failure (%)	3	3	1	8	0.13
CVA/TIA (%)	28	27	32	26	0.59
Cardiovascular risk factors					
Smoking					0.17
No	19	4	5	28	
Current	33	37	27	26	
History	56	52	69	57	
Hypertension	56	53	58	70	0.12
Hypercholesterolemia	55	50	60	69	0.09
Renal failure	11	10	13	12	0.75
COPD	27	30	22	23	0.30
Medication use					
Preoperative					
Statin	71	67	79	77	0.06
B-blocking agents	83	82	85	84	0.78
Diuretics	26	22	33	33	0.07
ACE inhibitors	32	31	35	30	0.75
Calcium Antagonists	20	21	18	21	0.90
Angiotensin II antagonists	11	10	10	19	0.25
Nitrates	10	10	12	9	0.78
Aspirin	62	63	57	67	0.42
Follow-up					
Statin	72	68	76	87	0.12
B-blocking agents	69	65	73	87	0.09
Diuretics	28	28	28	32	0.92
ACE inhibitors	32	29	38	30	0.47
Calcium Antagonists	20	20	24	13	0.57
Angiotensin II antagonists	13	12	15	17	0.68
Nitrates	10	8	13	17	0.29
Aspirin	64	65	58	71	0.52

IGT, Impaired glucose tolerance; DM, diabetes mellitus; PCI/CABG, percutaneous coronary intervention/coronary artery bypass grafting; CVA/TIA, cerebrovascular accident/trainsient ischemic attack; COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme

During follow-up, 87 (22%) patients died, of which 40 (46%) were classified as cardiovascular. All cause mortality was not significantly increased in patients with IGT and DM compared to patients with normal test results. However, multivariate analysis showed a significant increase in cardiovascular death in patients with IGT (HR 2.06, 95% CI: 1.03 to 4.12). This association was not found in patients with DM (*Table 2 and Figure 3*).

Table 2 **Cardiovascular events and mortality**

	Events	**Univariate**		**Multivariate**	
	N (%)	HR	[95%-CI]	HR	[95%-CI]
Cardiovascular events					
Normal (N=257)	67 (25)	Ref.		Ref.	
IGT (N=104)	49 (46)	2.41	1.65-3.53	2.68	1.80-3.98
DM (N=43)	15 (35)	1.68	0.96-2.95	1.59	0.89-2.82
All-cause mortality					
Normal (N=257)	49 (18)	Ref.		Ref.	
IGT (N=104)	27 (26)	1.35	0.83-2.20	1.54	0.93-2.55
DM (N=43)	11 (26)	1.43	0.72-2.83	1.49	0.73-3.01
Cardiovascular mortality					
Normal (N=257)	20 (8)	Ref.		Ref.	
IGT (N=104)	17 (16)	2.10	1.10-4.01	2.06	1.03-4.12
DM (N=43)	3 (7)	0.97	0.29-3.25	0.88	0.25-3.13

The following variables were entered into the multivariate Cox proportional hazards model: age, gender, history of myocardial infarction, angina pectors, PCI/CABG, congestive heart failure, CVA/TIA, smoking, COPD, hypertension, hypercholesterolemia, renal insufficiency, and type of surgery

Table 3 **Prognostic value of Lee cardiac risk index**

	Events	**Univariate**		**Multivariate**	
	N (%)	HR	[95%-CI]	HR	[95%-CI]
Cardiovascular events					
Lee risk factors					
No	54 (26)	Ref.		Ref.	
1	49 (33)	1.37	0.93-2.02	1.22	0.81-1.83
≥ 2	28 (62)	3.14	1.98-4.96	2.69	1.66-4.34
All-cause mortality					
No	37 (18)	Ref.		Ref.	
1	35 (23)	1.43	0.90-2.28	1.57	0.96-2.57
≥ 2	15 (33)	2.50	1.37-4.56	2.41	1.27-4.56
Cardiovascular mortality					
No	13 (6)	Ref.		Ref.	
1	16 (11)	1.86	0.89-3.86	1.60	0.74-3.46
≥ 2	11 (24)	5.03	2.25-11.25	3.96	1.70-9.19

The following variables were entered into the multivariate Cox proportional hazards model: age, gender, history of myocardial infarction, angina pectors, PCI/CABG, congestive heart failure, CVA/TIA, smoking, COPD, hypertension, hypercholesterolemia, renal insufficiency, and type of surgery

Figure 2. *Cardiovascular event free survival during long-term follow-up after glucose loading test*

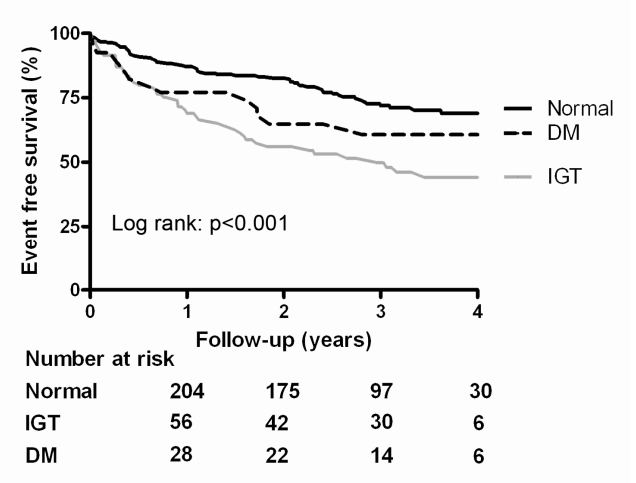
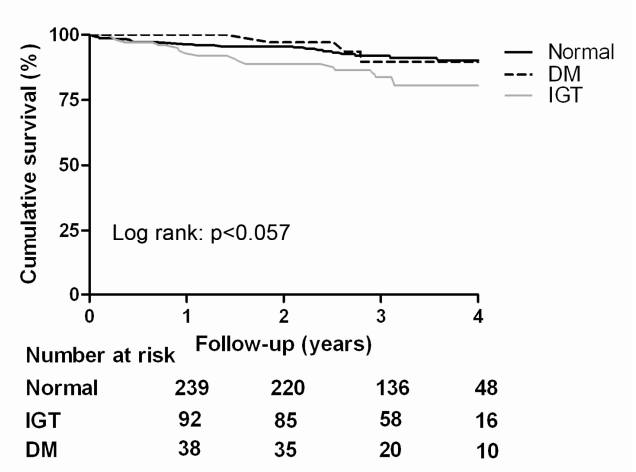


Figure 3. *Cardiovascular survival in patients undergoing preoperative oral glucose loading test*



Lee risk index

At baseline, 208 (51%) patients had no cardiac risk factors and 151 (37%) patients had one risk factor. In the remaining 45 patients, 2 or 3 clinical risk factors were present in 42 (10%) patients and 3 (1%) patients, respectively. Fasting plasma glucose measurement detected DM in 12 patients, thereby increasing the risk score from 0 to 1 or 1 to ≥2 in 7 and 5 patients, respectively. Glucose loading testing detected an additional 31 patients with DM. A total of 19 patients reached an increased cardiac risk score of ≥2 after testing. A Lee index of ≥2 risk factors prior to surgery was significantly and independently associated with increased long-term cardiovascular events (HR 2.69, 95% CI: 1.66 to 4.34, p < 0.001), all cause

mortality (HR 2.41, 95% CI: 1.27 to 4.56) and cardiovascular mortality (HR 3.96, 95% CI: 1.70 to 9.19), respectively (*Table 3*). These associations remained after performing glucose loading tests.

DISCUSSION

To our knowledge, this study is the first to describe long-term cardiovascular outcome in vascular surgery patients who underwent a pre-operative glucose-loading test. The present data show a significant increase in cardiovascular events and mortality during the follow-up in patients with IGT. Patients scheduled for vascular surgery diagnosed with IGT by OGTT seem to have an adverse prognosis. Until now, only in nonsurgical patients, IGT was shown as an important cardiovascular risk factor with a strong influence on cardiovascular outcome.[1,4-7,12] We showed that especially patients with IGT had adverse prognosis, even worse than patients with DM. A possible explanation for this difference in outcome could be undertreatment of vascular surgery patients with IGT.[13] We found a nonsignificant trend for less use of statins and β-blocking agents in patients with IGT compared to DM. Nowadays, vascular surgery patients with IGT are not recognized as being at increased risk of diminished cardiovascular outcome. As a result, they may receive less pharmacological preventive treatment. In our center, in addition to medical therapy all diabetics are followed at a special outpatient clinic with dedicated nursing staff. During visits life-style changes are recommended and followed, such as smoking cessation, weight control and exercise. This care was not provided for the patients with IGT, and might have further influenced outcome.

As patients with IGT have an increased risk for the development of cardiovascular events, this has especially long-term prognostic implications. Therefore, establishing the diagnosis of IGT or DM in the pre-operative phase should lead to more aggressive management of risk factors such as hypertension and hypercholesterolemia. Long-term glucose control may prevent micro –and macrovascular complications, at least in patients with newly diagnosed type 2 DM.[14] In contrast to patients with IGT, most patients with PAD and concomitant DM will receive standard care and treatment according the ACC/AHA guidelines, including ACE-inhibition, aspirin and statins.[15] The reduction of cardiovascular events in diabetic patients by pharmacological treatment is an important topic, as the elderly population is growing and the incidence of type 2 DM is increasing as well.[16]

During follow-up, a significant increase in cardiovascular mortality in patients with IGT was shown. In patients with DM, no relationship with cardiovascular death was shown; however this is possibly to be due to a power problem. All-cause mortality showed a nonsignificant association for higher rates in patients with IGT and DM. There seems to be a discrepancy in IGT patients as there is a significant increase in cardiovascular mortality but not in all-cause mortality. A reasonable explanation for this could be the suggested undertreatment of patients with IGT resulting in higher rates of cardiovascular mortality. However, the lack of study power to reach a significant increase in all-cause mortality could have influenced the results as well. The DECODE study showed an increased risk of cardiovascular death in patients with OGTT compared to patients with only fasting plasma glucose measured as well.[4] These findings were confirmed in several other trials, all showing a superiority of 2-hour glucose loading to fasting glucose in assessing the risk of future cardiac events.[1,6]

In this study we used the cutoff values for IFG according the 2003 guidelines of the ADA. The ADA lowered, in 2003, the cutoff value of plasma glucose for IFG from 6.1 to 5.6 mmol/l.[17,18] There has been debate about the influence of this lower cutoff for the prediction of cardiovascular events. Nowadays, the new cutoff is used in most studies comparing IFG and 2-hr glucose loading.[2] In the present study, use of OGTT showed a clear additional effect on diagnosing IGT and DM. Seventy-five percent of the patients with IGT and 72% of patients with DM would have been missed, if only the fasting glucose levels were measured. Compared to the use of IFG, the current study shows that OGTT adds significantly in the diagnosis of IGT and DM. As patients with IGT have an adverse prognosis, detection of this glucose regulation disorder has major implications for the management of risk factors, but also for the prevention of complications.

The ACC/AHA identified DM as an atherosclerotic risk factor for perioperative cardiac complications in patients with PAD scheduled for vascular surgery.[10,19] Pre-operative risk stratification according to the Lee cardiac index has a proven association with perioperative outcome.[11] The detection of IGT and DM has a significant clinical relevance, both in pre-operative cardiovascular risk stratification and treatment. In the present study, DM was detected in 43 (11%) patients. Addition of this clinical risk factor to the pre-operative cardiac risk score resulted in a Lee risk index of ≥ 2 in 19 patients. Use of the OGTT provides the physician to make more accurate risk stratification and the possibility to perform additional pre-operative (non-) invasive testing and subsequent treatment. These patients with newly found DM need additional treatment, compared to PAD patients without DM. Target blood pressure should be lowered to 130/80 mmHg in

stead of 140/90 mmHg, using ACE-inhibitors and β-blocking agents. The presence of DM deserves attention during the perioperative and postoperative phase as well. Plasma glucose levels need to be close monitoring during surgery.[10] In a recent study by Hoeks *et al.* the pre-operative Lee Risk Index was shown to be an important prognostic factor for late mortality and impaired health status in patients with PAD.[20] The present study confirmed these results by showing a significant increase in cardiovascular events and mortality during long-term follow-up if ≥2 clinical risk factors are present at baseline in patients with IGT. Currently, the use of pre-operative OGTT is only recommended in patients undergoing cardiac surgery with ≥2 clinical risk factors.[10] The ACC/AHA guidelines for pre-operative management in patients with peripheral arterial disease (PAD) undergoing noncardiac surgery do not recommend a pre-operative glucose-loading test. This study showed that patients with IGT and DM have a worse prognosis following vascular surgery during long-term follow-up. Therefore, pre-operative glucose loading testing and subsequent expanded medical treatment should be recommended in patients with ≥2 clinical risk factors. However, cost-effectiveness analysis regarding the use of OGTT in this specific setting needs to be evaluated, before applying the test in all high-risk vascular surgery patients. There are several arguments why OGTT should be used in the pre-operative phase: (i) patients with newly detected DM have an increased risk of peri-operative ischemia[21], (ii) the relative simple OGTT can easily be performed within the first 2 in-hospital days prior to surgery, and (iii) the known risk of perioperative hyperglycemia could influence the OGTT if performed post-operatively.

The first limitation of this study was the single measurement of fasting glucose levels. The World Health Organization recommends a repeated measurement for diagnostic purposes. This could have influenced the prevalence of the detected glucose regulation disorders. Cardiovascular events were not significantly increased in patients with DM, however a trend was shown. The lack of significance in the DM group is possibly due to a study power problem as this group consisted only of 43 patients. Although all medical records were reviewed by two authors (JPK and MD) and there was a close agreement between these data, the potential limitation of recall bias cannot be ruled out completely.

CONCLUSION

Pre-operative OGTT should be part of a routine assessment in patients with PAD, as OGTT adds significantly to fasting glucose in the diagnosis of IGT and DM. Furthermore, patients with IGT detected by pre-operative glucose loading test, have

an increased risk in cardiovascular events and mortality during long-term follow-up. Therefore, it is recommended that non-diabetic vascular surgery patients should be tested for glucose regulation disorders prior to surgery and receive more aggressive risk factor management and adequate pharmacological treatment for the prevention of micro- and macrovascular complications during long-term follow-up.

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Chapter 12

Metabolic syndrome is an independent predictor of cardiovascular events in high-risk patients with occlusive and aneurysmatic peripheral arterial disease

Jan-Peter van Kuijk
Willem-Jan Flu
Michel Chonchol
Hence J.M.Verhagen
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Objective: Metabolic syndrome (MetSyn) is a well-known risk factor for cardiovascular (CV) disease in the general population; however, the additional predictive value for CV events in high-risk patients with peripheral arterial disease (PAD) is unknown. The aims of the current study were to assess and compare the (i) prevalence of MetSyn, and (ii) predictive value of MetSyn for CV events, in patients with either occlusive or aneurysmatic PAD.

Methods: We screened 2.069 patients scheduled for lower occlusive arterial revascularization (N=1.031) or abdominal aortic aneurysm repair (N=1.038) for the presence of MetSyn. Adult Treatment Panel III report (ATP III) was used for defining MetSyn. Central obesity was defined as body-mass-index >30 kg/m^2. Main outcomes were the occurrence of CV events and CV mortality during a median follow-up of 6 years (IQR 2-9 yrs).

Results: Metabolic syndrome was diagnosed in 421 (41%) and 432 (42%) patients with occlusive and aneurysmatic PAD, respectively (p = 0.72). Patients with occlusive or aneurysmatic PAD and MetSyn had an increased risk for the development of CV events, when compared to patients without MetSyn (27 vs 18% and 27 vs 19%, p < 0.001, respectively). In occlusive and aneurysmatic PAD, MetSyn was independently associated with an increased risk of CV events (HR 1.6, 95% CI: 1.2 to 2.1 and HR 1.4, 95% CI: 1.1 to 1.8). No significant association between the presence of MetSyn and CV mortality was observed.

Conclusions: Metabolic syndrome is highly prevalent in high-risk PAD patients. In occlusive and aneurysmatic PAD patients, MetSyn is an independent predictor of long-term CV events.

INTRODUCTION

The metabolic syndrome (MetSyn), also known as the insulin resistance syndrome or Syndrome X, is the concurrence of multiple metabolic abnormalities associated with cardiovascular (CV) disease. The prevalence of MetSyn in the general healthy population is 9 to 22%, and increases up to 50% in patients with known cerebrocardiovascular disease.[1-3] Importantly, the prevalence depends on the definition of MetSyn.[4] In 1988, Raeven was the first who defined MetSyn, based on the fundamental pathogenic process of insulin resistance.[5] In 1999, the World Health Organization (WHO) defined specific metabolic components and laboratory thresholds for the definition of MetSyn, primarily based on the presence of insulin resistance.[6] The U.S. National Cholesterol Education Program (NCEP) redefined the MetSyn in 2003, in an attempt to simplify the clinical application of its criteria.[7] Of note, the fundamental pathogenic mechanism was not longer insulin resistance, but the presence of abdominal obesity.[8]

Metabolic syndrome was primarily developed as a predictor of CV disease in healthy populations, however, only recently studies have indeed demonstrated the association between MetSyn and increased risk of CV events.[1,9-11] Important to notice is that these studies had different definitions of MetSyn and varying study populations. In patients with known cerebrocardiovascular disease it has been demonstrated that MetSyn was associated with increased risk for CV events and CV mortality.[9] However, the prevalence and predictive value of MetSyn in patients with occlusive peripheral arterial disease (PAD) or abdominal aortic aneurysms (AAA) has been examined only in low to intermediate risk patients or small groups of AAA patients.[1,12-15] Therefore, the primary aim of the current study was to assess the prevalence of MetSyn in these two high-risk populations. In addition, as data about the predictive value of MetSyn in these high-risk patients is scarce,[3,11] the secondary aim of the current study was to assess the long-term predictive value of MetSyn in patients with either established occlusive or aneurysmatic PAD which has not been previously examined.

METHODS

Study design and population

This retrospective study included a total of 2.933 patients with PAD, scheduled for elective lower extremity revascularization (N=1.031), abdominal aortic aneurysm surgery (N=1.038) and carotid endarterectomy (N=864) during the time period 1990 to 2008. The focus of the current study was to examine the prevalence and

predictive value of MetSyn in patients with occlusive lower extremity arterial disease (symptomatic PAD requiring surgical intervention) or aneurysmatic PAD (N=2.069). Patients undergoing surgery for occlusive disease with a history of aneurysmatic PAD were regarded as occlusive disease (3%), while patients undergoing surgery for aneurysmatic PAD and a history of occlusive disease were regarded as aneurysmatic PAD (10%). Patient enrolment was performed after approval of the hospital's ethics committee.

Patient data

At baseline all medical records were reviewed to determine the presence of documented ischemic heart disease and cerebrovascular disease. Ischemic heart disease was defined as a composite of previous angina pectoris, myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting. In addition, all (cardiac) risk factors were determined at baseline, including age, gender, body-mass-index (BMI), smoking status, chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseaseas-classification[16]) and chronic renal insufficiency (serum creatinine >2,0 mg/dL). During pre-operative evaluation fasting glucose and lipid-profiles (total cholesterol, HDL, LDL, triglycerides) were measured. Finally, the use of the following medication was recorded: aspirin, statins, β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitor, oral anticoagulants and ticlopidines.

Metabolic syndrome

The presence of MetSyn was defined according the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III report (ATP III), which identified the MetSyn as a multiplex risk factor for CV disease.[17] According the ATP III report, diagnosis of MetSyn can be made when 3 out of 5 of the following characteristics are present: (i) abdominal obesity (waist circumference men >102cm, women >88cm), (ii) triglycerides ≥150 mg/dL (>1.695 mmol/L), (iii) HDL cholesterol in men <40mg/dL (<0.9 mmol/L) or in women <50mg/dL (<1.0 mmol/L), (iv) systolic blood pressure ≥130mmHg or diastolic blood pressure ≥85mmHg, and (v) fasting glucose ≥110mg/dL (>6.1 mmol/L). For the current study we defined abdominal obesity as BMI >30 kg/m^2.[18]

Follow-up and endpoints

The median follow-up of all patients was 6 years (interquartile (IQR) range 2 – 9). Primary study endpoint was the occurrence of CV events, defined as a composite of myocardial infarction, percutaneous coronary intervention / coronary artery bypass grafting or cerebrovascular accident / transient ischemic attack. Follow-up data were recorded by reviewing the medical records. Secondary endpoint included

CV mortality. Survival status was completed by reviewing the municipal civil registries. Cause of death was ascertained by examining the death certificates, and otherwise by reviewing the medical records. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and included death following myocardial infarction, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular event or transient ischemic attack), surgery related bleeding complications (only a post-operative cause of death), and others. Sudden unexpected death was classified as a CV death as well.

Statistics

Continuous data were compared using analyses of variance, and are expressed as mean ± Standard Deviation (SD). Categorical data are presented as percentage frequencies and compared using x^2 tests. Cumulative estimated event rates of patients with or without MetSyn were determined by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox regression models were used to investigate the association between MetSyn (patients without MetSyn as reference group) and prespecified endpoints. Multivariate analyses were adjusted for potential confounders (age, gender, smoking, heart failure, chronic renal insufficiency, and history of cerebrocardiovascular disease). We used interaction terms to study a possible interaction between these potential confounders and the primary endpoint for both groups of patients. Statistical analyses were performed using SPSS software (SPSS version 15.0; SPSS, Inc., Chicago, Illinois). Hazard ratios (HR) were calculated from these models along with their 95% confidence intervals (C.I.). A two-sided *p*-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study population

A total of 2.069 eligible patients, referred for lower extremity revascularization (N=1.031) or abdominal aortic aneurysm repair (N=1.038) comprised the study population (*Table 1*). Diagnosis of MetSyn was established in 421 (41%) and 432 (42%) patients with occlusive and aneurysmatic PAD, respectively (p = 0.72). The distribution of the number of MetSyn components among occlusive and aneurysmatic PAD patients with or without MetSyn is shown in *Figure 1*. In addition, baseline characteristics of patients with occlusive and aneurysmatic PAD and MetSyn are shown in *Table 1*.

Table 1 **Baseline characteristics of the study population**

	Metabolic Syndrome				MetSyn in group 1 vs. MetSyn in group 2 (N=853)
	Group 1 occlusive disease		Group 2 Aneurysmatic disease		
	Yes [N=421]	No [N=610]	Yes [N=432]	No [N=606]	*P*-value
Demographics					
Age >70 years (%)	142 (34)	254 (42)	207 (48)	355 (39)	<0.001
Male (%)	372 (65)	442 (73)	365 (85)	505 (83)	<0.001
Medical history					
Ischemic heart disease	215 (51)	239 (39)	239 (55)	277 (46)	0.19
CVA/TIA	80 (19)	64 (11)	81 (19)	71 (12)	0.90
Metabolic syndrome components					
Abdominal obesity	89 (21)	32 (5)	388 (68)	141 (30)	0.21
Triglycerides ≥150mg/dl	394 (94)	123 (20)	433 (76)	50 (11)	0.05
HDL Cholesterol					
Men <40 mg/dl	255 (94)	81 (18)	369 (75)	39 (10)	0.09
Women <50 mg/dl	140 (94)	27 (16)	67 (81)	10 (12)	0.25
Blood pressure ≥130/85	409 (94)	433 (71)	537 (94)	334 (72)	0.22
Fasting glucose 6.1 mmol/l	112 (27)	55 (9)	324 (57)	131 (28)	<0.001
Additional risk factors					
Smoking					0.08
No	120 (29)	260 (43)	148 (34)	249 (41)	
Current	185 (44)	233 (38)	158 (37)	220 (36)	
History	116 (27)	117 (19)	126 (29)	137 (23)	
Renal insufficiency	69 (16)	51 (8)	60 (14)	67 (11)	0.29
Chronic heart failure	54 (11)	37 (7)	36 (8)	45 (7)	0.10
COPD	69 (16)	101 (17)	124 (29)	171 (28)	<0.001
Medication at discharge					
Aspirin	223 (53)	192 (32)	215 (50)	219 (36)	0.31
Statin	255 (61)	121 (20)	223 (52)	159 (26)	0.01
B-blocking agents	237 (56)	167 (27)	260 (60)	261 (43)	0.25
ACE-inhibitors	142 (34)	136 (22)	143 (33)	132 (22)	0.87
Diuretics	138 (33)	124 (20)	131 (30)	129 (21)	0.46
Oral anticoagulants	201 (48)	382 (63)	115 (27)	191 (32)	<0.001
Ticlopidines	30 (7)	15 (3)	14 (3)	19 (3)	0.01

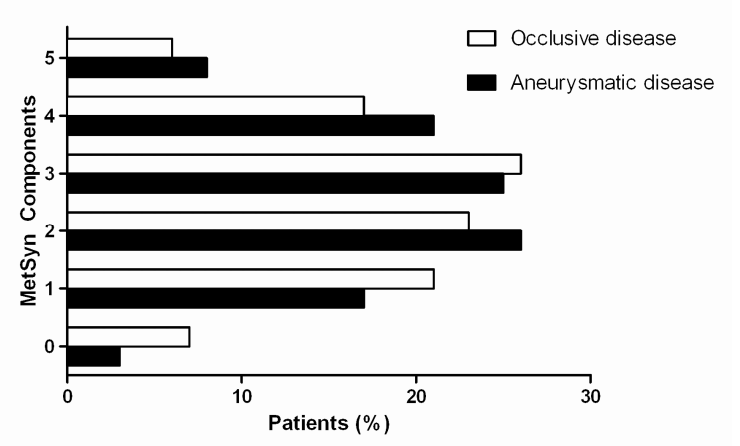
Abbreviations: PAD; peripheral arterial disease, MetSyn; Metabolic syndrome, CVA/TIA; Cerebrovascular accident / transient ischemic attack, COPD; Chronic obstructive pulmonary disease

Occlusive peripheral arterial disease

Patients with occlusive PAD and MetSyn were more likely to have a history of cerebrocardiovascular disease (ischemic heart disease/cerebrovascular disease), smoking habits (current or history), chronic renal insufficiency and chronic heart failure ($p < 0.001$), compared to patients without MetSyn. Lipid spectrum disorders and hypertension were the most often present components in patients with MetSyn. Medical treatment with aspirin, statins and β-blockade was higher in patients with MetSyn ($p < 0.001$). In addition, patients with MetSyn were more

often treated with antihypertensive drugs ($p < 0.001$). During a median follow-up of 6 years (IQR 2 – 9), 228 (22%) occlusive disease patients developed CV events. Patients with MetSyn had an increased risk for the occurrence of CV events, compared to patients without MetSyn (27 vs 19%, $p = 0.001$). Kaplan-Meier estimates for long-term CV event rates showed that patients with MetSyn had higher event rates compared to patients without MetSyn (*Figure 2a*).

Figure 1. *Distribution of the metabolic syndrome components among patients with occlusive or aneurysmatic peripheral arterial disease*



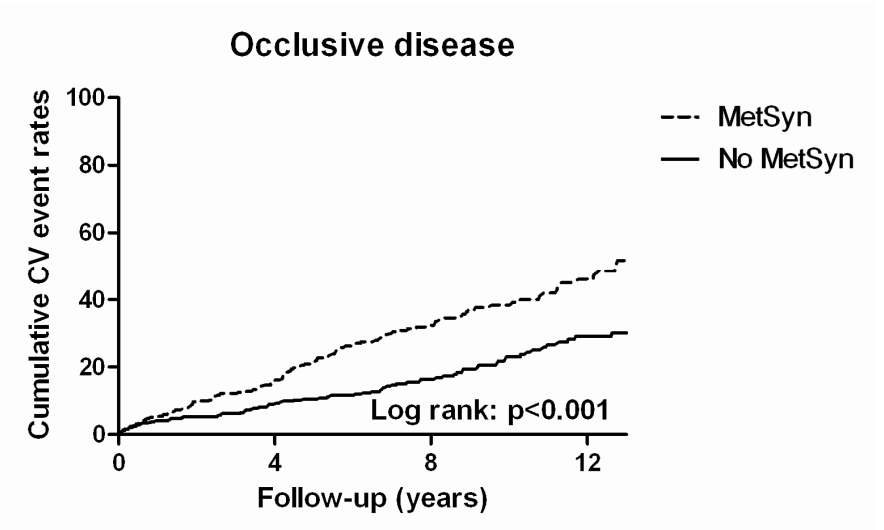
Moreover, the presence of MetSyn proved to be an independent prognostic factor for long-term cardiovascular events (HR 1.61, 95% CI: 1.2 to 2.1). For the occurrence of late cardiovascular events, diabetes mellitus, and BMI >30 kg/m^2 were the independent prognostic factors contributing to the MetSyn (*Table 2*).

Table 2 **Long-term cardiovascular events**

	Hazard Ratio	95% CI
Occlusive peripheral arterial disease		
Metabolic syndrome	1.61	1.23-2.11
Abdominal obesity	1.79	1.25-2.58
Triglycerides ≥ 150 mg/dL	1.10	0.80-1.52
HDL Cholesterol	1.31	0.88-1.96
Blood pressure ≥ 130/85	1.15	0.77-1.71
Fasting glucose ≥ 6.1 mmol/L	2.07	1.49-2.86
Aneurysmatic peripheral arterial disease		
Metabolic syndrome	1.36	1.05-1.76
Abdominal obesity	0.95	0.57-1.60
Triglycerides ≥ 150 mg/dL	1.50	1.09-2.07
HDL Cholesterol	0.98	0.71-1.35
Blood pressure ≥ 130/85	0.88	0.61-1.25
Fasting glucose ≥ 6.1 mmol/L	1.10	0.84-1.44

Furthermore, age (HR 1.02, 95% CI: 1.0 to 1.1), ischemic heart disease (HR 2.16, 95% CI: 1.6 to 2.9) and chronic renal insufficiency (HR 2.93, 95% CI: 2.1 to 4.2) were independent predictors for long-term cardiovascular events. No interaction between age, gender, smoking, heart failure, chronic renal insufficiency, and history of cerebrocardiovascular disease and the occurrence of cardiovascular events in patients with MetSyn was observed. The secondary endpoint CV mortality occurred in 337 (33%) patients. Regression analyses demonstrated no association between the presence of MetSyn and the occurrence of all cause or CV mortality.

Figure 2a. *Kaplan-Meier estimates of cardiovascular event rates during long-term follow-up in patients with occlusive arterial disease. MetSyn; metabolic syndrome, CV: Cardiovascular*

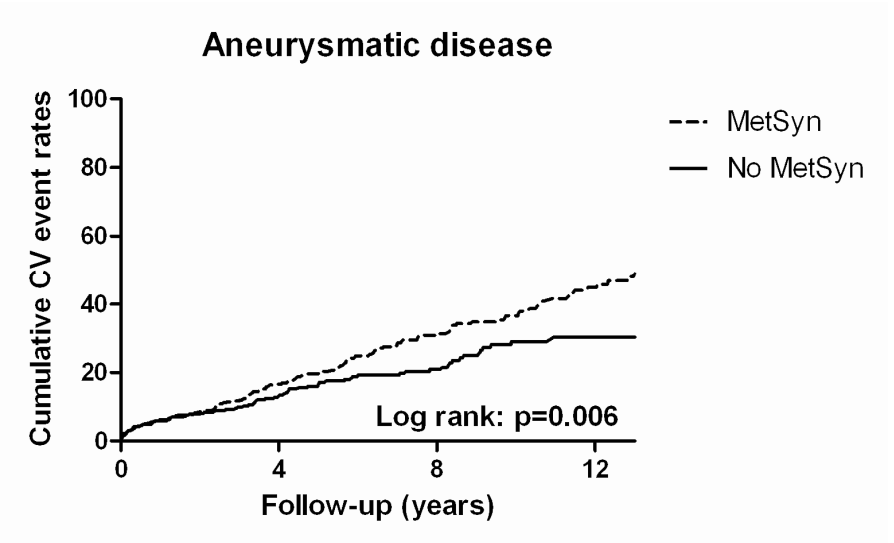


Aneurysmatic peripheral arterial disease

Aneurysmatic PAD patients with MetSyn were significantly younger and had more often a history of cerebrocardiovascular disease ($p < 0.05$). At discharge, patients with MetSyn were more often treated with aspirin, statins and β-blocking agents, compared to aneursymatic patients without MetSyn ($p < 0.001$). Hypertension was the most frequent component of MetSyn and medical treatment was in line with this finding as the majority of the MetSyn patients were treated with diuretics or ACE-inhibitors ($p < 0.001$). Cardiovascular events occurred in 153 (27%) aneurysmatic PAD patients with MetSyn, compared to 88 (19%) of the patients without MetSyn ($p = 0.001$). Estimates for long-term CV event rates according the Kaplan-Meier curves, demonstrated that patients with MetSyn had significantly higher event rates compared to patients without MetSyn (Log-rank test, $p = 0.006$) (*Figure 2b*). Using multivariate analyses, the presence of MetSyn in patients with aneurysmatic PAD was an independent predictor for long-term CV events (HR 1.36, 95% CI: 1.1 to 1.8). Of the components contributing to the MetSyn, only elevated

triglycerides were significantly associated with an increased risk of long-term CV events. In line with occlusive disease patients, age (HR 1.03, 95% CI: 1.0 to 1.1), ischemic heart disease (HR 1.45, 95% CI: 1.1 to 1.9) and chronic renal insufficiency (HR 3.60, 95% CI: 2.6 to 4.9) were independent predictors for long-term cardiovascular events. Using interaction terms, no significant interaction for age, gender, smoking, heart failure, chronic renal insufficiency, and history of cerebrocardiovascular disease were demonstrated. Of note, during long-term follow-up 324 (31%) patients died due to a CV cause.

Figure 2b. *Kaplan-Meier estimates of cardiovascular event rates during long-term follow-up in patients with aneurysmatic peripheral arterial disease. MetSyn: Metabolic Syndrome, CV: cardiovascular*



However, no association between the presence of MetSyn and CV mortality was observed in patients with aneurysmatic PAD. Additional analyses were performed to study the predictive usefulness of MetSyn in patients without diabetes. After excluding the patients with known DM (N=362, 17%), and those with a fasting glucose >7.0 mmol/L (N=142), there was a remaining population of 1.564 patients (76%). Using multivariate Cox regression analysis, MetSyn remained to be an independent predictor of adverse cardiovascular events with a HR of 1.4 (95% CI: 1.09 to 1.81). Furthermore, we evaluated the predictive value of MetSyn using three (N=563, 27%), four (N=256, 12%) or five (N=34, 1,6%) criteria for the diagnosis of MetSyn. In multivariate analyses, MetSyn defined with the three, four and five criteria were all independently associated with a 1.3 (95% CI: 1.1 to 1.6), 1.8 (95% CI: 1.3 to 2.3) and 2.2-fold (95% CI: 1.2 to 4.1) increased risk of cardiovascular events.

DISCUSSION

To our knowledge, this is the first study demonstrating the predictive value of MetSyn on the occurrence of CV events in patients with symptomatic occlusive and aneurysmatic PAD. We found a high prevalence of MetSyn in both groups of patients. In addition, in both occlusive and aneurysmatic PAD patients, MetSyn was an independent predictor for the occurrence of CV events during long-term follow-up, compared to PAD patients without MetSyn. No association between the presence of MetSyn and the occurrence of CV mortality was observed.

Metabolic syndrome has two potential pathophysiological processes, including (i) insulin resistance, and (ii) obesity and disorders of adipose tissue. In line with Raeven[5] who proposed the first definition of MetSyn, the WHO identified insulin resistance as the fundamental mechanism. Insulin resistance and hyperinsulinemia directly causes other metabolic risk factors, including an increased body fat content.[6] The emphasis of insulin resistance as the basic pathophysiological mechanism is based on the presence of reduced insulin sensitivities throughout several degrees of obesity.[10] In contrast, by the NCEP expert panel[7,17] the rising prevalence of MetSyn was considered to be a direct consequence of the "obesity epidemic", as obesity directly or indirectly contributes to hypertension, high serum cholesterol, low HDL cholesterol and hyperglycemia. Although there is no definite consensus about the leading pathophysiological mechanism of MetSyn, a combined process of increased obesity and insulin resistance with a strong interaction seems most appropriate mechanism.

A direct consequence of the lack of consensus about the pathogenic mechanisms of MetSyn, are the differences in clinical criteria for the diagnosis recommended by at least 3 organizations, including the ATP III[17], the WHO[6] and the American Association of Clinical Endocrinologists (AACE).[19] Although their criteria are similar in several aspects, they reveal fundamental differences in positioning of the predominant causes of the syndrome. In the ATP III criteria, priority is given to abdominal obesity as a contributor of MetSyn, recognized by increased waist circumference.[17] In contrast, the WHO regarded insulin resistance as a required component for diagnosis, while this was not explicitly required in the ATP III definition.[6] Furthermore, abdominal obesity was defined as a BMI >30 kg/m^2. The AACE criteria appear to be a hybrid of the ATP III and WHO criteria. In this set of criteria, abdominal obesity is a major criteria and is defined as BMI >30 kg/m^2.[19] These different abdominal obesity parameters could influence the prevalence of MetSyn and its predictive value for CV events. However, a meta-analysis by Gami *et al.* demonstrated that the heterogenity between the predictive

values of the WHO and ATP III criteria was not explained by the use of different obesity metrics. Currently, ATP III criteria are most commonly used as they provide a practical tool to identify patients at increased risk for CV disease.[20] Furthermore, WHO and AACE criteria require additional oral glucose tolerance testing if impaired fasting glucose and diabetes are absent.

The prevalence of MetSyn is strongly related to the definition of MetSyn, but to the target population as well. The impact of MetSyn as a growing and pressing problem for the general population is reflected by the high prevalence of the condition in healthy subjects (9 to 22%).[1,2] The current study showed a prevalence of 41 and 42% of MetSyn in patients with symptomatic occlusive and aneurysmatic PAD, respectively. Previous studies reported that the prevalence of MetSyn in PAD patients can be up to 58%, which is even higher than in patients with coronary heart disease (41%) or cerebrovascular disease (43%).[3,11] These findings have important clinical implications, considering that PAD is highly prevalent in the adult population and is associated with an increased risk of CV events.[21,22] The current study observed no difference in prevalence of MetSyn in patients with aneurysmatic compared to patients with occlusive PAD. These findings have not been examined by previous studies, however, the difference in prevalence might be a result of the small sample size of previous studies compared to the present study.[3,23] In addition, the use of different criteria for defining MetSyn could have influenced the observed prevalence. In the present study we used ATP III criteria as these provide a practical tool to identify patients at increased risk for CV events and have been acknowledged as a reliable prognostic indicator of adverse cardiac outcome.[20]

In this study the presence of MetSyn in patients with established occlusive or aneurysmatic PAD was independently associated with an increased risk for the occurrence of CV events during long-term follow-up. Although patients undergoing vascular surgery are classified as being a high-risk population for perioperative and long-term adverse cardiac outcome, the present study demonstrated that diagnosing MetSyn has an additional value for long-term prognosis. Therefore, based on our results we support the clinical use of MetSyn as a prognostic factor for long-term cardiac outcome in both patients with occlusive and aneurysmatic PAD. Despite the high prevalence of MetSyn in patients with aneurysmatic PAD, the correlation between MetSyn and CV events seemed to be less strong compared to patients with occlusive disease. The most reasonable explanation for this low correlation could be the difference in risk factors and the pathophysiological processes. Occlusive arterial disease is a direct consequence of atherosclerotic wall damage, while aneurysmatic PAD is an inflammatory process of the arterial wall

with subsequent weakening of the aortic wall as a result of connective tissue degradation.[24] In the present study these differences were underlined by different risk factor patterns, especially lower age at presentation in patients with occlusive disease and high prevalence of COPD (a connective tissue disease as well) in patients with aneurysmatic PAD.

Some studies have demonstrated no additional effect of MetSyn above its individual components for the prediction of cardiovascular events.[20] In the present study of patients with occlusive PAD, obesity and elevated fasting glucose levels were independent predictors. In aneurysmatic PAD patients, only hypertriglyceridemia was an independent predictor of adverse outcome. MetSyn is a unique and uniform entity, requiring at least three out of five diagnostic components; therefore, it is reasonable that the combination of components (MetSyn) has an additional value in the current study. In addition, using only the significant individual components for predicting future cardiovascular events, the importance of the nonsignificant components would be under-estimated. To study the specific influence of diabetes as an individual component on the predictive value of MetSyn, we performed additional analyses in which we excluded patients with known DM and/or fasting glucose levels >7.0 mmol/L. Importantly, MetSyn remained to be an independent predictor of cardiovascular events during long-term follow-up. The kind, magnitude and number of the diagnostic components are likely to influence the prognostic information of MetSyn; therefore, future studies should be performed using MetSyn as a weighted-risk model in which each component has its own predictive value.

Previous studies in patients with PAD have been performed and observed a predictive value of MetSyn for future vascular events.[12-15] However, most of these studies included patients out of the general population[12,13] (low-risk) or patients with symptomatic PAD (intermediate-risk).[14,15] Of note, one study included a small number of patients with AAA, but no association between the presence of MetSyn and future vascular events or all-cause mortality was detected.[15] In contrast, the current study included high-risk patients and a large cohort of AAA patients.

No relation between the presence of MetSyn and CV mortality was observed in patients with either occlusive or aneurysmatic PAD. According to the WHO and ATP III definition, the primary clinical outcome of MetSyn as a multiplex risk factor is the development of CV disease in patients free of cardiac history.[6, 17] A meta-analysis addressing MetSyn and CV risk showed an increased risk for the development of CV events (RR 2.18, 95% CI 1.6 to 2.9) and CV death (RR 1.91, 95% CI 1.5 to 2.5).[25] However, this meta-analysis included a diversity of study

populations evaluating studies with and without previous histories of CV disease. In addition, definitions of MetSyn were different between the included studies. We performed additional analyses using a diagnosis of MetSyn based on three, four or even five diagnostic criteria for MetSyn to explore whether the risk estimates changed with the number of criteria. These analyses demonstrated that with an increased number of diagnostic criteria the risk of cardiovascular events increased as well, however; the accuracy of the risk estimates diminished. Importantly, the current study included high-risk PAD patients of which almost 50% had a history of CV disease. This could be a possible explanation for the absence of a relation between the presence of MetSyn and the risk of CV mortality as well. Patients with PAD are known to be at increased risk of CV mortality, and based on the present study the presence of MetSyn had no incremental risk for CV mortality in these patients. Therefore, the presence of MetSyn only has an additional value as a predictor for CV events in high-risk PAD patients. Finally, patients with MetSyn received more optimal medical treatment. Although this did not influence the risk of developing CV events, medical treatment could possibly be related to a stabilization of the risk for CV mortality.

Potential limitations of the current study merit consideration. First, we used the ATP III criteria for the definition of MetSyn; however, abdominal obesity was defined as BMI >30 kg/m^2 instead of increased waist circumference. Although this abdominal obesity parameter could have influenced the outcome parameters, the meta-analysis discussed above demonstrated that obesity metrics did not influence the predictive value of MetSyn.[25] Second, for the current study we used ATP III criteria for defining MetSyn. As there are other definitions using different combinations of diagnostic criteria, this could have influenced the prognostic information in this study. Third, this study has the inherent limitations of a retrospective study design. Although the present study found no association between MetSyn and increased CV mortality risk, other studies did show this relation. This might be related to the associations between target population, cardiovascular disease history, and the prevalence of MetSyn. Finally, although medication at discharge was recorded, no data on medication during the follow-up period were available.

CONCLUSION

Patients with occlusive or aneurysmatic PAD have a high prevalence of metabolic syndrome. In both patients with occlusive or aneurysmatic PAD, the presence of metabolic syndrome was independently associated with an increased risk for the

occurrence of CV events during long-term follow-up. Concomitant presence of metabolic syndrome in patients with occlusive or aneurysmatic PAD was not associated with an increased long-term risk of CV mortality.

Conflicts of Interest

The results presented in this paper have not been published elsewhere. There are no conflicts of interest, including specific financial interest and relationships and affiliations relevant to the subject matter or materials discussed in this study.

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Chapter 13

Influence of left ventricular dysfunction (diastolic versus systolic) on long-term prognosis in patients with versus without diabetes mellitus having elective peripheral arterial surgery

Jan-Peter van Kuijk
Willem-Jan Flu
Tabita M. Valentijn
Michel Chonchol
Ruud J. Kuiper
Hence J.M.Verhagen
Jeroen J. Bax
Don Poldermans

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PART III

RENAL DISEASE

Chapter 14

The prevalence and prognostic implications of polyvascular atherosclerotic disease in patients with chronic kidney disease

Jan-Peter van Kuijk
Willem-Jan Flu
Michel Chonchol
Gijs M.J.M. Welten
Hence J.M.Verhagen
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Background: Atherosclerotic disease is often extended to multiple affected vascular beds (AVB). Polyvascular disease (PVD) and chronic kidney disease (CKD) have both separately been associated with an adverse cardiovascular outcome. We assessed the prevalence of PVD in vascular surgery patients with preoperative CKD and studied the influence on long-term cardiovascular survival.

Methods: Consecutive patients (2.933) were preoperatively screened for PVD, defined as 1-, 2-, or 3-AVB. Preoperative glomerular filtration rate (GFR in ml/min/1.73m^2 body-surface area) was estimated by the Modification of Diet in Renal Disease (MDRD) prediction equation, and patients were categorized according their estimated GFR. Primary endpoint was (cardiovascular) mortality during a median follow of 6.0 years (IQR 2-9).

Results: Preoperative MDRD-GFR was classified as normal kidney function (GFR ≥90), or mild (GFR 60-89), moderate (GFR 30-59) and severe (GFR <30) kidney disease in 779 (27%), 1423 (48%), 605 (21%) and 124 (4%) patients, respectively. One-vessel disease was present in 54% of the patients with normal kidney function, while 62% of the patients with CKD (GFR <60) had PVD. In patients with moderate or severe kidney disease, the presence of PVD was independently associated with even higher cardiovascular mortality rates (2-AVB: HR 1.65, 95% CI: 1.09 to 2.48; 3-AVB: 2.07, 95% CI: 1.08 to 3.99), compared to 1-AVB.

Conclusion: Patients with CKD had a high prevalence of PVD, which was independently associated with increased all-cause and cardiovascular mortality.

INTRODUCTION

With aging of the population, the prevalence of atherosclerotic disease and its associated adverse outcomes is increasing. It has to be noted that the process of established atherothrombosis is not limited to a single arterial location. The Reduction of Atherothrombosis for Continued Health (REACH) registry showed that one out of 6 patients with peripheral arterial disease (PAD), cerebrovascular disease (CVD) or coronary artery disease (CAD) had involvement of 1 or 2 other arterial beds.[1] The presence of polyvascular disease has been demonstrated to be an independent predictor of long-term cardiovascular outcome in the general population.[2-4]

Chronic kidney disease (CKD), defined as an estimated GFR of less than 60 ml/min/1.73m^2, is a worldwide public health problem with poor outcomes and high costs[5], and kidney failure requiring treatment with chronic dialysis or kidney transplantation is the most visible outcome of this patient population. However, patients with CKD also frequently have associated cardiovascular disease, as individuals with CKD are more likely to die of a cardiovascular event than to develop kidney failure.[6]

The studies mentioned above have shown a worse prognosis of patients in the general population with polyvascular disease, and other studies have demonstrated a graded relationship between a reduced estimated glomerular filtration rate (GFR) and the risk of death and cardiovascular events.[2,3,7,8] However, no prior studies have examined the influence of preoperative reduced estimated GFR and polyvascular disease on long-term outcome in PAD patients undergoing elective vascular surgery. Therefore, the aim of the current study was to assess (i) the prevalence of polyvascular disease in PAD patients with preoperative CKD, and (ii) the influence of polyvascular disease in CKD patients on long-term outcome.

MATERIALS AND METHODS

Study design and population

This retrospective study comprised a population of 2.933 consecutive patients with PAD, referred for elective major vascular surgery. All patients underwent a major vascular surgery procedure during the time period 1990 to 2008, and included lower extremity revascularization, aneurysmatic abdominal aortic surgery or carotid surgery. From 1990 until 2001, standard pre-operative screening included a detailed cardiac history, physical examination, electrocardiogram (ECG), standard

laboratory measurements and additional (stress)-testing if indicated. After 2002, standard pre-operative echocardiography was added to the screening program. The study complies with the Declaration of Helsinki. Patient enrolment was performed after approval of the hospital's ethics committee and after informed consent of all patients (or their guardians) at time of inclusion.

Renal function measurement

Prior to surgery (1-3 days), serum creatinine was measured in all patients. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) prediction equation. Patients were categorized using the MDRD-GFR in the following categories according the National Kidney foundation criteria[5]: (i) normal kidney function (GFR ≥90 ml/min/1.73m^2), (ii) mild kidney disease (GFR 60-89 ml/min/1.73m^2), (iii) moderate kidney disease (GFR 30-59 ml/min/1.73m^2) and (iv) severe kidney disease (GFR<30 ml/min/1.73m^2).

Patient data

At baseline, all medical records were reviewed to determine the presence of documented CAD and CVD. Patients undergoing lower extremity revascularization or abdominal aortic surgery were screened for the concomitant presence of documented CAD and CVD. Patients undergoing carotid surgery were screened for CAD and PAD. Coronary artery disease was defined as a documented history of ischemic heart disease (composite of angina pectoris, myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting) using myocardial stress testing [ergometry, stress-echocardiography or computed tomography] or coronary angiogram. Patients with stable or unstable angina pectoris were classified as having documented CAD according the European Society of Cardiology (ESC) guidelines.[9] The presence of coronary ischemia was established by one of the following techniques: exercise ECG (horizontal or down-sloping ST-segment depression or elevation [≥1 mm (0.1 mV) for ≥60-80 ms after the end of the QRS complex]) or exercise testing with echocardiography or CT-scan (≥50% stenosis in one or more of the coronary arteries).[10] The presence of documented CVD was defined as a history of Cerebrovascular Accident (confirmed by a CT-scanning report) or Transient Ischemic Attack (confirmed by a neurologist report). Lower extremity arterial disease was defined as current intermittent claudication with Ankle-Brachial-Index (ABI) <0.9, or a history of intermittent claudication with a previous intervention. Polyvascular disease was defined as the presence of 2 or 3 affected vascular beds (AVB). One-AVB included: PAD, 2-AVB included: PAD and CAD or CVD, 3-AVB included: PAD and CAD and CVD. Finally, the use of the following medication was recorded at discharge: angiotensin-converting enzyme

(ACE) inhibitors, angiotensin receptor blockers, diuretics, β-blockers, calcium antagonists, statins, aspirin, oral anticoagulants, and ticlopidines.

Risk factors

All cardiac risk factors were determined at baseline, including age, gender, body mass index, smoking status, hypertension (blood pressure ≥140/90 mmHg in nondiabetics and ≥130/80 mmHg diabetics or requirement of antihypertensive medication), diabetes mellitus (fasting blood glucose ≥7.0 mmol/l or requirement for insulin and/or oral anti-diabetic medication), hypercholesterolemia (LDL cholesterol > 135 mg/dL and/or the requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases-classification).[11]

Follow-up and endpoints

The median follow-up of all patients was 6 years (interquartile range 2-9). Primary study endpoint was the occurrence of all-cause mortality. Survival status was assessed by reviewing the municipal civil registries. Cause of death, classified as either cardiovascular or noncardiovascular death, was ascertained by examining death certificates, or by reviewing medical records. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and includes death following myocardial infarction, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular event or transient ischemic attack). Surgery related bleeding complications were classified as a cardiovascular cause of death only when patients died within 30 days after surgery. During long-term follow-up, surgery related bleeding complications were not classified as a cardiovascular cause of death. Sudden unexpected death was classified as a cardiovascular death.

Statistics

Continuous data were compared using analyses of variance, and are expressed as mean ± SD. Categorical data are presented as percentage frequencies and compared using x^2 tests. For all baseline characteristics (including age), analyses for trends between the kidney function groups were performed with linear-by-linear association. Logistic regression analyses were used to determine the association between kidney function (mild, moderate or severe kidney disease compared to normal kidney function) and short-term mortality (30 days). Cumulative survival of patients with kidney disease was determined by the Kaplan-Meier method and compared using the log-rank test. Cox regression models were used to investigate the association between kidney disease (patients with normal kidney function as

reference group) and mortality during long-term follow-up. All multivariate analyses were primarily adjusted for demographics (age and gender) and cardiovascular risk factors (smoking, hypertension, diabetes mellitus, hypercholesterolemia, heart failure, pre-operative Hemoglobin levels and COPD). Secondary adjustments were made for medications usage recommended in PAD patients, including aspirin, statins, and β-blockers in case of prior myocardial infarction and angiotensin-converting enzyme (ACE) inhibitors in patients with heart failure.[1] Statistical analyses were performed using SPSS software (SPSS version 15.0; SPSS, Inc., Chicago, Illinois). Odds and Hazard ratios (OR/HR) were calculated from these models along with their 95% confidence intervals (C.I.). A *p*-value < 0.05 (two-sided) was considered statistically significant.

RESULTS

Description of the study population

The study population consisted of 2.933 consecutive patients with PAD referred for elective major vascular surgery. Lower extremity revascularization was performed in 1.031 (35%) patients, abdominal aortic surgery in 1.170 (40%) patients, and carotid surgery in 732 (25%) patients, respectively. At baseline, MDRD-GFR categorized all patients into their pre-operative kidney function, and included normal kidney function, mild, moderate and severe kidney disease in 779 (27%), 1423 (48%), 605 (21%) and 124 (4%) patients, respectively (*Table 1*). Coronary artery and CVD were detected in 1248 (43%) and 1037 (35%) patients, respectively.

The number of affected vascular beds at baseline was calculated for all kidney function groups and presented in *Figure 1*. The majority of the patients with normal kidney function had 1-AVB (54%), while only 8% had 3-AVB. In contrast patients with moderate and severe kidney disease had 1-AVB in 38 and 39% respectively, while the majority had 2 or 3-AVB (62 and 61%, respectively). These differences in the number of affected vascular beds were also reflected in the distribution of cardiovascular risk factors.

Patients with severe kidney disease most frequently had concomitant hypertension (73%), diabetes mellitus (27%) and chronic heart failure (22%) (p < 0.001). Remarkably, patients with normal kidney function were most frequent current smokers (41%), while patients with severe kidney disease were more often non- or previous smokers (52%) (p = 0.03).

Figure 1. *Distribution of the number of affected vascular beds among the four categories of baseline kidney function; AVB: Affected vascular beds*

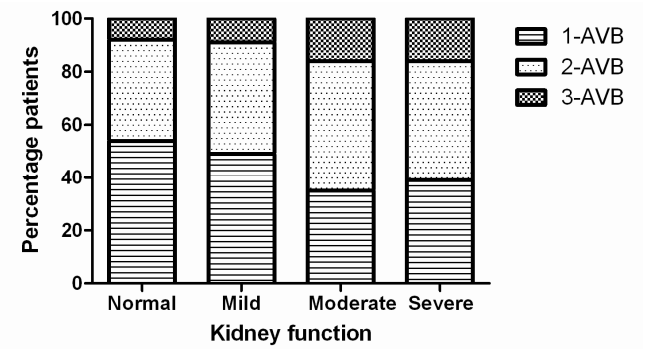


Table 1 **Baseline characteristics of the study population**

	Normal [N=779]	**Mild** [N=1.423]	**Moderate** [N=605]	**Severe** [N=124]	***P*-value for trend**
Demographics					
Age (year), mean ± SD	61.4 ± 12	67.4 ± 10	71.2 ± 9	64.1 ± 12	<0.001
Male (%)	608 (78)	1059 (74)	438 (72)	83 (67)	0.02
Previous history					
CVA/TIA	255 (33)	528 (37)	227 (38)	27 (22)	0.99
Lower-extremity arterial disease	228 (29)	348 (25)	159 (26)	30 (24)	0.14
Aortic aneurysmatic disease	10 (1)	29 (2)	25 (4)	3 (2)	<0.001
Ischemic heart disease	288 (37)	581 (41)	315 (52)	63 (51)	<0.001
Cardiovascular risk factors					
Smoking					
No	282 (36)	548 (39)	245 (41)	64 (52)	0.03
Current	320 (41)	524 (37)	212 (35)	36 (29)	0.02
History	177 (23)	351 (25)	148 (25)	24 (19)	0.94
Hypertension	322 (41)	735 (52)	365 (60)	91 (73)	<0.001
Diabetes mellitus	116 (15)	218 (15)	123 (20)	34 (27)	<0.001
Dyslipidemia	223 (29)	374 (26)	164 (27)	36 (29)	0.71
Chronic heart failure	37 (5)	67 (5)	75 (12)	27 (22)	<0.001
COPD	134 (17)	286 (20)	124 (21)	13 (11)	0.91
Medication at discharge					
Aspirin	406 (52)	766 (54)	282 (47)	47 (38)	0.002
Statin	311 (40)	573 (40)	211 (35)	35 (28)	0.006
ß-blocking agents	318 (41)	628 (44)	280 (46)	65 (52)	0.006
Diuretics	121 (16)	335 (24)	193 (32)	47 (38)	<0.001
ACE inhibitors	154 (20)	344 (24)	201 (33)	41 (33)	<0.001
Calcium Antagonists	146 (19)	342 (24)	170 (28)	52 (42)	<0.001
Angiotensin receptor blockers	34 (4)	79 (6)	37 (6)	7 (6)	0.18
Oral anticoagulants	301 (39)	513 (36)	249 (41)	45 (36)	0.63
Ticlopidines	26 (3)	61 (4)	38 (6)	7 (6)	0.01

Abbreviations: CVA/TIA: Cerebrovascular accident/transient ischemic attack; COPD: chronic obstructive pulmonary disease; ACE -inhibitors: angiotensin converting enzyme-inhibitors.

Medication use and kidney disease

Medication use at time of hospital discharge was registered and compared between the different patient groups (*Table 1*). Aspirin and statin use was lower in patients with moderate or severe kidney disease, compared to patients with normal kidney function ($p < 0.01$). Blood pressure lowering agents were significantly more often prescribed in patients with moderate and severe kidney disease. ß-blocking agents and diuretics were used in 52 and 38% of the patients with severe kidney disease, compared to 41 and 16% of the patients with normal kidney function ($p < 0.01$). The same association was detected between these patient groups regarding the use of ACE-inhibitors, calcium antagonists, and angiotensin receptor blockers ($p < 0.001$)

Short-term outcome

During the first 30 postoperative days, 112 (3.8%) patients died, of which 90 (80%) patients died secondary to a cardiovascular cause. Using univariate regression analyses, patients with moderate or severe kidney disease had an increased risk for all-cause mortality compared to patients with normal kidney function (moderate: OR 3.0, 95% CI: 1.73 to 5.35, severe: OR 4.9, 95% CI: 2.33 to 10.26). This increased risk was present for the occurrence of cardiovascular mortality as well (moderate: OR 2.8, 95% CI: 1.51 to 5.25, severe: OR 4.9, 95% CI: 2.20 to 10.90). In multivariate analyses these associations were not longer present for both all-cause and cardiovascular mortality.

Long-term outcome

During long-term follow-up, 1.389 (47%) patients reached the primary endpoint of all-cause mortality. A cardiovascular or non-cardiovascular cause of death was detected in 849 (61%) and 434 (31%) patients, respectively. In the remaining 106 (3.6%) patients, no specific cause of death could be determined. The occurrence of all-cause mortality showed a significant association with the decrease in kidney function (normal 39%, mild 44%, moderate 61%, severe 75%, $p < 0.001$). Kaplan-Meier estimates for long-term mortality stratified according to kidney disease severity demonstrated that patients with mild, moderate or severe kidney disease had lower survival rates compared to patients with normal kidney function (*Figure 2*). Log-rank test was used to compare cumulative survival between normal vs mild ($p = 0.006$), mild vs moderate, and moderate vs severe kidney disease and demonstrated a significant difference in survival between the three compared groups ($p < 0.001$). In multivariate regression analyses, adjusted for baseline demographics, vascular disease at baseline, risk factors and medication, an evident relationship between the degree of kidney disease and the risk of all-cause and cardiovascular mortality was detected (*Table 2*). Patients with moderate or severe

kidney disease had an increased risk for the occurrence of all-cause mortality (moderate: HR 1.3, 95% CI: 1.09 to 1.50; severe: HR 2.9, 95% CI 2.25 to 3.72), and also for the occurrence of cardiovascular mortality (moderate: HR 1.5, 95% CI 1.23 to 1.87; severe: HR 3.8, 95% CI 2.80 to 5.11), compared to patients with normal kidney function, respectively.

Figure 2. *Kaplan-Meier estimates for long-term all-cause mortality, stratified according the four categories of baseline kidney function*

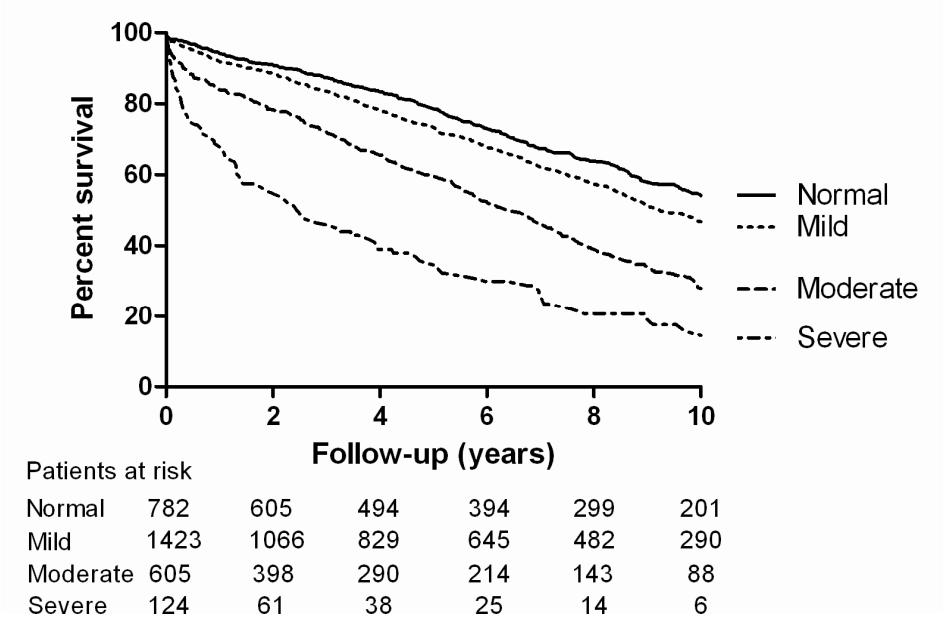


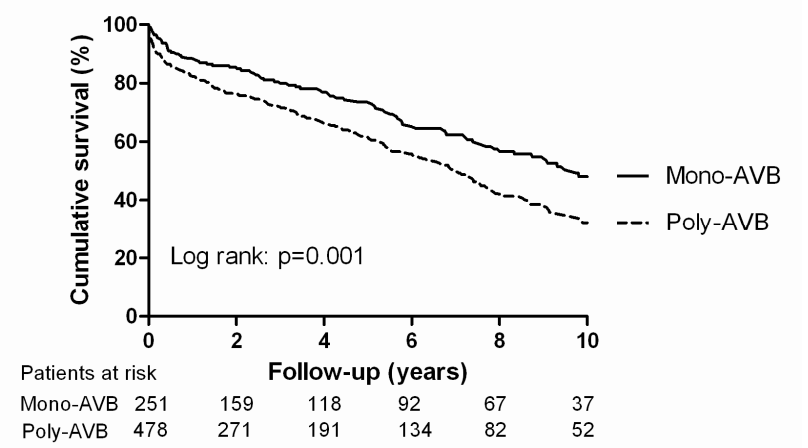
Table 2 **Long-term survival of all patients**

	Events	Univariate		Multivariate	
	N (%)	HR	95% CI	HR	95% CI
All cause mortality					
Normal [N=770]	302 (39)	Ref.		Ref.	
Mild [N=1408]	625 (44)	1.2	1.05-1.40	1.0	0.85-1.13
Moderate [N=604]	369 (61)	2.0	1.75-2.37	1.3	1.09-1.51
Severe [N=124]	93 (75)	3.7	2.94-4.69	2.9	2.24-3.71
Cardiovascular mortality					
Normal [N=770]	167 (22)	Ref.		Ref.	
Mild [N=1408]	364 (27)	1.3	1.06-1.52	1.0	0.85-1.23
Moderate [N=604]	245 (43)	2.5	2.03-3.02	1.6	1.25-1.91
Severe [N=124]	73 (60)	5.0	3.82-6.64	3.8	2.81-5.15

Multivariate: adjustment for age, gender, history of vascular disease (cerebrovascular disease, peripheral arterial disease, ischemic heart disease), smoking, hypertension, diabetes mellitus, dyslipidemia, heart failure, chronic obstructive pulmonary disease, haemoglobin, aspirin, statins, ß-blockers and ACE-inhibitors

Additional analyses on the influence of the number of affected vascular beds in those patients with moderate and severe kidney disease demonstrated an independent association between polyvascular disease (2 or 3-AVB) and the occurrence of all-cause and cardiovascular mortality (*Figure 3*).

Figure 3. *Kaplan-Meier estimates for long-term cardiovascular mortality in patients with moderate or severe kidney disease (N=729) prior to surgery and concomitant presence of polyvascular disease, compared to monovascular disease*



Using multivariate regression analyses in patients with moderate or severe kidney disease, the presence of 2- or 3-AVB was associated with an increased risk for the occurrence of all-cause mortality (2-AVB: HR 1.20, 95% CI 1.01 to 1.49; 3-AVB: HR 1.66, 95% CI: 1.24 to 2.23) and for the occurrence of cardiovascular mortality (2-AVB: HR 1.46, 95% CI: 1.12 to 1.90; 3-AVB: HR 1.78, 95% CI: 1.24 to 2.55) as well, compared to patients with 1-AVB (*Table 3*).

Table 3 **Long-term survival in patients with renal dysfunction [N=729]**

	Events	**Univariate**		**Multivariate**	
	N (%)	HR	95% CI	HR	95% CI
All cause mortality					
1-AVB [N=251]	150 (60)	Ref.		Ref.	
2-AVB [N=355]	233 (66)	1.22	1.04-1.50	1.20	1.01-1.49
3-AVB [N=123]	79 (64)	1.53	1.16-2.01	1.66	1.01-2.87
Cardiovascular mortality					
1-AVB [N=251]	92 (40)	Ref.		Ref.	
2-AVB [N=355]	173 (51)	1.49	1.15-1.91	1.65	1.09-2.48
3-AVB [N=123]	53 (44)	1.63	1.16-2.29	2.07	1.08-3.99

Multivariate: adjustment for age, gender, history of vascular disease (cerebrovascular disease, peripheral arterial disease, ischemic heart disease), smoking, hypertension, diabetes mellitus, dyslipidemia, heart failure, chronic obstructive pulmonary disease, haemoglobin, aspirin, statins, ß-blockers and ACE-inhibitors

DISCUSSION

To our knowledge, the current study is the first to demonstrate an independent graded association between a preoperative reduced estimated GFR and the number of affected vascular beds in a population of almost 3.000 atherosclerotic PAD patients. Preoperative moderate or severe kidney disease had an increased risk for long-term cardiovascular mortality. Of note, in patients with preoperative CKD, the presence of polyvascular disease was associated with higher mortality rates compared to patients with a single affected vascular bed.

In CKD, 2 subtypes of arterial vascular disease can be considered, namely, atherosclerosis and large-vessel remodelling arteriosclerosis.[12] Atherosclerosis is a highly prevalent intimal disease in CKD and is characterized by the presence of plaques and occlusive lesions.[13] Clinical presentations of atherosclerosis include ischemic heart disease, cerebrovascular disease and PAD, which are all common in CKD. Arteriosclerosis is characterized by diffuse non-occlusive arterial remodelling and arterial stiffening due to haemodynamic alterations.[12] The main adverse effects of arterial stiffening are (i) left ventricular hypertrophy due to an elevated left ventricular afterload, and (ii) altered coronary perfusion and blood flow distribution with relative subendocardial ischemia.[12] These factors have been identified as independent predictors of overall and cardiac mortality in patients with advanced CKD.[13] In addition, the frequent association between CVD and CKD is important, because individuals with CKD are more likely to die of CVD than to require renal replacement therapy.[14,15]

We observed in our population of PAD patients that 54% of the patients with normal kidney function had monovascular disease, while the majority of patients with moderate and severe kidney disease had polyvascular disease (62 and 61%, respectively). Data on the prevalence of polyvascular disease most often come from the general population in the primary care setting or from registries.[1,4,16] The REACH registry found a prevalence of polyvascular disease (PAD and CVD) of 16% in the primary care setting.[1] More recent data from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA guidelines (CRUSCADE) investigators in patients presenting with non-ST-segment elevation acute coronary syndrome, reported a prevalence of 12, 10 and 43% for established PAD, documented CVD, and prior CAD, respectively.[3] Objective determination of polyvascular disease by screening and/or additional testing was performed primary by Hertzer *et al.* who observed a prevalence of CAD in 44, 30 and 33% of the PAD patients, respectively.[17] Analyses of the REACH registry showed that 2 or 3-AVB is present in 48 or 14% of PAD

patients, respectively.[2] Of note, the presence of polyvascular disease in patients with PAD has been shown to be independently related to an increased risk of long-term cardiovascular mortality in several studies.[2-4] Eagle *et al.* and Sutton *et al.* observed that during a 10-year follow-up, CAD patients with concomitant PAD had a 25% greater likely-hood of mortality compared to CAD patients without PAD at any point in time. Hence, patients with combined PAD, CAD and/or CVD had the worst prognosis. However, data on the prevalence of polyvascular disease in patients with CKD are scarce. There have been several reports detailing the co-morbid prevalence of PAD and their relationship to atherosclerotic renovascular disease, but these included only small groups of PAD patients.[18-21] For example, Missouris *et al.* reported a prevalence of 45% renal artery stenosis in patients referred for angiography for PAD.[19] Other studies have reported a prevalence of renal artery stenosis in patients with PAD between 28 and 45%.[20,21] Nonetheless, the prevalence of atherosclerosis in other vascular beds has not been thoroughly examined.

In 2004, Go *et al.* demonstrated an independent, graded association between a reduced estimated GFR and the risk of death, cardiovascular events, and hospitalization in a large community-based cohort of 1.120.295 adults.[8] These findings highlighted the clinical and public health importance of CKD. Glynn *et al.* confirmed these results in a cohort of 1.609 patients with established CVD as they observed that patients with CKD had an increased mortality risk compared to patients with normal kidney function.[22] In the present study, patients with moderate or several kidney disease had an increased risk of all-cause and cardiovascular mortality during long-term follow-up.

No previous studies investigated the influence of the number of affected vascular beds in patients with CKD on the long-term survival. In the current study we found that the presence of polyvascular disease was independently associated with an increased risk of all-cause and cardiovascular mortality in PAD patients with CKD. Although PAD patients with CKD already have an increased mortality risk compared to patients with normal kidney function, the additional presence of multiple affected vascular territories was associated with an even higher mortality risk. Shurrab *et al.* studied a cohort of 95 patients with atherosclerotic renovascular disease during 50 months follow-up, and observed that patients with both coronary heart disease and PAD had the highest mortality rates (64%).[23] Furthermore, those patients with solely coronary heart disease had significantly higher mortality than patients with isolated renovascular disease (55 vs 22%).

Potential limitations of the current study merit consideration. First, this study has the disadvantage of a retrospective design. Second, the standardized protocol for pre-operative screening did not include echocardiography before 2002; therefore there could be an underestimation of subclinical atherosclerosis in patients undergoing surgery before this date. Third, in the present study the presence of CAD and CVD was based on reviewing the medical history and screening reports. Consequently, not all patients underwent additional testing for the detection of nonclinical atherosclerosis. Screening with stress testing for polyvascular disease was not systematic but dictated by the risk of clinical findings. Although there is a possible underestimation of significant atherosclerotic lesions, the association between CKD and polyvascular disease would become even stronger if all patients should be screened more extensively. In addition, no data were available about the presence of renal artery stenosis. Finally, diagnostic methods and accuracy have changed over time, which could have influenced the criteria for the presence of documented CAD or CVD.

CONCLUSION

In conclusion, in this large cohort of PAD patients, a high prevalence of preoperative reduced kidney function was observed. Reduced preoperative estimated GFR appeared to be a graded and independent risk factor for all-cause and cardiovascular mortality during long-term follow-up. In addition, patients with CKD had a high incidence of polyvascular disease, which was independently associated with increased mortality rates.

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Chapter 15

Temporary perioperative decline of renal function is an independent predictor for chronic kidney disease

Jan-Peter van Kuijk
Willem-Jan Flu
Michel Chonchol
Sanne E. Hoeks
Tamara A. Winkel
Hence J.M.Verhagen
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Background and objectives: Acute kidney injury is an independent predictor of short- and long-term survival; however, data on the relationship between reversible transitory decline in kidney function and chronic kidney disease (CKD) are lacking. We assessed the prognostic value of temporary renal function decline on the development of long-term CKD.

Design, setting, participants, & measurements: The study included 1.308 patients undergoing major vascular surgery (aortic aneurysm repair, lower extremity revascularization or carotid surgery), divided into three groups on the basis of changes in Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimated GFR on days 1, 2, and 3 after surgery, compared with baseline: Group 1, improved or unchanged (change in CKD-EPI-eGFR ±10%); group 2, temporary decline (decline>10% at day 1 or 2, followed by complete recovery within 10% to baseline at day 3); and group 3, persistent decline (>10% decrease). Primary endpoint was the development of incident CKD during a median follow-up of 5.0 years (IQR 2.6-8.5).

Results: Perioperative renal function was classified as unchanged, temporary and persistent decline in 739 (57%), 294 (22%) and 275 (21%) patients, respectively. During follow-up, 272 (21%) patients developed CKD. In multivariate logistic regression analyses, temporary and persistent declines in renal function both were independent predictors of long-term CKD, compared to unchanged renal function.

Conclusion: Vascular surgery patients have a high incidence of temporary or persistent perioperative renal function declines, both of which were independent predictors for development of long-term incident CKD.

INTRODUCTION

Acute kidney injury (AKI) is a common and serious complication in hospitalized patients and is associated with a high rate of in-hospital morbidity and mortality and prolonged length of stay.[1] The incidence of AKI ranges between 2 and 45% and depends on the type of population, underlying comorbidities, and the definition used to define AKI.[2-4] During the last decade, the incidence of AKI has increased to approximately 500 events per 100.000 in the general population.[1]

Although episodes of AKI seem to be reversible, there is a silent, ongoing inflammatory and fibrotic process, that leads to progressive structural kidney damage.[5,6] This process predisposes to worsening blood pressure (BP) control, proteinuria, and more rapid decreases in glomerular filtration rate (GFR), which are well known risk factors for incident chronic kidney disease (CKD) and cardiovascular disease.[7] Meta-analyses have demonstrated an increased risk for short- and long-term mortality after an episode of AKI.[6,8] In these analyses, several definitions of AKI were used, including small temporary kidney function decline. In fact, a meta-analyses by Coca *et al.*[8] demonstrated that even patients with a 10 to 24% increase in serum creatinine (Scr) levels was strongly associated with an in increased mortality risk; therefore, small changes in Scr levels seem to provide a sensitive definition of AKI and could promote early prevention or treatment strategies.

Although numerous studies[4,6,9,10] have investigated the predictive value of AKI for long-term cardiovascular disease and mortality, data regarding the relationship between a temporary decline in renal function during the perioperative period with incident CKD are lacking; therefore, we performed this study to assess the relationship between temporary decline of renal function and the development of CKD during long-term follow-up.

METHODS

Study design and population

This single-center retrospective study comprised a source population of 2.933 consecutive patients who had peripheral arterial disease (PAD) and were referred for elective major vascular surgery. All patients underwent a major vascular surgery procedure during the time period 1990 to 2008, and included lower extremity revascularization (N=1.031 [35%]), aneurysmatic abdominal aortic surgery (N=1.170 [40%]) or carotid surgery (N=732 [25%]). Patients with known

CKD at baseline or unavailable Scr levels prior to surgery were excluded (N=481 [16%]). Scr levels during the perioperative period were available for all patients (N=2.452). Patients with an estimated GFR (eGFR) <60 mL/min/1.73m^2 at day 3 after surgery were excluded for the analyses that examined the primary endpoint (N=234). Of the remaining 2.218 patients, 1.308 (59%) had a Scr measurement at least 1 year after surgery. These 1.308 patients composed the final analyzed study population. Baseline characteristics between the source population and the final study population were compared to rule out the possibility of selection bias. No significant differences with respect to all baseline characteristics, cardiac risk factors and medication use at discharge between the two populations were observed. The study complies with the Declaration of Helsinki, and enrolment was performed after approval of the hospital's ethics committee and after informed consent of all patients (or their guardians).

Renal function assessment

Scr was assessed by means of a nonkinetic alkaline picrate (Jaffé) method.[11] Estimated GFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula: eGFR = 141 x min (Scr/κ, 1)^a x max (Scr/κ, 1)$^{-1.209}$ x 0.993^{age} x 1.018 [if female] x 1.159 [if black].[12] Scr is micromoles per liter, κ is 0.7 for females and 0.9 for males, *a* is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Renal function groups

Before surgery (1 to 3 days) Scr level was measured at baseline in all patients. Scr level was measured at day 1 or 2, and 3 after surgery. Patients were divided into 3 groups on the basis of changes in CKD-EPI eGFR from baseline to day 1 or 2 and from day 1 or 2 to day 3: Group 1, unchanged or improved renal function (change in CKD-EPI GFR function –10% to +10% compared to baseline); group 2, temporary decline of renal function (temporary decline >10% at day 1 or 2, then complete recovery within 10% of baseline value at day 3); and group 3, persistent decline of renal function (>10% decrease compared with baseline). Baseline CKD-EPI eGFR was defined as the value recorded within 3 days before surgery. The purpose of this study was to investigate the prognostic value for the risk of developing CKD after small decrements in renal function. On the basis of our previous studies, we used a cut-off value of ±10% in eGFR.[8,10] To confirm the validity of our initial definition we performed additional sensitivity analyses by repeating all analyses using the Risk, Injury, Failure, Loss, and ESRD (RIFLE) classification for AKI.[13]

Follow-up and endpoints

During the follow-up period, long-term Scr level was used to determine the primary endpoint of the development of incident CKD. Long-term creatinine measurements had to be obtained at least 1 year after surgery. The median follow-up period between date of surgery and last Scr recorded was 5.0 years (Interquartile range [IQR] 2.6–8.5). The primary outcome of interest, incident CKD, was defined using the National Kidney Foundation Disease Outcome Quality Initiative (NKF/DOQI) definition of eGFR <60 mL/min/1.73m^2, calculated using CKD-EPI equation.[11] In addition, for prevention of the occurrence of information bias as a result of misclassification of CKD, patients were classified as having CKD only when the CKD-EPI eGFR was decreased by at least 25% from the baseline GFR. In 916 (70%) patients, more than one Scr measurement was used to define the presence of CKD.

Statistical analyses

Continuous data were described as mean with standard deviation (SD) or median (IQR). Categorical data were presented as percentage frequencies and compared using x^2 tests. Differences in baseline characteristics between the perioperative renal function groups were analyzed with x^2 test for trend and ANOVA for trend, when appropriate. We performed multivariate logistic regression analyses to investigate the independent value of perioperative temporary or persistent decline in renal function and the development of CKD. Adjustments were made for demographics (age, gender), cerebrocardiovascular history, cardiovascular risk factors (body mass index, smoking status, hypertension (BP ≥140/90mmHg in patients who did not have diabetes and ≥130/90mmHg in patients who had diabetes or need for antihypertensive medication), diabetes mellitus (fasting blood glucose ≥6.1 mmol/l or need for insulin and/or oral anti-diabetic medication), hypercholesterolemia (low density lipoprotein cholesterol >135 mg/dL and/or the need for lipid-lowering medication), chronic obstructive pulmonary disease[14]), baseline CKD-EPI eGFR, and BP lowering drugs (diuretics, angiotensin converting enzyme (ACE)-inhibitors, calcium antagonists and angiotensin receptor blockers). Furthermore, because the Scr levels were not measured at a prespecified time point after surgery but at least 1 year after surgery, we also adjusted for time between surgery and last Scr recorded and used for prediction of CKD-EPI eGFR. To evaluate further the strength of the 10% change in CKD-EPI eGFR, we performed additional sensitivity analyses using a 20, 30, 40 and 50% cut-off value for renal function decline. Because the incidence of the outcome of interest (CKD) in the study population was >10%, we calculated relative risks (RR) along with their 95% confidence intervals (C.I.) from the adjusted Odds ratios (OR). Zhang *et al.* proposed the following formula to calculate RR from OR, because this better represents the true relative risk: RR = OR / ((1-P_o) + (P_0 x OR). P_0 indicates the

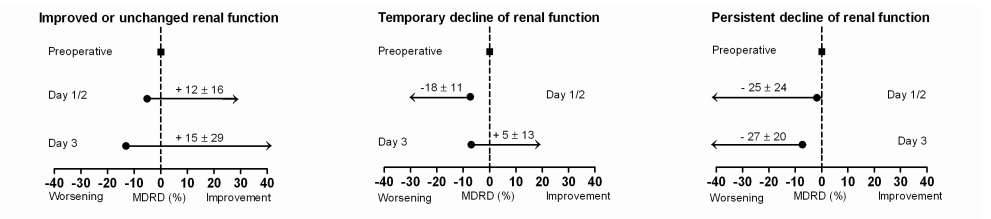
incidence of the outcome of interest in the nonexposed group. Statistical analyses were performed using SPSS 15.0 (SPSS, Inc., Chicago, Illinois). $P < 0.05$ (two-sided) was considered statistically significant.

RESULTS

Description of the study population

The study population consisted of 1.308 patients who had peripheral arterial disease and were referred for elective major vascular surgery. Lower extremity revascularization was performed in 527 (40%) patients, abdominal aortic surgery in 514 (39%) patients, and carotid surgery in 267 (21%) patients. In the source population (N=2.452), 1.569 (64%) patients were classified as normal or improved renal function, whereas 441 (18%) and 436 (18%) had temporary or persistent declines in renal function, respectively. Of the patients in the final study population, 815 (62%) patients had no change or improved in CKD-EPI eGFR compared with baseline during the first 3 postoperative days. Temporary and persistent declines of renal function was observed in 261 (20%) and 232 (18%) patients, respectively. At baseline, patients with temporary renal function decline had a significant lower CKD-EPI eGFR compared to patients with normal renal function ($p = 0.01$). Mean changes in CKD-EPI eGFR on day 1 or 2 and day 3 for the groups are described in *Figure 1*. Patients with temporary or persistent renal function decline more often had vascular disease, resulting in a higher incidence of polyvascular disease ($p = 0.03$; *Table 1*). Risk factors for CKD, including hypertension and chronic heart failure, were more often present in patients with temporary or persistent renal function decline ($p = 0.05$). There was a significant trend for increased use of statins, diuretics and angiotensin-converting enzyme inhibitors in patients with temporary or persistent renal function decline ($p < 0.05$).

Figure 1. *Subdivision of renal function groups on the basis of CKD-EPI eGFR, with changes in CKD-EPI eGFR (mean* ± SD).



(Left) Improved or unchanged renal function; ΔCKD-EPI -10 to 10% function compared with baseline. (Middle) Temporary decline of renal function; temporary decline >10% at day 1 or 2, then complete recovery within 10% of baseline at day 3. (Right) Persistent decline of renal function of >10% compared with baseline

Table 1	Baseline characteristics of the study population			
	No change / Improved [N=815]	**Temporary Decline** [N=261]	**Persistent Decline** [N=232]	***P*-value for trend**
Demographics				
Age (year), mean ± SD	64 ± 11	67 ± 10	64 ± 11	0.01
Male (%)	605 (74)	201 (77)	167 (72)	0.73
Baseline eGFR (mean ± SD)	77 ± 20	74 ± 19	76 ± 22	0.01
Cardiac history (N [%])				
Ischemic heart disease	358 (44)	148 (57)	125 (54)	0.01
CVA/TIA	276 (34)	71 (27)	54 (23)	0.01
Lower-extremity arterial disease	197 (24)	70 (27)	59 (25)	0.55
Aortic aneurysmatic disease	20 (3)	8 (3)	6 (3)	0.80
Polyvascular disease	440 (54)	168 (64)	145 (63)	0.03
Cardiovascular risk factors (N [%])				
Smoking				0.87
No	304 (37)	92 (35)	83 (36)	
Current	321 (39)	101 (39)	89 (38)	
History	190 (23)	68 (26)	60 (26)	
Hypertension	377 (46)	142 (54)	124 (53)	0.02
Diabetes	115 (14)	51 (20)	36 (16)	0.28
Hypercholesterolemia	223 (27)	64 (25)	69 (30)	0.71
Chronic heart failure	40 (5)	20 (8)	18 (8)	0.05
COPD	140 (17)	52 (20)	47 (20)	0.21
Medication at discharge (N [%])				
Aspirin	382 (47)	121 (46)	109 (47)	0.91
Statin	278 (34)	92 (35)	99 (43)	0.03
ß-blocking agents	306 (38)	108 (41)	91 (41)	0.29
Diuretics	158 (19)	65 (25)	56 (24)	0.05
ACE inhibitors	181 (22)	72 (28)	69 (30)	0.01
Calcium Antagonists	196 (24)	77 (30)	59 (25)	0.37
Angiotensin receptor blockers	36 (4)	13 (5)	12 (5)	0.59

Abbreviations: CVA/TIA: Cerebrovascular accident/transient ischemic attack; COPD: chronic obstructive pulmonary disease; ACE -inhibitors: angiotensin converting enzyme-inhibitors.

Long-term incident chronic kidney disease

Median follow-up between surgery and the last Scr recorded was 5.0 years (IQR 2.6–8.5). Median CKD-EPI eGFR during long-term follow-up in patients with normal or improved renal function, temporary decline of renal function, and persistent decline of renal function was 81 mL/min/1.73m^2 (IQR 63-95 mL/min/1.73m^2), 61 mL/min/1.73m^2 (IQR 40-82 mL/min/1.73m^2) and 59 mL/min/1.73m^2 (IQR 36-76 mL/min/1.73m^2). During the observation period 272 (21%) patients developed CKD. Of the patients without a change or an improvement in perioperative renal function, 87 (11%) developed CKD. In contrast, 94 (32%) and 84 (36%) patients with temporary and persistent renal function declines, respectively, developed CKD. There was a significant association between the presence of perioperative renal function decline and the development of CKD in

unadjusted analyses ($p < 0.001$). In multivariate regression analyses, adjusted for demographics, cerebrovascular history, cardiovascular risk factors, BP-lowering agents, and time of Scr measurement the presence of temporary renal function decline was independently associated with an increased risk for CKD (RR 3.4, 95% CI: 2.7 to 4.1) compared with no change or improvement in renal function. Persistent renal function decline in the perioperative period was associated with a 3.6 fold increased risk of CKD (RR 3.6, 95% CI: 2.8 to 4.4). Other covariates that were significantly associated with the outcome of interest were age (RR 1.04, 95% CI: 1.02 to 1.06), diabetes (RR 1.9, 95% CI: 1.4 to 2.5) and smoking (RR 1.2, 95% CI: 1.0 to 1.4).

Sensitivity analyses

To evaluate the strength of the 10% cut-off value for temporary changes in CKD-EPI eGFR, we performed additional analyses using 20, 30, 40 and 50% cut-off values, respectively (*Table 2*). Using a 20% change in CKD-EPI eGFR compared with baseline, temporary renal function decline was independently associated with a 3.5 fold increased risk (RR 3.5, 95% CI: 2.8 to 4.2). Furthermore, for a 50% change in CKD-EPI eGFR compared with baseline, a comparable independent association was observed (RR 3.8, 95% CI: 2.9 to 4.3). Importantly, as the change in CKD-EPI eGFR cut-off values increased, the independent risk remained stable for patients with a temporary decline of renal function. In contrast, performing the same analyses in patients with a persistent decline of perioperative renal function, there was a graded relation between the cutoff value and the estimated risk of CKD up to a cutoff value of 30%. Using a 30% change in CKD-EPI eGFR, there was a 4.3 fold increased risk (RR 4.3, 95% CI: 3.3 to 5.4); however, when a cutoff value of 40 or 50% was used, the risk estimates stabilized at a fourfold increased risk (RR 3.9, 95% CI: 2.8 to 5.1).

We performed additional sensitivity analyses to test more specific definitions of CKD, using eGFR<45 and <30 ml/min, respectively. In total, 252 (19%) patients had an eGFR<45 ml/min and 124 (9%) patients had eGFR <30 ml/min. For both definitions, temporary renal function decline remained an independent predictor of long-term CKD (eGFR <45: RR 2.2, 95% CI: 1.7 to 2.8, eGFR <30: RR 3.1, 95% CI: 2.1 to 4.5).

To confirm the validity of the results, we repeated all analyses using the RIFLE classification for AKI. Logistic regression analyses demonstrated that Risk (RR 3.6, 95% CI: 2.6 to 4.8), Injury (RR 3.3, 95% CI: 1.8 to 5.1), and Failure (RR 4.6, 95% CI: 2.6 to 6.6) were independent predictors of CKD. Finally, to address the fact that death is a competing endpoint of CKD, we studied the combined endpoint

of death and CKD. Using the combined endpoint, temporary and persistent decline remained independent predictors of the primary endpoint incident CKD and death (temporary; RR 2.1, 95% CI: 1.6 to 3.0, persistent; RR 2.2, 95% CI: 1.6 to 3.1); however the magnitude of the odds ratio's decreased.

Table 2 **Predictive value of temporary renal dysfunction on long-term CKD, using various (small) changes in CKD-EPI eGFR**

Cutoff Values		No change	Temporary Decline	Persistent Decline
10%				
	Patients (n [%])	815 (62)	261 (20)	232 (18)
	RR (95% CI)	Ref.	3.4 (2.7 to 4.1	3.6 (2.8 to 4.4)
20%				
	Patients (n [%])	856 (65)	313 (24)	139 (11)
	RR (95% CI)	Ref.	3.5 (2.8 to 4.2)	4.2 (3.2 to 5.2)
30%				
	Patients (n [%])	863 (66)	337 (26)	108 (8)
	RR (95% CI)	Ref.	3.5 (2.8 to 4.2)	4.3 (3.3 to 5.4)
40%				
	Patients (n [%])	866 (66)	355 (27)	87 (7)
	RR (95% CI)	Ref.	3.6 (2.9 to 4.3)	3.9 (2.8 to 5.1)
50%				
	Patients (n [%])	866 (66)	365 (28)	77 (6)
	RR (95% CI)	Ref.	3.8 (2.9 to 4.3)	3.9 (2.8 to 5.1)

Adjustment for demographics (age, gender), cerebrovascular history, cardiovascular risk factors (polyvascular disease, smoking, hypertension, diabetes, hypercholesterolemia, heart failure, chronic obstructive pulmonary disease), baseline CKD-EPI eGFR, and BP-lowering drugs (diuretics, angiotensin-converting enzyme inhibitors, calcium antagonists, and angiotensin receptor blockers)

DISCUSSION

To our knowledge, this study is the first to show that temporary perioperative renal function decline is an independent predictor for the development of incident CKD during long-term follow-up. During the perioperative period, >40% of the patients developed temporary or persistent renal function decline, which was invariably associated with the development of CKD independent of other important confounders that are known to be associated with kidney disease progression.

Ischemia-reperfusion injury due to hypotension or sepsis is one of the major causes of AKI.[15] Ischemia and/or reperfusion initiate changes in vascular endothelial cells, tubular epithelial cells, and leukocytes that result in the loss of immune system homeostasis in the kidney with a consequent inflammatory response.[16] Animal studies have demonstrated that AKI causes permanent damage to the microvasculature with subsequent abnormalities in kidney structure and

function.[17] Basile *et al.* demonstrated that recovery from ischemia-reperfusion injury in rats is not complete, and that it compromises sodium hemostasis and predisposes to hypertension and secondary renal disease.[18] In addition, this same group of investigators have reported that in rats that were recovering from acute renal failure, genes with known inflammatory, remodeling, and vasoactive activities were identified, some of which may play a role in altering long-term renal function.[19-21] In human studies it has been demonstrated that after an episode of AKI, residual kidney injury promotes the release of inflammatory markers such as C-reactive protein, Interleukin-6, and D-dimer.[22] In combination with fibrotic signaling pathways, these inflammatory pathways can lead to progressive structural kidney damage.[6] This silent, ongoing process predisposes to worsening hypertension, proteinuria, and more rapid decreases in renal function, all of which are widely known risk factors for kidney disease progression and establishment of cardiovascular disease.[5,7]

The incidence of AKI varies between 2 and 45%, depending on the study population and the definition used for AKI.[2-4] Especially, patients who undergo surgical procedures and have a high risk for ischemia-reperfusion injury as a consequence of hemodynamic instabilities are at increased risk for AKI.[2,4] The association between the development of AKI and increased rates of in-hospital mortality has been widely known for decades and has been reported in several studies[4,23,24]; however, the association of AKI and long-term outcome, especially incident CKD, has been less studied. This could be a result of the apparent reversibility of the clinical episode as observed by improvements in Scr levels. Better understanding of the impact of AKI on long-term outcomes may identify a segment of patients who may need extended follow-up after discharge. A meta-analysis by Coca *et al.* demonstrated that in hospitalized patients, AKI is common and an independent predictor of long-term myocardial infarction and all-cause mortality (RRs 1.6 to 2.6 and 1.6 to 3.9, respectively)[6]; however, in this analysis, the relative risk for incident CKD after AKI was unattainable because of lack of follow-up studies with appropriate controls who did not have AKI. In this study, 11% of the patients with a normal or improved renal function during the perioperative period developed CKD during long-term follow-up. These findings are in line with several (general) population studies in which the incidence of CKD ranged between 10 to 17%.[7,25] Chronic kidney disease was defined according the NKF/DOQI-definition, using a cut-off value of eGFR <60 mL/min/1.73m^2. Stevens *et al.* have demonstrated that GFR estimates near 60 mL/min/1.73m^2 should be interpreted with caution[26,27]; therefore, we performed additional sensitivity analyses using more specific definitions of CKD (eGFR <45 mL/min/1.73m^2 and <30 mL/min/1.73m^2), which demonstrated a change in the strength of the predictive

value. Both temporary and persistent renal function decline remained independent predictors of long-term CKD, however. Importantly, because the number of patients with more advance CKD decreased significantly, the results for these cutoffs need to be interpreted with some caution.

In this study we are the first to describe the value of a small, temporary impairment in renal function as an independent predictor of long-term CKD. The prognostic importance of small, acute decrements in renal function has been studied in several surgical and intensive care unit populations. Coca *et al.* summarized these results in a meta-analysis and demonstrated that patients with a 10 to 24% increase in Scr levels had a RR for death of 1.8 (95% CI 1.3 to 2.5).[8] A graded relation between the increase in Scr levels and adverse outcome in a variety of clinical settings and patient types was observed. Welten *et al.* demonstrated that although renal function may recover completely after aortic surgery, temporary decline of renal function was still associated with increased mortality during long-term follow-up.[10] It has been noted by other investigators that the use of smaller changes in Scr levels to define AKI are more likely to be only a reflection of hemodynamic changes than real kidney injury[28] and that small or very temporary increases in Scr are simply markers for comorbid conditions. In this study we used a cutoff value of 10% change in CKD-EPI GFR compared with baseline preoperative CKD-EPI eGFR. To evaluate the predictive strength of this small, temporary change in CKD-EPI eGFR, we performed additional sensitivity analyses using a stepwise increased cutoff value of 20, 30, 40 and 50% change in CKD-EPI GFR compared with baseline. It is interesting that there seemed to be a dosage-dependent relationship between the magnitude of exposure and the risk for outcome in patients with a temporary decline in renal function. In patients with a persistent decline of renal function after the perioperative period, the dosage-dependent relationship was observed up to a cut-off of 30%. Although the graded association was not completely observed for both groups, these findings strongly suggest that even small temporary deteriorations in renal function are already an independent predictor for developing long-term CKD. Importantly, in additional sensitivity analyses using the RIFLE-criteria for AKI, both temporary and persistent declines in renal function became even stronger predictors for developing long-term CKD; however, as the focus of the present study was on small changes of renal function in relation to outcome, the 10% definition was used for the study outcomes.

This study supports the use of small changes in renal function in daily clinical practice, as both a temporary and persistent declines in renal function were independent predictors of developing CKD. These small changes in Scr are a reflection of the onset of AKI; therefore, early management of AKI should be

initiated. Despite the seeming reversible nature of clinical AKI, more attention should be given to perioperative impairment in renal function. Episodes of AKI confer increased risk of CKD and cardiovascular disease; therefore, follow-up and risk factor should be monitored more closely. In addition, medical therapies that are known to prevent these outcomes could be applied earlier and more aggressively.

Potential limitations of the current study merit consideration. This study has the disadvantage of a retrospective design. As a consequence, data on long-term Scr levels were not available for all patients in the source population, but for 59% of the patients. To study the possibility of selection bias, we compared the source population and the study population regarding baseline characteristics and no significant differences were observed. Furthermore, patients with established CKD before surgery were excluded from the study population. As a consequence of the study design we were not able to study the influence of AKI on kidney disease progression in those patients with established CKD. During the follow-up period Scr levels were not measured at prespecified time-points. Multivariate analyses were adjusted for the time between surgery and the last Scr level recorded, and additional sensitivity analyses were performed; however, the presence of potential survival bias in patients with multiple Scr measurements during long-term follow-up has to be acknowledged. There is a possibility of ascertainment bias as patients with increased risk for CKD were likely to have more frequent Scr measurements. In addition, informative censoring could not be completely ruled out regarding the influence of CKD and death on the occurrence of the endpoint; however, sensitivity analyses using a combined endpoint of CKD and death demonstrated that temporary and persistent renal function declines remained independent predictors of the primary endpoint. There are several definitions for AKI; however, none of them includes small changes in renal function. In addition we evaluated the presence of AKI only during the first 3 postoperative days and did not examine specific causes of AKI. Furthermore, Scr levels at day of hospital discharge were not available. In the literature there is a growing consensus to use the RIFLE criteria, but these do not include small changes in Scr levels; therefore, in this study, we used the cutoff value of 10% in CKD-EPI eGFR on the basis of previous studies and a meta-analyses.[8,10] It has to be noted that, independent of what prediction equation is used to estimate GFR, the changes in GFR in the acute setting are always difficult to interpret and a limitation of this study. Finally, although a minor dosage-dependent relationship between the magnitude of exposure (*e.g.* higher cutoff values) and the risk of outcome was observed, these data should be viewed as hypothesis-generating for future studies.

CONCLUSION

Temporary or persistent perioperative decline in renal function has a high incidence in the vascular surgery population. Temporary decline of renal function was an independent prognostic predictor for the development of CKD during long-term follow-up.

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Chapter 16

Preoperative left ventricular dysfunction predisposes to postoperative acute kidney injury and long-term cardiovascular mortality in vascular surgery patients

Jan-Peter van Kuijk
Willem-Jan Flu
Tabita M. Valentijn
Michel Chonchol
Michiel T. Voute
Ruud J. Kuiper
Hence J.M.Verhagen
Jeroen J. Bax
Don Poldermans

Submitted

Chapter 17

Elevated preoperative phosphorus levels are an independent risk factor for cardiovascular mortality

Jan-Peter van Kuijk
Willem-Jan Flu
Michel Chonchol
Tabita M. Valentijn
Hence J.M.Verhagen
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Background and Aims: Serum phosphorus levels have been associated with adverse long-term outcome in several populations; however, no prior studies evaluated short-term postoperative outcome. The present study evaluated the predictive value of phosphorus levels on 30-day outcome after vascular surgery.

Methods: The study included patients scheduled for major vascular surgery (aortic aneurysm repair, lower extremity revascularization or carotid surgery), divided into 4 quartiles based on the preoperative fasting phosphorus level. The endpoints of the analyses were all-cause and cardiovascular mortality during the first 30 postoperative days and during long-term follow-up (median 3.6 years, interquartile range 1.8-8.0).

Results: Prior to surgery, 1.798 patients were categorized into the following quartiles: <2.9 mg/dL (N=459), 2.9-3.4 mg/dL (N=456), 3.4-3.8 mg/dL (N=444) and >3.8 mg/dL (N=439), respectively. During the first 30 postoperative days, 81 (4.5%) patients died of which 66 (81%) to a cardiovascular cause. In multivariate analyses, an independent association was observed between phosphorus level >3.8 mg/dL and all-cause (OR 2.53, 95% CI: 1.2 to 5.4) or cardiovascular mortality (OR 2.37, 95% CI: 1.1 to 5.7). Baseline serum phosphorus >3.8 mg/dL was also significantly associated with long-term all-cause mortality (HR 1.38, 95% CI: 1.1 to 1.7).

Conclusions: Preoperative elevated serum phosphorus demonstrated an independent relationship with the occurrence of all-cause and cardiovascular mortality during the first 30 days after major vascular surgery. In addition, an elevated serum phosphorus was independently associated with long-term mortality.

INTRODUCTION

Phosphorus is essential for multiple and diverse biological functions, including cellular signal transduction and energy exchange. Approximately 85% of phosphorus is located in bones and teeth. Serum phosphorus primarily occurs in the form of inorganic phosphate, which is maintained within the physiological range (2.5 to 4.5 mg/dL) by regulation of dietary intake, gastrointestinal absorption, renal excretion, and shifts between the intracellular and extracellular spaces.[1-3]

There has been considerable interest in the relation between serum phosphorus levels and adverse cardiovascular outcomes.[4] Several studies have examined the relationship between phosphorus levels and long-term survival in patients with normal renal function, chronic kidney disease (CKD) not requiring chronic dialysis and end-stage renal disease.[5-7] However, none of these studies have examined the association between serum phosphorus levels and short-term outcome after a surgical procedure. Patients referred for major vascular surgery are at increased risk of developing perioperative complications due to altered hemodynamics, surgical stress and a hypercoagulable state. In addition, these patients are characterized by extended atherosclerosis of the vascular beds, which creates the perfect substrate for ischemic complications. The mechanisms explaining the association between serum phosphorus level and adverse outcome are unclear, but several potential factors have been postulated, of which vascular calcification appears to be the most important.[8,9] As the combination of generalized atherosclerosis and vascular calcification provides a significant increased risk of perioperative complications[10], we hypothesized that higher preoperative serum phosphorus levels would be associated with increased mortality during the first 30 postoperative days.

METHODS

Study design and participants

This single center retrospective study comprised a source population of 2.933 consecutive patients with peripheral arterial disease (PAD) referred for elective major vascular surgery. All patients underwent a major vascular surgery procedure during the time period 1990 to 2008. Fasting serum phosphorus levels were obtained prior to surgery in 1.798 (61%) patients, and these patients comprised the final study population. Baseline characteristics between the source population and the final study population were compared to rule out the possibility of selection

bias. No significant differences with respect to all baseline characteristics, cardiac risk factors and medication use at discharge between the two populations were observed. The study complies with the Declaration of Helsinki and enrolment was performed after approval of the hospital's ethics committee, and after informed consent of all patients (or their guardians).

Measurement of serum phosphorus and kidney function

Fasting blood samples were obtained at baseline, including serum phosphorus and serum creatinine levels. We elected to evaluate quartiles of baseline serum phosphorus as our primary predictor variable (<2.9, 2.9-3.4, 3.4-3.8, >3.8 mg/dL). Estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR = 141 x min (Scr/κ, 1)^{a} x max (Scr/κ, 1)$^{-1.209}$ x 0.993^{age} x 1.018 [if female] x 1.159 [if black].[11] Scr is serum creatinine level (micromoll per liter), κ is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. The CKD-EPI equation was chosen over the widely used Modification of Diet in Renal Diseases (MDRD) equation due to the reported improved performance at higher GFR values.[12,13] In sensitivity analyses, the models were also adjusted for the four variable abbreviated MDRD study equation as an alternative estimate of kidney function. Furthermore, patients with eGFR <30 ml/min/1.73m^2 were excluded for sensitivity analyses in patients without CKD. This sensitivity analyses was performed to exclude those with more severe CKD, to show that the association was not driven by those patients with more severe kidney disease.

Follow-up and endpoints

For the purpose of this analysis the main endpoint was all-cause mortality during the first 30 postoperative days. All-cause death during the long-term follow-up was also examined (median 3.6 years, IQR 1.8-8.0). Survival status was assessed by reviewing the municipal civil registries. Cause of death was ascertained by examining death certificates, and otherwise by reviewing medical records. Cause of death was further classified as either cardiovascular or noncardiovascular death. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and included death following myocardial infarction, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular event or trainsient ischemic attack), and surgery related bleeding (only considered a 30-day postoperative cause of death). Sudden unexpected death was classified as a cardiovascular death.

Statistical analyses

Summary statistics (mean and standard devation [SD] for continuous variables and percentages for categorical variables) were performed for all covariates. Chi-squared tests were used to compare categorical variables across phosphorus groups. To test differences in continuous factors we used 1-way ANOVA. Logistic regression analysis was used to determine the association between serum phosphorus level (lowest quartile as reference) and short-term mortality (30 days). Cumulative survival was determined by the Kaplan-Meier method and compared using the log-rank test. We used unadjusted and adjusted Cox regression models to examine the association between serum phosphorus levels and long-term mortality. The covariates included in the adjusted models were chosen by running a univariate Cox regression model for each covariate by itself. The covariates that were significant at the $p < 0.2$ level, or were deemed clinically meaningful, were selected for inclusion in the final adjusted model for the relation between phosphorus and death. Covariates considered for inclusion in the adjusted models included: age, gender, diabetes mellitus, dyslipidemia, cerebrovascular disease, ischemic heart disease, heart failure, chronic obstructive pulmonary disease, smoking, systolic blood pressure, body mass index, and CKD-EPI GFR. Two sensitivity analyses were run on the final adjusted models: first by replacing the CKD-EPI GFR by the MDRD prediction equation and second by excluding a subset of the population with and eGFR <30 ml/min/1.73m^2. Statistical analyses were performed using SPSS software (SPSS version 15.0; SPSS, Inc., Chicago, Illinois). A p-value < 0.05 (2-sided) was considered statistically significant.

RESULTS

Description of the study population

Baseline characteristics of the final study population by phosphorus level are described in *Table 1*. Patients in the highest phosphorus quartile were younger and more often female ($p < 0.01$). Serum phosphorus level above the normal range (>4.5 mg/dL) was detected in 88 (4.9%) patients. Aortic abdominal aneurysm repair occurred in 816 (45%) patients, while lower extremity revascularization and carotid surgery were performed in 574 (32%) and 408 (23%) patients, respectively. Estimated CKD-EPI GFR was lowest in subjects in the higher quartiles of phosphorus, and these patients were also characterized by an increased prevalence of chronic heart failure.

Table 1 **Baseline characteristics of the study population**

	Serum phosphorus quartiles (mg/dL)				
	<2.9 [N=459]	**2.9-3.4** [N=456]	**3.4-3.8** [N=444]	**>3.8** [N=439]	***P*-value**
Demographics					
Age (year), mean ± SD	68 ± 9	68 ± 10	67 ± 11	65 ± 11	<0.01
Male (%)	396 (86)	370 (81)	307 (69)	272 (62)	<0.01
CVA/TIA	161 (35)	157 (34)	166 (37)	118 (27)	<0.01
Ischemic heart disease	205 (45)	208 (46)	209 (47)	201 (46)	0.91
Type of surgery					
Abdominal aortic aneurysm	226 (49)	216 (47)	185 (42)	189 (43)	0.08
Lower extremity revascularization	125 (27)	133 (29)	140 (32)	176 (40)	<0.01
Carotid surgery	108 (24)	107 (24)	119 (27)	74 (17)	<0.01
Cardiovascular risk factors					
Current smoker	164 (36)	182 (40)	174 (39)	165 (38)	0.57
Diabetes mellitus	75 (16)	75 (16)	89 (20)	89 (20)	0.23
Hypercholesterolaemia	120 (26)	148 (33)	137 (31)	148 (34)	0.07
Chronic heart failure	23 (5)	32 (7)	45 (10)	42 (10)	0.02
COPD	95 (21)	87 (19)	92 (21)	89 (20)	0.92
Measurements					
SBP (mmHg)	149 ± 25	145 ± 23	150 ± 69	144 ± 63	0.29
DBP (mmHg)	84 ± 13	82 ± 12	83 ± 13	79 ± 13	0.13
BMI	25 ± 3.6	25 ± 3.8	26 ± 4.0	25 ± 4.1	0.04
CKD-EPI GFR ml/min/1.73 m^2	70 ± 19	71 ± 21	72 ± 21	65 ± 29	<0.01
Phosphorus (mg/dL)	2.6 ± 0.3	3.2 ± 0.1	3.6 ± 0.1	4.4 ± 0.9	<0.01

Abbreviations: CVA/TIA; cerebrovascular accident / transient ischemic attack, COPD; chronic obstructive pulmonary disease, SBP; systolic blood pressure, DBP; diastolic blood pressure, BMI; body mass index, CKD-EPI GFR; chronic kidney disease-epidemiology collaboration estimated glomerular filtration rate

Short-term outcome

During the first 30 days after surgery, 81 (4.5%) patients died of which 66 (81%) secondary to a cardiovascular cause. Using multivariate logistic regression analyses, patients within the highest phosphorus quartile showed a significant association with the risk of all-cause mortality during short-term follow-up (*Table 2a*). The presence of a baseline phosphorus level >3.8 mg/dL was associated with a 2.5 fold increased risk of all-cause mortality (OR 2.53, 95% CI: 1.2 to 5.4). This association was demonstrated for the occurrence of 30 day cardiovascular mortality as well, as patients within the highest quartile of serum phosphorus had a 2.4 fold increased cardiovascular mortality risk (OR 2.37, 95% CI: 1.1 to 5.7) (*Table 2b*).

Long-term outcome

After a median follow-up period of 3.6 (IQR 1.8-8.0) years, the mortality endpoint was reached in 813 (45%) patients, of which 509 (63%) died secondary to a cardiovascular cause and 304 (37%) died of non-cardiovascular causes.

Table 2a	**30 days all-cause mortality**			
	All-cause		**Sensitivity 1**	
	OR	95% CI	OR	95% CI
Serum phosphorus quartiles (N=1.798)				
< 2.9 (N=459)	Ref.		Ref.	
2.9-3.4 (N=456)	0.98	0.4-2.3	0.99	0.4-2.3
3.4-3.8 (N=444)	1.68	0.8-3.7	1.68	0.8-3.7
> 3.8 (N=439)	2.53	1.2-5.4	2.60	1.2-5.5

Multivariate analyses with adjustment for: Age, gender, ischemic heart disease, cerebrovascular disease, current smoking, baseline serum creatinine, dyslipidemia, diabetes mellitus, heart failure, COPD, systolic blood pressure and body mass index. Sensitivity 1: GFR estimated by CKD-EPI prediction equation replaced by GFR estimated by the four variable abbreviated MDRD formula

Table 2b	**30 days cardiovascular mortality**			
	Cardiovascular		**Sensitivity 1**	
	OR	95% CI	OR	95% CI
Serum phosphorus quartiles (N=1.798)				
< 2.9 (N=459)	Ref.		Ref.	
2.9-3.4 (N=456)	1.23	0.5-3.2	1.23	0.5-3.2
3.4-3.8 (N=444)	1.78	0.7-4.4	1.78	0.7-4.4
> 3.8 (N=439)	2.37	1.1-5.7	2.45	1.0-5.9

Multivariate analyses with adjustment for: Age, gender, ischemic heart disease, cerebrovascular disease, current smoking, baseline serum creatinine, dyslipidemia, diabetes mellitus, heart failure, COPD, systolic blood pressure and body mass index. Sensitivity 1: GFR estimated by CKD-EPI prediction equation replaced by GFR estimated by the four variable abbreviated MDRD formula

Kaplan-Meier estimates for long-term all-cause mortality stratified by phosphorus level showed that patients within the highest quartile had lower survival compared to patients within the lowest quartile (*Figure 1*). Log-rank test compared cumulative survival between the groups and showed a significant difference in survival between the highest and lowest quartile (p = 0.01). Using multivariate Cox regression analyses, a relationship between the highest phosphorus quartile and the risk of all-cause mortality was detected (HR 1.38, 95% CI: 1.1-1.7) (*Table 3*). During long-term follow-up, no association was observed between the phosphorus quartiles and cardiovascular mortality risk.

Sensitivity analyses

After replacing eGFR assessed by the CKD-EPI prediction equation with the MDRD formula (*Table 2a and 2b*, sensitivity 1) in the multivariate regression model, the predictive values of the highest quartiles regarding the occurrence of short-term all-cause or cardiovascular mortality remained consistent (*Table 2a and 2b*). In addition, risk estimate of long-term all-cause mortality remained the same for the highest quartile (HR 1.40, 95% CI: 1.1 to 1.7) and the risk estimate for long-term

cardiovascular mortality for the highest quartile was not significant (HR 1.18, 95% CI: 0.90 to 1.56). In a second sensitivity analyses, patients with a CKD-EPI GFR <30 ml/min/1.73m^2 were excluded (N=124 [7%]) to confirm that our main results were not driven by the patients with severe CKD. Repeating multivariate regression analyses on short-term all-cause mortality, demonstrated a consistent predictive value for the highest phosphorus quartile (OR 2.52, 95% CI: 1.2 to 5.5). Similar results were observed for the association between the highest phosphorus quartile and short-term cardiovascular mortality (OR 2.43, 95% CI: 1.0 to 6.0).

Figure 1. *Kaplan-Meier estimates of cumulative survival according the four groups of preoperative phosphorus level*

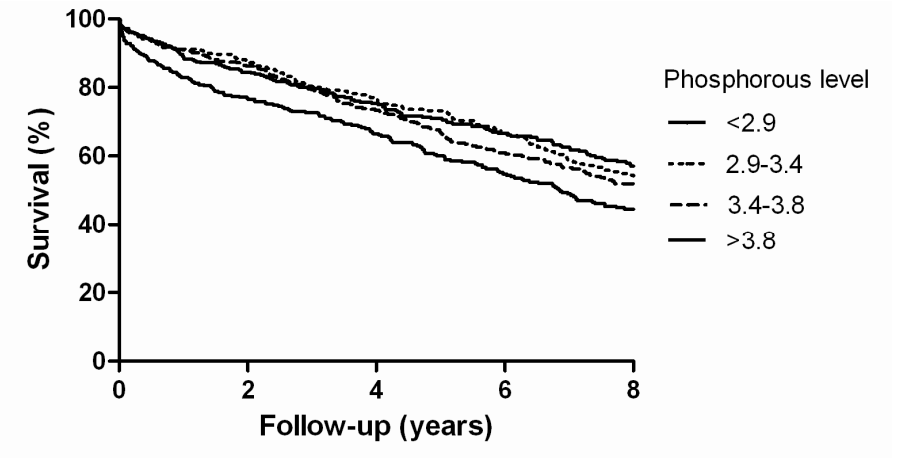

Table 3 **Long-term outcome**

	All-cause		Cardiovascular	
	HR	95% CI	HR	95% CI
Serum phosphorus quartiles (N=1.798)				
< 2.9 (N=459)	Ref.		Ref.	
2.9-3.4 (N=456)	1.05	0.9-1.3	0.98	0.8-1.3
3.4-3.8 (N=444)	1.09	0.9-1.4	0.95	0.7-1.2
> 3.8 (N=439)	1.38	1.1-1.7	1.16	0.9-1.5

Multivariate analyses with adjustment for: Age, gender, ischemic heart disease, cerebrovascular disease, current smoking, baseline eGFR, dyslipidemia, diabetes mellitus, heart failure, COPD, systolic blood pressure and body mass index

DISCUSSION

In the present study we observed an independent association between baseline fasting serum phosphorus level >3.8 mg/dL and the risk of all-cause and cardiovascular mortality during the first 30 days after major vascular surgery.

Furthermore, preoperative phosphorus >3.8 mg/dL was an independent predictor of long-term all-cause mortality in patients undergoing a major peripheral vascular surgery.

Vascular surgery patients are characterized by a diversity of atherosclerotic risk factors, including smoking, hypertension, diabetes mellitus, and dyslipidemia.[7] Importantly, previous studies have demonstrated that these risk factors are often associated with higher serum phosphorus levels.[6,7] Although the risk factors for hyperphosphatemia have been described in several studies, little is known about the potential mechanism for the association between serum phosphorus levels and adverse outcomes. Phosphorus excess may influence mortality by increasing circulation parathyroid hormone levels or decreasing 1,25 dihydroxyvitamin D levels by increasing secretion of fibroblast growth factor-23.[14,15] Alternatively, the increased risk of death associated with elevated serum phosphorus in population based studies could be secondary to vascular calcification[16-18] Foley *et al.* have demonstrated in healthy young adults that higher serum phosphorus levels, even within the normal range, were independently associated with the development of coronary artery calcification 15 years later.[9] Vascular surgery patients are characterized by extended atherosclerosis in multiple vascular territories, and abnormalities in phosphorus homeostasis have been shown to be also related to the development of vascular calcification in the general population.[9] Although the present study results need to be confirmed in future prospective studies, our study results indicate that elevated pre-operative serum phosphorus level could have incremental predictive value towards short- and long-term prognosis in vascular surgery patients.

Recently, several studies examined the presence of the relationship between phosphorus levels and (cardiovascular) outcome in individuals with normal kidney function.[5-7] However, no prior studies investigated the predictive value of preoperative phosphorus levels in vascular surgery patients towards the occurrence of short-term mortality. The present study demonstrated that baseline serum phosphorus level >3.8 mg/dL has an independent relation with the risk of death during the first 30 postoperative days. Although patients with CKD or end-stage renal disease are at increased risk for developing perioperative complications, hyperphosphatemia is mainly seen as a marker of adverse long-term prognosis. In patients with CKD and end-stage renal disease, phosphorus excess has been independently linked with coronary artery and aorta calcification, as well as cardiovascular and all-cause mortality during long-term follow-up. As the present study demonstrated an independent association between elevated phosphorus and short-term outcome, it could be argued that this association is due to the inclusion

of patients with a severe decline in kidney function, as these patients are at high risk for developing perioperative complications. In addition, higher serum phosphorus levels might indicate impaired kidney function, even after adjustment for estimated GFR, and that the severity of renal disease rather than phosphorus levels per se might account for the association between elevated phosphorus and adverse clinical outcome. Therefore, we performed additional sensitivity analyses, excluding patients with severe CKD (CKD-EPI GFR <30 ml/min/1.73m^2) which showed that a baseline phosphorus level >3.8 mg/dL was still independently associated with adverse short-term outcome. During the long-term follow-up, only patients in the highest preoperative phosphorus quartile had an increased risk of all-cause mortality. These results are in line with Tonelli *et al.* who described an increase in all-cause mortality in patients with elevated serum phosphorus without a decline in renal function, which could be related to the presence of generalized atherosclerotic disease in these patients.[7]

In clinical practice, phosphorus is not routinely measured prior to vascular surgery. Risk factor stratification includes measurement of serum creatinine, but only when indicated in patients with established CKD, additional serum phosphorus and calcium levels are determined. The present study emphasizes the use of serum phosphorus measurement prior to vascular surgery as a predictor of perioperative mortality. Importantly, both in patients with or without a decline in renal function, serum phosphorus >3.8 mg/dL was independently associated with all-cause and cardiovascular mortality during short-term follow-up. Routine measurement of serum phosphorus in patients scheduled for vascular surgery provides a simple and effective way of additional risk factor analyses in patients at high-risk for perioperative events.

Strengths of our study include the large number of patients and the ability to adjust for multiple factors that may affect phosphorus levels and mortality rates. However, our study also has potential limitations that should be considered. First, this study has the disadvantage of a retrospective design. As a consequence, data on preoperative phosphorus levels were not available for all patients in the source population, but for 61% of the patients. To study the possibility of selection bias we compared the source population and the study population regarding baseline characteristics and no significant differences were observed. Second, because this study was an observational analysis, we cannot rule out the possibility of residual confounding. However, we adjusted for multiple confounders, including characteristics associated with serum phosphorus levels in this cohort. Third, the present study included vascular surgery patients, which limits the generalizability of the results in other surgical populations. Fourth, we cannot exclude the

possibility that our findings were influenced by dietary intake of phosphorus and thus that dietary habits might confound the association between phosphorus levels and mortality rates. Finally, in the present study 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, or intact parathyroid hormone levels were not measured.

In conclusion, we found an independent relation between serum phosphorus level >3.8 mg/dL and the risk of all-cause and cardiovascular death during the first 30 postoperative days after vascular surgery. Furthermore, phosphorus >3.8 mg/dL was independently associated with all-cause mortality during long-term follow-up. Based on the ready availability and low cost of serum phosphorus assays, these findings could have a potential clinical use, however, the results of this study should be viewed as hypothesis generating. Additional prospective studies are required to determine the explanation for this association and to confirm that this relationship is present in other surgical populations.

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PART IV

RISK REDUCTION STRATEGIES AND FUTURE PERSPECTIVES

Chapter 18

The influence of statins on the expansion rate and rupture risk of abdominal aortic aneurysms

Jan-Peter van Kuijk
Willem-Jan Flu
Olivier P. Witteveen
Michiel T. Voute
Jeroen J. Bax
Don Poldermans

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INTRODUCTION

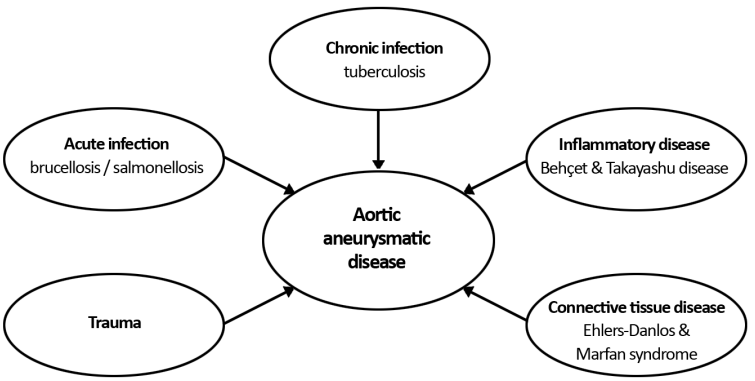
Abdominal aortic aneurysms (AAA) have a prevalence between 1.3 – 8.9% in men and 1.0 – 2.2% in women aged above 55 years.[1,2] Furthermore, AAA cause 1 – 3% of all deaths among men aged 65-85 years in developed countries.[2,3] As the disorder is invariably associated with severe atherosclerotic damage of the arterial wall, it has traditionally been regarded as a direct consequence of generalized atherosclerotic disease.[4] In patients with occlusive aortic disease, dyslipidemia is a well established risk factor. However, in patients with aneursymatic aortic disease, the association between dyslipidemia and the development of AAA is less clear. Large clinical trials in patients with cardiac and peripheral arterial disease have shown the strong relation between dyslipidemia, statin therapy and the risk of cardiovascular disease.[5-9] Importantly, the effects of statin therapy were still present irrespective of the decrease in serum cholesterol levels. These findings resulted in the discussion of potential non-lipid lowering effects of statin therapy. These "pleiotropic effects" compose a diversity of cellular events which have an effect on several components of the arterial wall, including: (i) endothelial cells, (ii) smooth muscle cells, (iii) platelets, (iv) monocytes/macrophages, and (v) the process of inflammation.[10,11] In the general population the role of dyslipidemia as an independent risk factor for AAA is debated. However, as patients with AAA frequently have concomitant arterial disease, statin therapy is often recommended. As a result, the non-lipid lowering effects of statins on aneurysm expansion rate are hardly studied, and most evidence comes from experimental and animal studies. In the current review article we provide an overview of all available literature on the effects of dyslipidemia, statin therapy and the risk of AAA expansion and rupture. In the first part we summarize all population-based studies that investigated the relation between hypercholesterolemia and the development of AAA. In the second part, the available literature regarding the effects of statins on aneurysm growth, expansion rate and the risk of rupture is summarized, including in vitro, animal and clinical human studies.

ETIOLOGY

Atherosclerosis is the underlying disorder in the majority of patients with cardiovascular disease. Although, AAA has traditionally been regarded as a direct consequence of atherosclerosis, insights regarding the pathogenic processes in aortic diseases are changing. Aortic disease includes (i) occlusive disease, (ii) aneurysmatic disease, and (iii) combined occlusive and aneursymatic disease. Aortic occlusive disease is a direct consequence of atherosclerotic plaque formation

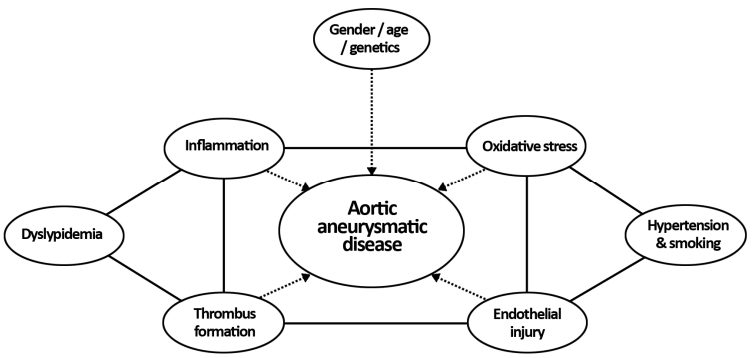
with a subsequent damaging of the vessel wall and narrowing of the arterial lumen. In contrast, aneurysmatic disease is the result of inflammatory processes in the arterial wall, leading to elastin and collagen degradation and eventually aneurysmatic wall dilatation. As shown in *Figure 1a*, aneurysmtic disease can have a specific cause including trauma, acute infection (brucellosis, salmonellosis), chronic infection (tuberculosis), inflammatory diseases (Behçet and Takayasu disease), and (inherited) connective tissue disorders (Ehlers-Danlos type IV, Marfan Syndrome).[12,13]

***Figure 1a**. Specific causes of abdominal aortic aneurysm*



However, most AAA are called non-specific, as no direct pathogenic mechanism can be identified (*Figure 1b*). In these patients connective tissue alterations in the arterial wall are a result of endothelial injury with subsequent atherosclerotic plaque formation and inflammation.

***Figure 1b.** Schematic representation of the risk factors and pathogenic mechanisms and the interactions in the development of non-specific Aortic Aneurysms*



Hypercholesterolemia has an important role in this multifactorial process and the pathogenic aspects will be discussed in the next paragraph.

PATHOPHYSIOLOGY

Atherosclerosis and hypercholesterolemia

The development of atherosclerosis in patients with cardiovascular disease is a multifactorial process in which a clear association between elevated serum cholesterol levels and atherosclerotic disease is present.[8] Additionally, large clinical trials have demonstrated that statins decrease the incidence of coronary heart disease in patients with hypercholesterolemia and atherosclerosis.[6,9] As serum cholesterol levels are strongly associated with coronary atherosclerotic disease, it has been generally assumed that cholesterol reduction by statins is the predominant, if not the only, mechanism underlying their beneficial effects in cardiovascular diseases. However, subgroup analyses of large clinical trials like the West of Scotland Coronary Prevention (WOSCOP) and the Cholesterol and Recurrent Events (CARE) studies, indicates that despite comparable serum cholesterol levels among statin-treated and placebo groups, individuals treated with statins have a significantly lower risk of coronary heart disease compared to age-matched placebo-controlled patients.[7,9] These findings suggest that statins have beneficial effects beyond lowering of serum cholesterol levels.

In addition, angiographic trials have demonstrated clinical improvements with statins that far exceed changes in the size of atherosclerotic lesions.[14,15] Therefore, it is believed that some other actions of statins, especially improvement of endothelial function, may have contributed to these additional benefits.[16] These additional beneficial effects of statins are called pleiotropic effects.[16]

Atherosclerosis and pleiotropic effects of statins

The 3-hydroxy-3-methylglutaryl coenzyme A inhibitors or statins inhibit the synthesis of 1-mevalonic acid; thereby preventing the synthesis of other important isoprenoid intermediates of the cholesterol biosynthetic pathway was well.[17] These intermediates serve as important lipid attachments for the posttranslational modification of a variety of intracellular signalling proteins, especially Ras and Rho proteins. Ras and Rho proteins are small Guanosine Triphosphate (GTP)-binding proteins that are crucial in a variety of cellular events, including cytoskeleton organization, membrane trafficking, secretion, transcriptional regulation, and growth control and development.[10,11] These cellular events have effects on several components of the arterial wall, including endothelial cells, smooth muscle cells (SMC), platelets, monocytes/macorphages and the process of inflammation.[10,11] As these are important aspects of aneurismal degeneration, it has been postulated that statin treatment might also have an impact on the development and progression of AAA.

Statins and endothelial function

The vascular endothelium serves as an important autocrine and paracrine organ that has a regulatory function for the vascular wall contractile state and cellular composition. Endothelial dysfunction is one of the earliest manifestations of atherosclerosis, that occurs without the presence of angiographic evidence of disease.[18] The most important effect of endothelial dysfunction is the impaired synthesis, release and activity of endothelium-derived Nitric Oxide (NO). Endothelium-derived NO mediates vascular relaxation, platelet aggregation, vascular smooth muscle cell proliferation, and endothelium-leukocyte interactions, thereby inhibiting the atherosclerotic process.[19,20] Endothelium-dependent vasodilatation is improved by acute plasma LDL lowering, suggesting that statins could restore endothelial function, at least in part by lowering serum cholesterol levels.

Statins increase bioavailability of NO by stimulating and upregulating endothelial NO-synthase (eNOS).[21] Furthermore, statins exert many additional favourable effects on the endothelium, like increased expression of tissue-type plasminogen activator and inhibit the expression of endothelin-1, a potent vasoconstrictor.[22] These effects of statins may attenuate endothelial dysfunction in the presence of atherosclerotic risk factors. The antioxidant effects of statins may be another mechanism by which statins may improve endothelial function. Statins enhance endothelium-dependent relaxation by inhibiting the production of reactive oxygen species (ROS).[23]

Statins and smooth muscle cell proliferation

Smooth muscle cell (SMC) proliferation is a central event in the pathogenesis of vascular lesions. It is suggested that statins inhibit SMC proliferation by arresting the cell cycle.[24] Studies showed that inhibition of isoprenoid syntheses, but not cholesterol syntheses, by statins decreased platelet-derived growth factor-induced DNA synthesis in SMCs.[24,25] Furthermore, it was indicated that inhibition of Rho proteins by statins is the predominant mechanism by which statins inhibit SMC proliferation.[25]

Statins and platelets

Hypercholesterolemia is associated with increased platelet reactivity, most presumably to increases in the cholesterol/phospholipids ratio in platelets and increased thromboxane A2 biosynthesis.[26] As statins have been shown to inhibit platelet function, this is potentially derived by a reduction in thromboxane A2 production and modifications in the cholesterol content of platelet membranes.[27]

Statins and plaque stability

Atherosclerotic lesions contain a highly thrombogenic lipid core that is separated from the blood stream by a fibrous collagen cap. Plaque rupture and ensuing thrombosis results from fissuring, erosion, and ulceration of the fibrous cap.[28] In AAA, most patients have an associated thrombus as well. Due to a maintained blood flow, there is a persistent remodelling of the thrombus components. An increasing thickness of the thrombus leads to local hypoxia at the inner layer of the media, resulting in increased medial neovascularization and inflammatory cells. The collagen layer in the fibrous cap provides the strength and the stability of the plaque. However, as macrophages are capable of degrading the collagen-containing fibrous cap, they play an important role in the development and subsequent instability of atherosclerotic plaques.[29] Activated macrophages release proteolytic enzymes, such as matrix metalloproteinases (MMPs), which weaken the fibrous cap, leading to plaque instability and rupture with thrombosis. The main action of statins on contributing to plaque stability seems not to be the lipid lowering effects, but rather the inhibiting effects on macrophage accumulation and subsequent reduction in MMP secretion.[30]

Statins and vascular inflammation

The presence of monocytes or macrophages and T-lymphocytes in the atherosclerotic plaques characterizes the complex inflammatory processes in atherosclerosis. Endothelial function, SMC proliferation, collagen degradation, and thrombosis are all modified by the inflammatory cytokines that are released by macrophages and T-lymphocytes.[31] A recent study suggested that statins possess anti-inflammatory properties by their ability to reduce the number of inflammatory cells in atherosclerotic plaques.[27] An important clinical marker of low-grade systemic inflammation is high-sensitive C-reactive protein (hs-CRP), which is an acute-phase reactant produced by the liver in response to pro-inflammatory cytokines, such as Interleuking-6.[32] Elevated hs-CRP levels are present in patients with coronary artery disease, coronary ischemia, and myocardial infarction and have been shown to be associated with an increased risk of coronary artery disease in apparently healthy men and women.[33] Furthermore, the CARE trial showed that statins significantly decreased plasma hs-CRP levels over a 5-year period in patients who did not experience recurrent coronary events.[34] The JUPITER trial study group investigated the effect of statin therapy on lowering LDL-cholesterol and hs-CRP.[35] Treatment with rosuvastatin in initially healthy men and women resulted in a significant decrease in both LDL-cholesterol and hs-CRP. Furthermore, these effects resulted in a significant decrease in the risk of cardiovascular events during a 5-year follow-up period. These promising results

need to be further studied in patients with aneurysmatic disease, before implementing them into the medical treatment of AAA.

RISK FACTORS

Risk factor patterns for the development of abdominal aortic aneurysms

Risk factor patterns for the development of an AAA are well established and include (i) increasing age, (ii) male gender, (iii) genetic predisposition, (iv) diabetes mellitus, (v) hypertension, (vi) tobacco smoking, and (vii) dyslipidemia.[36-38]

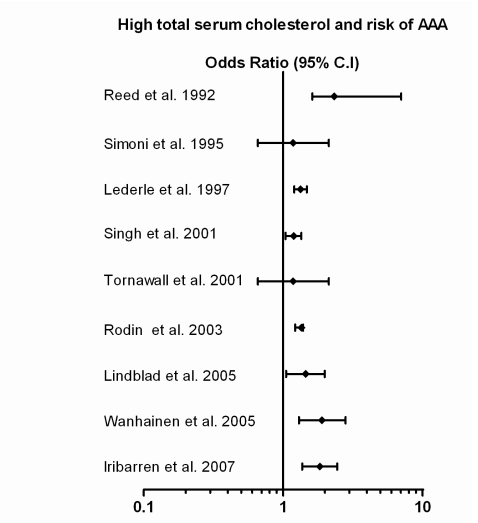
Age and male gender have been identified as non-modifiable risk factors for AAA in epidemiological screening studies.[1,37] In the ADAM Program, a prevalence of 4.2% of AAA was observed in patients with a mean age of 66 years. A strong association between male gender, increasing age and the development of AAA was found. On the contrary, female gender showed a negative association with AAA.[1] Familial screening studies for the detection of AAA have drawn attention to a possible genetic background of the disorder. One multinational study, including 653 affected members, observed an autosomal recessive inheritance mode in 72% of the families and autosomal dominant in 25%.[39] Ongoing multi-center studies are generating data, as some small previous studies have identified several candidate genes, without establishing a genetic profile.[40] Diabetes mellitus (DM) is an established risk factor for the atherosclerotic process.[41] However, several large registries observed a negative association between diabetes and the development of AAA.[37,42] The effect of diabetes on the vessel wall mainly includes increasing stiffness, especially in the medial layers of the peripheral arteries. Although it was previously proposed that increasing stiffness could stabilize the aorta and resist aneurismatic dilatation, others found increased aortic wall stiffness in AAA as well.[43,44] This discrepancy could possibly be explained by a difference in AAA wall constitution between diabetic and non-diabetic individuals.

Hypertension results in an increased shear stress on the arterial wall with a subsequent production of radical oxygen species by smooth muscle cells.[45] These effects have a leading role in the atherosclerotic process and could play an important role in the pathogenesis of AAA as well. Hypertension is suspected to have a detrimental effect on AAA development, growth rate and risk of rupture. The ADAM Program observed an odds ratio of 1.23 (95% CI: 1.14 to 1.32) for the presence of hypertension and the risk of AAA development.[1] The REACH registry emphasized the use of blood pressure lowering therapy to decrease growth rate and rupture risk, as they showed an increased mortality in patients with AAA and

current high blood pressure, compared to AAA patients with normalized blood pressure.[42] More recent studies indicated that hypertension is a moderate predictor for AAA development, but an important risk factor for AAA expansion and rupture.[3] Smoking leads to endothelial dysfunction, with a subsequent inflammatory process and plaque formation. Additionally, vascular disease is promoted as smoking also influences (i) hemodynamic stress, (ii) oxidant injury, (iii) disturbed lipid profiles, (iv) enhanced thrombosis, and (v) increased blood velocity. Several large studies and registries have identified tobacco smoking as the most important variable associated with an increased risk of AAA development.[1,13,42,43]

High levels of serum cholesterol, LDL-cholesterol and low HDL-cholesterol have an established role in the pathogenesis of atherosclerosis. However, in AAA patients there are conflicting results about the presence of dyslipidemia as a risk factor for AAA development, expansion rate and risk of rupture. In a small case-control study, Hobbs *et al.* demonstrated that patients, who developed a small AAA, had significantly higher LDL cholesterol levels (OR 1.30, 95% CI: 1.02 to 1.65), compared to patients that did not developed AAA.[46] In contrast, Blanchard *et al.* observed no differences in serum total cholesterol, LDL cholesterol or triglycerides between AAA patients and matched controls (OR 0.84, 95% CI: 0.56 to 1.25).[47]

Figure 2. *Predictive value of high serum cholesterol for the development of new abdominal aortic aneurysm in population-based studies*



In addition to these case-control studies, several large population-based studies have been performed during the last two decades. (*Table 1 and Figure 2*)[2,4,37,48-53] All included studies investigated the incidence of AAA in several cohorts of patients with varying age and distribution of gender. The incidence of newly

developed AAA ranged between 0.4 and 14.4%, depending on the study population. Reed *et al.* were the first who described a large cohort of Japanese men (7.862 individuals), in which they observed an incidence of 1.9% of new AAAs.[4] High total serum cholesterol was an independent risk factor for the development of an AAA in this cohort (OR 2.32, 95% CI: 1.62 to 7.04). The majority of the population-based studies summarized in *Table 1* found high serum total cholesterol to be a predictor for the development of AAA. (*Figure 2*) Additionally, three studies observed that high serum HDL cholesterol has a protective effect on the development of new AAAs.[2,48,49] Elevated triglycerides were measured in 4 studies, but only 1 of these observed a positive association between the presence of high triglycerides and the development of AAA (OR 1.9, 95% CI: 1.2 to 3.1).[2,4,51,52] Noteworthy, this study had the smallest study population of all included population-based studies.[52] One study observed no association between the presence of dsylipidemia and AAA development at all.[54]

Table 1

	Year	**Patients**	**Age**	**AAA**	**Odds Ratios [95%CI]**		
		[N]	[yr]	[%]	Total Chol	High HDL	High TGL
Reed *et al.*	1992	7.862	>45	1.9	2.3 [1.6-7.0]	n.a.	1.1 [0.9-1.4]
Pleumeekers *et al.*	1995	5.419	>55	2.1	6.6 vs 6.3 P=0.04	n.a.	n.a.
Simoni *et al.*	1995	1.601	>65	4.3	1.2 [0.7-2.1]	n.a.	n.a.
Alcorn *et al.*	1996	4.741	>65	9.5	n.a.	0.5 [0.4-0.6]	n.a.
Lederle *et al.*	1997	73.451	>50	4.6	1.3 [1.2-1.5]	n.a.	n.a.
Singh *et al.*	2001	6.386	>50	5.3	1.2 [1.0-1.4]	0.6 [0.5-0.8]	0.96 [0.8-1.1]
Tornwall *et al.*	2001	29.133	>50	0.6	1.2 [0.7-2.1]	0.4 [0.3-0.6]	n.a.
Rodin *et al.*	2003	19.274	>40	2.2	1.4 [1.2-1.4]	n.a.	n.a.
Lindblad *et al*	2005	33.426	>40	0.4	1.5 [1.1-2.0]	n.a.	1.3 [0.9-1.8]
Wanhainen *et al.*	2005	504	>60	14.4	1.9 [1.3-2.8]	n.a.	1.9 [1.2-3.1]
Iribarren *et al.*	2007	104.813	>18	0.6	1.8 [1.4-2.4]	n.a.	n.a.

Description of the included population-based studies demonstrating the relation between hypercholesterolemia and the risk of AAA development. AAA; abdominal aortic aneurysm, n.a.; not available

Statins and aneurysm expansion rate

Abdominal aortic aneurysm is a vascular inflammatory degenerative disease. The aneurysmatic wall is characterized by the presence of inflammatory cells that produce MMPs that probably contribute to elastolysis and remodeling of the aneurysm. In human aneurysmatic aortic wall specimens, MMP-9 has been demonstrated to be most abundant and plasma MMP-9 levels are elevated in patients with AAA.[55] Several of the studies described above, have observed an association between the presence of AAA and total cholesterol. However, there is no clear relationship between total cholesterol and AAA expansion rate. Despite this absence of an association between cholesterol and growth rate, there is evidence from a number of studies to suggest that statins may influence aneurysm growth rate, presumably by pleiotropic effects. (*Table 2*) Several studies have been performed to identify risk factors that were associated with aneurysmal growth on the level of the human aorta itself using cell cultures obtained by aortic wall biopsies (*Table 2*). Important aspects in these studies were inflammation markers such as Interleukin-6, and specific MMPs such as MMP-9,[56,57] as these induce collagen and elastin degradation of the aortic wall.[58] Importantly, drugs with anti-inflammatory action such as prostaglandin synthetase inhibitors reduce the inflammatory response and are associated, in a case-control study with human subjects, with a reduced aneurysm growth rate.[59] Statins are known to be highly effective drugs for reducing LDL-cholesterol levels. Additionally, recent studies suggested the influence of the pleiotropic effects of statins on the inflammatory status of the aneurysmatic aortic wall.[60] Statins may alter the inflammatory status, e.g. a reduction of Interleukin-6 release, and may modulate the release of several substances in the arterial wall, of which MMPs are most important.

In vitro studies

Several in vitro studies have been performed in animal and human arterial wall tissues to demonstrate the ability of statins to suppress the expression of various inflammatory molecules, including MMPs (*Table 2*).[30,61-68] Ejiri *et al.* demonstrated that human thoracical aneurysmatic tissue had increased levels of ROS.[69] In patients with aneurysmatic aortic wall dilatation, elevated MMP-9 levels especially presented the inflammatory activity. Therefore, most in vitro studies are directed at influencing the production and release of MMPs in the arterial wall and serum. *Table 2* summarizes all in vitro studies performed to study the influence of statins on MMP levels. Cerivastatin, an intravenous statin, was used in two studies and was associated with a suppression of MMP-9 levels and macrophages in the arterial wall.

In vivo studies

In vivo studies have been performed in animals with elastase induced aneurysmatic disease, but also in human patients with AAA. Steinmetz *et al.* investigated the influence of simvastatin on elastase-induced AAA development in normal and hypercholesterolemic mice.[70] They demonstrated that simvastatin suppresses experimental AAA development and diameter in both normal and hypercholesterolemic mice. The mechanisms of these effects were independent of lipid-lowering and include preservation of medial elastin and smooth muscle cells, as well as altered aortic wall expression of MMPs and their inhibitors.

Table 2

In vitro studies

	Year	Statin type	Cell culture	Effect on MMP-9 activity
Bellosta *et al.*	1998	Fluvastatin	Mouse macrophages Human macrophages	Dose-dependent ↓ 40% Dose-dependent ↓ 45%
Ganne *et al.*	2000	Cerivastatin	Human monocytes	Dose-dependent ↓
Wang *et al.*	2000	Lovastatin	Human fibroblasts	Dose-dependent ↓ 60%
Crisby *et al.*	2001	Pravastatin	Human macrophages	No ↓
Aikawa *et al.*	2001	Cerivastatin	Rabbit macrophages	↓ 40%
Wong *et al.*	2001	Simvastatin	Human monocytes	Dose-dependent ↓ 50%
Nagashima *et al.*	2002	Cerivastatin	Human macrophages	Dose-dependent ↓ 50%
Luan *et al.*	2003	Cerivastatin Simvastatin Lovastatin	Rabbit macrophages	Dose-dependent ↓ 34% Dose-dependent ↓ 32% Dose-dependent ↓ 31%

Animal studies

	Year	Statin type	Subjects	Outcome vs controls
Steinmetz *et al.*	2005	Simvastatin	Normal mice [n=35] Hypercholesterol mice [n=53]	AAA development ↓ 33% Aortic diameter ↓ 21% AAA development ↓ 30% Aortic diameter ↓ 26%
Kalyanasundarm	2006	Simvastatin	Statin rats [n=17] Placebo rats [n=17]	Mean AAA diameter 3.4 vs 4.3, p<0.001

Human studies

Schouten *et al.*	2006	Simvastatin Fluvastatin	59 statin users 91 controls	Mean AAA grow rate: statin -1.16 [-0.3 to -2.0]
Sukhija *et al.*	2006	Atorvastatin Simvastatin	75 statin users 55 controls	Statin users: no change in AAA diameter No statin: significant increase in AAA diameter
Evans *et al.*	2007	Simvastatin	10 statin 11 placebo	Statin user: 40 ↓ in MMP-9 activity
Schlosser *et al.* (SMART study)	2008	n.a.	63 statin 84 controls	Mean AAA grow rate: Statin -1.2 [-2.3 to -0.1]
Mosorin *et al.*	2008	n.a.	34 statin 87 controls	Statin: 1.9±1.8 mm/yr Control: 2.6±2.4 mm/yr P=0.27

MMP-9; matrix metalloproteinase-9, AAA; abdominal aortic aneurysm, n.a.; not available

Kalyanasundaram *et al.* confirmed these results by demonstrating that simvastatin suppressed aneurysm expansion and reduced protein levels of MMP-9.[71] Gene array analysis of this study provided evidence that several mediators of inflammation, matrix remodeling, and oxidative stress are down regulated by simvastatin treatment.

Schouten *et al.* were the first who performed a retrospective clinical study in human subjects with AAA to investigate the effect of statins on aneurysmatic growth rate.[72] In a population of 150 patients with known AAA who did not require surgical intervention, 40% of the patients used statins during a median follow-up period of 3.1 years. The overall aneurysm growth rate in the total study population was 2.59 ± 2.8 mm/year. Patients treated with statins during the follow-up period had a 1.16 mm/year lower growth rate compared to patients without statin therapy (95% CI 0.33 to 1.99). They concluded that statins appear to be associated with attenuation of AAA growth rate, irrespective of other known factors influencing aneurysm growth.[72] Sukhija *et al.* also performed a clinical study on the influence of statins on aneurysm growth rate.[73] They demonstrated that patients with statin therapy had no change in aortic wall diameters during 24 months of follow-up, while patients without statins had a significant increase in aneurysms size compared to baseline. Mosorin *et al.* observed no influence of statin therapy on AAA growth rate in a retrospective cohort study including 131 patients.[74] Statin users had a lower AAA growth rate compared to control patients, however, this was not statistically significant (1.9 ± 1.8 mm/yr vs 2.6 ± 2.4 mm/yr, $p = 0.27$).

Although these associative data are intriguing, there are potential biases in these uncontrolled retrospective observational studies. The Second Manifestations of ARTerial disease (SMART) study group prospectively studied the influence of statin therapy on aneurysm growth rate in 147 patients with known AAA.[75] Statin users had a significantly decreased (-1.2 mm/yr, 95% CI: –2.34 to –0.06) aneurysm growth rate compared to patients without statin therapy. This study demonstrated that lipid-lowering drug treatment was independently associated with lower AAA growth rates. In addition, the risk of rupture in these patients was low, which pleads for watchful waiting.

Due to the high prevalence of concomitant cardiovascular and peripheral arterial disease in AAA patients, current guidelines recommend statin therapy in those patients.[76] Consequently, high prevalence of statin use among AAA patients will make it challenging to design trials to assess the specific role of statin therapy as an inhibitor of aneurysm expansion. At the present time the American College of Cardiology/American Heart Association guidelines provide a level B (small

randomized trials) and C evidence (case-series studies) to suggest that statins may inhibit aneurysm expansion.[76]

CONCLUSION

Analyses of large clinical trials have demonstrated that statin therapy has more effects than just lowering serum cholesterol levels. These additional benefits are called non-lipid lowering or pleiotropic effects and include a diversity of cellular events in the arterial wall. Hypercholesterolemia has been identified in the general population as an independent risk factor for the development of AAA. In vitro studies have clearly demonstrated the additional beneficial effects of statin therapy on the aneurysmatic arterial wall. Several clinical studies have reported beneficial effects of statin therapy in decreasing aneurysm growth rate and the subsequent risk of rupture. However, as these are small non-randomized trials, further large randomized controlled trials are required to establish the role of statin therapy as a preventive medical treatment possibility for AAA expansion and rupture.

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Chapter 19

Long-term outcome of prophylactic coronary revascularization in cardiac high-risk patients undergoing major vascular surgery (from the randomized DECREASE-V pilot study)

Olaf Schouten
Jan-Peter van Kuijk
Willem-Jan Flu
Tamara A. Winkel
Gijs M.J.M. Welten
Eric E. Boersma
Hence J.M. Verhagen
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Background: Prophylactic coronary revascularization in vascular surgery patients with extensive coronary artery disease was not associated with an improved immediate postoperative outcome. However, the potential long-term benefit was unknown. This study was performed to assess the long-term benefit of prophylactic coronary revascularization in these patients.

Methods: Of 1.880 patients scheduled for major vascular surgery, 430 had ≥3 risk factors (>70 yrs, angina pectoris, myocardial infarction, heart failure, stroke, diabetes mellitus, and renal failure). All underwent cardiac testing using dobutamine echocardiography or nuclear stress imaging. Patients with extensive stress-induced ischemia (≥5 segments or ≥3 walls) were randomly assigned to additional revascularization.

Results: In total, 101 patients showed extensive ischemia and were assigned to revascularization (N=49) or no-revascularization (N=52). After 2.8 years, the overall survival was 64% for patients randomly assigned to no preoperative coronary revascularization versus 61% for patients assigned to preoperative coronary revascularization (HR 1.18, 95% CI: 0.63 to 2.19, p = 0.61). Rates for survival free of all-cause death, nonfatal myocardial infarction, and coronary revascularization were similar in both groups at 49 and 42% for patients allocated to medical treatment or coronary revascularization, respectively (HR 1.51, 95% CI: 0.89 to 2.57, p = 0.13). Only two patients assigned to medical treatment required coronary revascularization during follow-up. Also, in patients who survived the first 30 days after surgery there was no apparent benefit of revascularization on cardiac events (HR 1.35, 95% CI: 0.72 to 2.52, p = 0.36).

Conclusions: Preoperative coronary revascularization in high-risk patients undergoing major vascular surgery was not associated with an improved postoperative or long-term outcome compared with the best medical treatment.

INTRODUCTION

According to the guidelines of the American College of Cardiology /American Heart Association, it is recommended to perform coronary angiography in patients with high-risk noninvasive test results. Subsequently, myocardial revascularization should be performed in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved.[1] However in both the Coronary Artery Revascularization Prophylaxis (CARP) trial and Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) V trial, prophylactic preoperative coronary revascularization was not associated with improved immediate postoperative outcome.[2,3] As recently shown, early surgery after coronary stent placement might lead to an increase in adverse cardiac events caused by in-stent thrombosis or bleeding complications.[4] This might explain the lack of perioperative benefit. However, it was expected that at least long term outcome, such as after the potentially hazardous perioperative period, should be improved in these patients. Therefore, we analyzed the long-term outcome of the randomized DECREASE V trial to assess whether there was a long-term benefit of prophylactic coronary revascularization in high-risk patients undergoing major vascular surgery.

METHODS

The study design and the perioperative results of the original DECREASE V trial have been published previously.[2] In brief, patients were considered eligible for the study if they were scheduled for elective open abdominal aortic or infrainguinal arterial reconstruction. Patients were screened for the prevalence of cardiac risk factors including age >70 years, angina pectoris, previous myocardial infarction, compensated congestive heart failure or history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction (serum creatinine >160 μmol/L), and prior stroke or transient ischemic attack. All patients with ≥3 risk factors underwent cardiac stress testing prior to surgery. Those who experienced extensive stress-induced ischemia were enrolled in the DECREASE V trial. All patients provided informed consent, and the Erasmus MC (Rotterdam, The Netherlands) medical ethics committee and local research ethics committees approved the study. Out of 1.880 screened patients, 101 (5.3%) were considered eligible, had ≥3 risk factors, had extensive stress induced myocardial ischemia and were subsequently randomized. A total of 49 patients were allocated to best medical treatment and preoperative coronary revascularization and 52 patients to best medical treatment only.

Cardiac stress testing was performed using dobutamine echocardiography or dobutamine or dipyridamole perfusion scintigraphy, as previously described.[5,6] Test results were scored according to the extent of stress-induced ischemia using a 17-segment model for dobutamine echocardiography and a 6-wall model for stress perfusion scintigraphy. Limited ischemia was defined by the presence of 1 to 4 ischemic segments or 1 to 2 ischemic walls, whereas extensive ischemia was defined as ≥5 ischemic segments or ≥3 ischemic walls.

All patients were monitored for cardiac events after screening. The 12-lead electrocardiogram and serum troponin-T level were systematically assessed 1, 3, 7, and 30 days after surgery. Outpatient follow-up was performed at 30 days if a patient had been discharged from the hospital. At the outpatient clinic, all patients were screened at 3-month intervals for cardiac events using clinical history and 12-lead electrocardiogram and additional tests were performed when indicated by the treating physicians. For this report, outcomes were long-term all-cause death and a combined end-point of all-cause death, nonfatal myocardial infarction, and coronary revascularization during follow-up.

Myocardial infarction was defined as the presence of two of the three criteria of (i) characteristic ischemic symptoms lasting >20 minutes; (ii) electrocardiographic changes, including acute ST elevation followed by the appearance of Q waves or loss of R waves; new left bundle branch block or new persistent T-wave inversion for ≥24 hours; or new ST segment depression that persisted >24 hours; and (iii) a positive troponin-T (i.e. >0.10 ng/ml) or peak creatinine kinase-MB >8% of increased total creatinine kinase with characteristic increase and decrease.

Continuous data were presented as median and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical and surgical characteristics between patients allocated to revascularization or no revascularization were evaluated by Wilcoxon's nonparametric tests, x^2 or Fisher's exact tests, as appropriate. The incidence of outcome events over time was examined by the Kaplan-Meier method. Multivariate (Cox) regression was used to compare differences in overall survival and cardiac event free survival between the allocated treatment strategies, adjusted for baseline clinical risk factors. Patients who had an event prior to surgery but after screening were included in the analyses as the day of screening was considered to be baseline. Analyses were performed according to the intention-to-treat principle. All statistical tests were 2 sided and a $p < 0.05$ was considered significant.

RESULTS

Baseline variables in patients who underwent preoperative coronary revascularization (N=49) or best medical treatment only (N=52) are shown in *Table 1*. In patients allocated to coronary revascularization, 32 underwent a percutaneous coronary intervention (PCI), with a bare-metal stent in two and drug-eluting stent in 30. Patients continued with dual-antiplatelet therapy during surgery. After surgery, patients with bare-metal stents stopped dual-antiplatelet therapy after three months and continued with aspirin afterward. Patients with drug-eluting stent continued dual-antiplatelet therapy during follow-up. A bypass procedure was performed in 17 patients. The impact of drug-eluting stents versus bare-metal stents could not be assessed because of the number of patients included in the study.

Table 1 **Baseline characteristics**

	Revascularization		
	Yes (N=49)	No (N=52)	*p*-value
Age (yrs)	71 (64,7)	70 (63,8)	
Men	42 (86%)	47 (90%)	0.55
Diabetes Mellitus	18 (37%)	15 (29%)	0.53
Current angina pectoris	25 (51%)	22 (42%)	0.43
Previous myocardial infarction	49 (100%)	50 (96%)	0.50
Previous heart failure	23 (47%)	24 (46%)	1.0
Previous cerebrovascular accident	20 (41%)	13 (25%)	0.14
Previous renal failure	9 (18%)	11 (21%)	0.81
Medication			
Aspirin	37 (76%)	30 (58%)	0.09
ß-blocker	34 (70%)	36 (69%)	1.0
ACE - inhibitor	28 (57%)	22 (42%)	0.17
Statin	34 (69%)	30 (58%)	0.30
Coronary artery narrowed >50%			
Right coronary	39 (80%)	–	
Left artery descending	46 (94%)	–	
Left circumflex	37 (76%)	–	
No. of narrowed arteries			
1	0	–	
2	12 (24%)	–	
3	33 (67%)	–	
Left main	4 (8%)	–	

The 30-day outcome of the study population has been described in detail previously.[2] Two patients died prior to vascular surgery because of a ruptured aneurysm after successful bypass surgery and 1 patient experienced myocardial infarction after unsuccessful coronary revascularization. Revascularization did not improve 30-day outcome after vascular surgery. The incidence of all-cause death or

non-fatal myocardial infarction for patients with preoperative revascularization or medical treatment only was 43 vs. 33% respectively (hazard ratio [HR] 1.4, 95% confidence interval [CI]: 0.7 to 2.8 p = 0.30).

During a median follow-up of 2.8 years (interquartile range 0.9 to 4.2 years) 42 of 101 patients died. After 2.8 years, the overall survival rate was 64% for patients randomly assigned to no preoperative coronary revascularization versus 61% for patients assigned to preoperative coronary revascularization (HR 1.18, 95% CI: 0.63 to 2.19, p = 0.61; *Figure 1*). As shown in *Figure 2*, the incidence of all-cause death, nonfatal myocardial infarction, and coronary revascularization was similar in both groups. Event-free survival after 2.8 years were 49% and 42% for patients allocated to medical treatment or coronary revascularization, respectively (HR 1.51, 95% CI: 0.89 to 2.57, p = 0.14). In the no-revascularization group, two patients (4%) underwent coronary revascularization during follow-up; one patient underwent coronary artery bypass surgery 12 months after vascular surgery because of unstable angina pectoris, and one patient underwent PCI using drug-eluting stents 27 months after vascular surgery because of progressive angina pectoris symptoms.

Figure 1. *Overall survival*

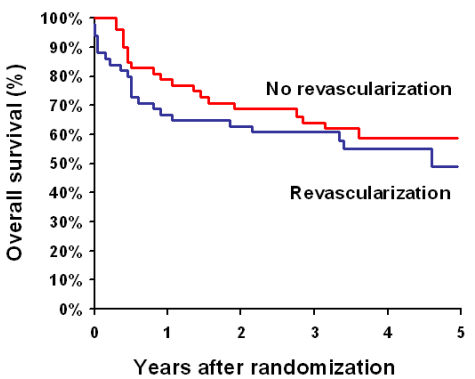
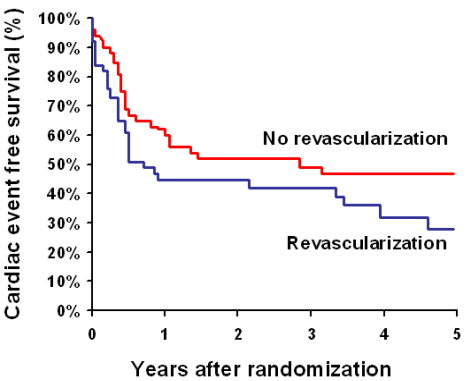


Figure 2. *Cardiac event-free survival*



It might be argued that preoperative coronary revascularization, in particular, stent placement, might lead to an increased 30-day risk for in-stent thrombosis or bleeding after discontinuation or continuation of antiplatelet therapy.[4] Therefore, we performed a separate analysis including only patients who survived ≥30 days after surgery (N=36 and N=46 for revascularization and medical treatment only, respectively). As shown in *Figures 3 and 4*, in these survivors, no apparent benefit of revascularization was observed. Of patients who underwent revascularization, 47% had an event within a median of 2.8 years of follow-up

versus 44% in those who did not undergo preoperative coronary revascularization (HR 1.35, 95% CI: 0.72 to 2.52, p = 0.36). In addition, all-cause mortality did not differ between groups (HR 0.79, 95% CI: 0.35 to 1.78, p = 0.57).

Figure 3. *Overall survival >30 days*

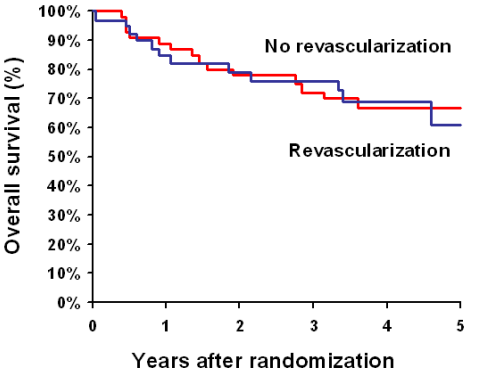
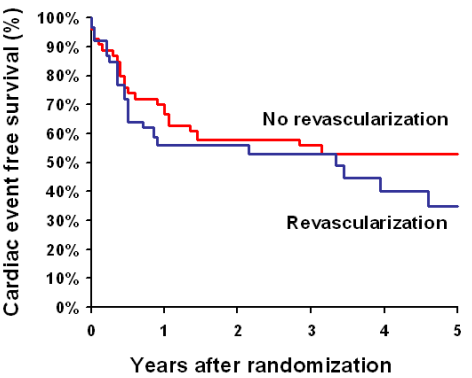
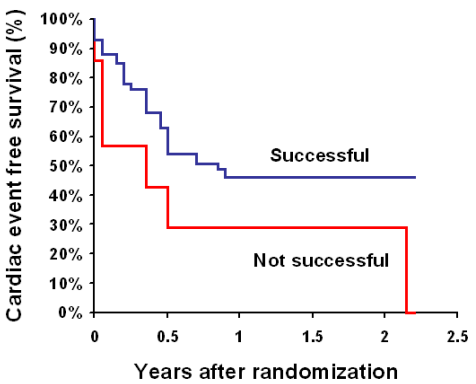


Figure 4. *Event-free survival >30 days*



There was no difference in long-term event free survival between patients who underwent preoperative PCI or coronary artery bypass grafting (HR 0.91, 95% CI: 0.44 to 1.88, p = 0.80). After a median of 2.8 years, event-free survival was 41% versus 44% for PCI and coronary artery bypass grafting, respectively. In addition, for the endpoint of all-cause death, no significant difference was observed (HR 0.81, 95% CI: 0.33 to 1.96, p = 0.64). However, patients with an incomplete revascularization procedure had the worst outcome; six of seven (86%) patients died within two years after the attempted revascularization compared with 13 of 42 (31%) with complete revascularization (HR 4.07, 95% CI: 1.53 to 10.82, p = 0.005, *Figure 5*).

Figure 5. *Cardiac event-free survival after successful or not successful preoperative revascularization*



DISCUSSION

The DECREASE-V study did not show a long-term benefit of prophylactic preoperative coronary revascularization in stable patients with multiple cardiac risk factors and extensive stress-induced myocardial ischemia scheduled for major vascular surgery.

The current findings were in line with results of large randomized trials in the nonsurgical population. Patients with stable multivessel coronary artery disease did not have better survival after coronary stent placement or bypass grafting compared with medical treatment only. The recent published Medicine, Angioplasty, or Surgery Study (MASS II) was the first randomized controlled clinical trial to report 5-year outcomes of nonsurgical patients with stable multivessel coronary artery disease treated with either bare-metal stent placement, coronary artery bypass grafting, or best medical treatment only.[7] That study showed that optimal medical therapy in patients with stable multivessel coronary artery disease resulted in similar long-term outcomes in terms of cardiac-related death or all-cause mortality. The investigators concluded that "patients with mild to moderate angina can be safely managed medically, whereas PCI or [coronary artery bypass grafting] CABG is appropriate if symptoms are not adequately controlled by medication or other high-risk features are apparent."[7] The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial also found no additional benefit of coronary revascularization in addition to optimal medical therapy in 2.287 patients with objective evidence of myocardial ischemia and significant coronary artery disease.[8] During a median follow-up of 4.6 years, cumulative event rate of all-cause death and myocardial infarction were 19.0 in the PCI group and 18.5% in the medical-therapy group. As discussed by the COURAGE trialists, these findings may be explained by differences in atherosclerotic plaque morphologic characteristics and vascular remodeling associated with acute coronary syndromes compared with stable coronary artery disease. Medical treatment in both MASS II and COURAGE included rigorous statin and aspirin therapy. This might have prevented vulnerable plaques, which are usually difficult to detect and impossible to treat using coronary angioplasty or bypass, to rupture and cause acute coronary syndromes. It is important to realize that vulnerable coronary lesions are not necessarily severely stenotic, and severely stenotic lesions are not necessarily unstable. Focal management of severely stenotic coronary lesions using PCI in both MASS II and COURAGE did not reduce the rate of death and myocardial infarction, presumably because the treated, severely stenotic lesions were not likely to trigger an acute coronary event.[8]

Remarkably, in MASS II and COURAGE, annual mortality rates were approximately 1 to 2% whereas in CARP and DECREASE V the annual mortality rates in patients who survived surgery were 6.8 and 8.2%, respectively. Baseline angiographic cardiac status in MASS II and COURAGE was not significantly better or worse than in CARP and DECREASE V: 3-vessel disease was present in 58 and 31% versus 33 and 75%, respectively. In line with these findings, it was recently shown that patients with so-called "polyvascular" disease, i.e. multiple vascular beds affected, have a significant worse outcome compared to patients with coronary artery disease only.[9] In Reduction of Atherothrombosis for Continued Health (REACH), event rates (cardiovascular death, MI, stroke, or hospitalization for a cardiovascular event) increased with the number of symptomatic vascular beds: 5.3% of patients with risk factors only to 12.6% with one, 21.1 with two, and 26.3% with three disease locations.[9] Because all patients in DECREASE V and CARP had proven coronary artery disease and were planned for noncardiac vascular surgery, these patients can be considered to have polyvascular disease. This indicated that patients scheduled for vascular surgery with extensive coronary artery disease should be considered to be a different population than patients without peripheral arterial disease, but with coronary artery disease only. However, also in this patient population with stable severe coronary artery disease, optimal medical therapy seems to be equal to coronary revascularization in addition to best medical treatment.

The findings of both CARP and DECREASE V support the current guidelines of the American College of Cardiology/American Heart Association for perioperative management in high-risk patients to reserve revascularization for cardiac unstable patients. Considering the high long-term mortality and cardiac event rates, these patients should be regularly screened for the presence of ischemic symptoms, and aggressive anti-ischemic medical therapy must be used.

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Chapter 20

Timing of noncardiac surgery after coronary artery stenting with bare metal or drug-eluting stents

Jan-Peter van Kuijk
Willem-Jan Flu
Olaf Schouten
Sanne E. Hoeks
Lisanne Schenkeveld
Peter P.T. de Jaegere
Jeroen J. Bax
Ron T. van Domburg
Patrick W. Serruys
Don Poldermans

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ABSTRACT

Background: The current guidelines have recommended postponing noncardiac surgery (NCS) for ≥6 weeks after bare metal stent (BMS) placement and 1 year after drug-eluting stent (DES) placement. However, much debate has ensued about these intervals. The aim of the present study was to assess the influence of different intervals between stenting and NCS and the use of dual antiplatelet therapy on the occurrence of perioperative major adverse cardiac events (MACEs).

Methods: We identified 550 patients (376 with a DES and 174 with a BMS) by cross-matching the Erasmus Medical Center percutaneous coronary intervention (PCI) database with the NCS database. The following intervals between PCI-BMS (<30 days, <3 months, >3 months) or PCI-DES (<30 days, <3 months, 3-6 months, 6-12 months and >12 months) and NCS were studied. MACEs included death, myocardial infarction and repeated revascularization.

Results: In the PCI-BMS group, the rates of MACEs during the intervals of <30, 30 days–3 months, and >3 months was 50, 14, and 4%, respectively (overall $p < 0.001$). In the PCI-DES group, the rate of MACE changed significantly with the interval after PCI (35, 13, 15, 6, and 9% for patients undergoing NCS <30 days, 30 days to 3 months, 3 to 6 months, 6 to 12 months, and >12 months after PCI-DES respectively, overall $p < 0.001$). Of the patients who experienced a MACE, 45 and 55% were receiving single and dual antiplatelet therapy at NCS, respectively ($p = 0.92$). The risk of severe bleeding in patients with single and dual therapy at NCS was 4 and 21%, respectively ($p < 0.001$).

Conclusions: We found an inverse relation between the interval from PCI to NCS and perioperative MACEs. Continuation of dual antiplatelet therapy until NCS did not provide complete protection against MACEs.

INTRODUCTION

Approximately 5% of patients who undergo coronary stenting require some form of noncardiac surgery (NCS) within one year.[1] Surgery increases the risk of thrombosis owing to a perioperative stress response; including sympathetic activation promoting reduced fibrinolytic activity, platelet activation, and hypercoagulability. In addition, dual antiplatelet therapy is often interrupted because of the fear of excessive perioperative bleeding complications. The prevention of cardiac complications versus the risk of severe bleeding creates a double-edged sword on the timing of surgery and the antiplatelet regimen. The current guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) have recommend delaying NCS for ≥6 weeks after PCI with a bare metal stent (BMS) and ≥1 year after PCI with a drug-eluting stent (DES).[2,3] However, in a recent large study including patients with DES placement these recommendations could not be confirmed.[4] Therefore, the aim of the present study was to assess the relation among the interval to NCS after PCI, medical therapy and the occurrence of perioperative major adverse cardiovascular events (MACEs).

METHODS

The present study included 1.000 patients who had undergone cardiac surgery or NCS after successful PCI because of severe ischemia between January 2000 and December 2007. The final study population included 550 patients who had undergone NCS. The patients were identified by cross matching the Erasmus Medical Centre PCI database with the NCS database (including 78.000 procedures). The PCI database is a prospectively maintained registry of 13.000 procedures performed from January 2000 to December 2007.[5]

All patients underwent PCI using either a BMS (2000 to March 2002) or DES (april 2002 to 2007; sirolimus or paclitaxel). The patient characteristics were prospectively collected directly after the PCI procedure and included the PCI-indication, number of affected and stented coronary arteries, left ventricular ejection fraction, and medication use during and after PCI. Patients with a BMS were prescribed lifelong aspirin and clopidogrel (loading dose 300mg, followed by 75mg daily) for ≥30 days. Patients with a DES usually were prescribed lifelong aspirin and clopidogrel for ≥3 months (sirolimus) to 6 months (paclitaxel), or longer, at the discretion of the treating physician. The treating physician determined the type of used stent at the PCI procedure.

All data on the surgical procedure were retrospectively collected by screening the medical charts. The type of surgery was classified and categorized according to the surgical risk, determined using the ACC/AHA classification.[6] In addition, cardiac history and cardiac risk factors were assessed at stenting and surgery. Medication use was assessed during the initial PCI procedures and was updated at the point of surgery. The use of proton pump inhibitors concomitantly with clopidogrel was also noted. No standard protocol for perioperative antiplatelet therapy was used in the present study population, becuse this was an observational study and the surgical procedures included all types of NCS. Consequently, some patients received aspirin and/or clopidogrel throughout the surgical procedure, but for other patients, aspirin and/or clopidogrel were discontinued five to ten days before surgery. All medical records were reviewed to categorize the maintenance of antiplatelet therapy (i.e. no therapy, aspirin, clopidogrel or dual antiplatelet therapy) in the period before NCS as discontinued >30 days, discontinued 7 to 30 days, or continued to within <7 days before NCS.

The perioperative complications were defined as the occurrence of MACEs (i.e. death, myocardial infarction [either ST-elevation or non-ST-elevation myocardial infarction], stent thrombosis, repeated revascularization) within 30 days after NCS. Perioperative myocardial infarction was defined according to the European Society of Cardiology/ACC criteria.[7] Bleeding complications were categorized as life-threatening or moderate bleedings, during the first 30 postoperative days. Life-threatening bleeding was defined as fatal bleeding, intracranial bleeding, or bleeding requiring surgical intervention or transfusion of ≥4 U of blood or blood products. Moderate bleeding was defined as bleeding requiring transfusion of 1 to 3 U of blood or blood products.[8]

Statistical analyses were performed using the Statistical Package for Social Sciences, version 15.0 (SPSS, Chicago, Illinois). Continuous data were compared using Student's t test and are expressed as mean ± SD. Categorical data are presented as percentages, and differences between proportions were compared using the x^2 test. To assess whether the risk of the occurrence of MACEs after NCS was associated with the interval from PCI to NCS, the interval from PCI to NCS was assessed as a categorical variable. Determined by the current guidelines and recommendations, the intervals used for patients with a BMS were <30days, <3 months, and >3 months and for a DES were <30 days, 30 days to 3 months, 3 to 6 months, 6 to 12 months, and >12 months.[3,4,9] Logistic regression analyses were used to calculate the association between the intervals from PCI to NCS and MACEs. Logistic regression analyses were also used to determine possible associations between the presence of cardiac risk factors and the development of

MACEs. Adjustments were made for age, gender, and all baseline cardiac risk factors (history of myocardial infarction, PCI/coronary artery bypass grafting, congestive heart failure, renal dysfunction, smoking, hypertension, diabetes mellitus, hypercholesterolemia, positive family history of cardiovascular (CV) disease), vessel/stent-diameter, lesion length and use of proton pump inhibitors during clopidogrel treatment. In all analyses, two-tailed tests were performed, and statistical significance was inferred at $p < 0.05$.

RESULTS

A total of 1.000 PCI procedures with stent placement followed by a surgical procedure were identified. NCS was performed in 550 patients either after PCI-BMS (N=174) or PCI-DES (N=376). No difference was found in the cardiac history or type of indication for PCI between the patients undergoing PCI-BMS and PCI-DES (*Table 1*). Most patients underwent intermediate to high-risk surgery; a trend was found for more emergency surgical procedures in patients with a DES ($p = 0.054$; *Table 2*).

The median interval between PCI–BMS and NCS was 3.6 years (interquartile range 1.8 to 5.4). Of the patients who underwent NCS after PCI-BMS, 8 (5%) patients had NCS within 30 days, 7 (4%) between 30 days and 3 months, and 159 (91%) after 3 months. During the first 30 days after NCS, 11 patients (6%) with PCI-BMS experienced a MACE (10 cardiovascular death and 1 myocardial infarction). An inverse relation was found between the rate of postoperative MACEs and the interval to NCS after PCI-BMS. The rate of MACEs for intervals of <30, 30 days to 3 months, and >3 months was 50, 14, and 4%, respectively (overall $p<0.001$; *Figure 1* and *Table 3*). When NCS was postponed for ≥3 months after PCI with a BMS, the lowest risk of perioperative MACE was observed (*Figure 1*).

Dual antiplatelet therapy was used in 100 and 75% of the patients who underwent NCS within 30 days or 30 days to 3 months after PCI-BMS, respectively. Overall, at NCS, 157 (91%) and 16 (9%) patients were receiving single and dual antiplatelet therapy, respectively. Of the patients who experienced a MACE, 5 (46%) and 6 (55%) had been receiving single or dual antiplatelet therapy at NCS ($p = 0.92$). All patients who underwent NCS within 30 days after PCI-BMS and experienced a MACE were receiving dual antiplatelet therapy until NCS. Patients with concomitant use of proton pump inhibitors and clopidogrel at NCS seemed to have greater rates of MACE than patients without proton pump inhibitor use (46 vs 20%); however, this was not statistically significance ($p = 0.33$). Of the patients

undergoing PCI-BMS, 81% had a large stent/vessel diameter (>3.0 mm) or a short lesion length (<25 mm). No association was found between the stent/vessel diameter or lesion length and the risk of MACEs in these patients.

Table 1 **Baseline characteristics**

	Total [N=550]	**BMS** [N=174	**DES** [N=376]	***P*-value**
Demographics				
Age (yrs), mean ± SD	62.6	61.2	63.3	0.04
Male	74.9%	75.3%	74.7%	0.89
Medical history				
Myocardial infarction	179 (33%)	56 (32%)	123 (33%)	0.77
CABG	66 (12%)	23 (13%)	43 (12%)	0.61
PCI	161 (30%)	52 (30%)	109 (30%)	0.95
Risk factors				
Smoking				
Current	253 (46%)	65 (37%)	188 (50%)	<0.001
History	86 (16%)	10 (6%)	76 (20%)	<0.001
Hypertension	118 (22%)	39 (22%)	79 (21%)	0.71
Diabetes Mellitus	119 (22%)	26 (15%)	93 (25%)	0.01
Dyslipidemia	296 (54%)	81 (47%)	215 (57%)	0.02
Renal failure	47 (9%)	7 (4%)	40 (11%)	0.01
LVEF <50%	236 (44%)	170 (46%)	66 (38%)	0.07
PCI indication:				0.31
Stable-Angina pectoris	245 (45%)	175 (47%)	70 (40%)	
Instable-Angian pectors	174 (32%)	112 (30%)	62 (36%)	
Acute myocardial infarction	131 (24%)	89 (24%)	42 (24%)	
Discharge medication				
Aspirin	503 (92%)	160 (92%)	343 (91%)	0.78
Statin	318 (58%)	90 (52%)	228 (61%)	0.05
ß-blocking agents	502 (91%)	158 (91%)	344 (92%)	0.79
ACE-inhibitors	149 (27%)	40 (23%)	109 (29%)	0.14
Diuretics	48 (9%)	10 (6%)	38 (10%)	0.09
Calcium antagonists	182 (33%)	84 (48%)	98 (26%)	<0.001
Nitrates	56 (10%)	13 (8%)	43 (11%)	0.15
Ticloxpidines	477 (87%)	151 (87%)	326 (87%)	0.98
Clopidogrel use (mo)				<0.001
Median	3	2	6	
Interquartile range	1-6	1-3	1-6	

Abbreviations: CABG; Coronary Artery Bypass Grafting, PCI; Percutaneous Coronary Intervention, LVEF; Left Ventricular Ejection Fraction, ACE: Angiotensin Converting Enzyme

The median time between PCI–DES and NCS was 1.4 years (interquartile range 0.5 to 2.6). NCS after PCI-DES was performed within 30 days, at 30 days to 3 months, 3 to 6 months, 6 to 12 months, and >12 months in 45 (12%), 25 (6%), 27 (7%), 47 (13%) and 232 (62%) patients, respectively. A total of 48 patients (13%) experienced a MACE within the first 30 postoperative days (36 [82%] cardiovascular death, 4 [9%] noncardiovascular death, 2 [5%] myocardial infarction, 6 [14%] stent

thrombosis). The MACE rate changed significantly with the interval after PCI-DES (35, 13, 15, 6, and 9% for patients undergoing NCS <30 days, 30 days to 3 months, 3 to 6 months, 6 to 12 months, and >12 months after PCI-DES respectively; overall $p < 0.001$; *Figure 1* and *Table 3*). In line with the ACC/AHA guidelines, NCS within one year after PCI-DES was associated with an increased rate of MACEs (18 vs 10%, $p = 0.015$).

Table 2 **Surgical Group catergorized according to ACC/AHA classification**

	BMS (N=174)	**DES** (N=376)
High risk		
Vascular System	23 (13%)	41 (11%)
Emergency	4 (2%)	40 (11%)
Intermediate risk		
Nose, mouth, pharynx	13 (8%)	15 (4%)
Eye	29 (17%)	42 (11%)
Digestive System	16 (9%)	48 (13%)
Musculoskeletal System	20 (12%)	39 (10%)
Respiratory System	4 (2%)	11 (3%)
Nervous System	6 (3%)	23 (6%)
Endocrine System	-	2 (1%)
Oncology	1 (1%)	1 (1%)
Low risk		
Urinary System	28 (16%)	49 (13%)
Cosmetic surgery	9 (5%)	18 (5%)
Dermatologic	9 (5%)	17 (5%)
Miscellaneous	12 (7%)	30 (8%)

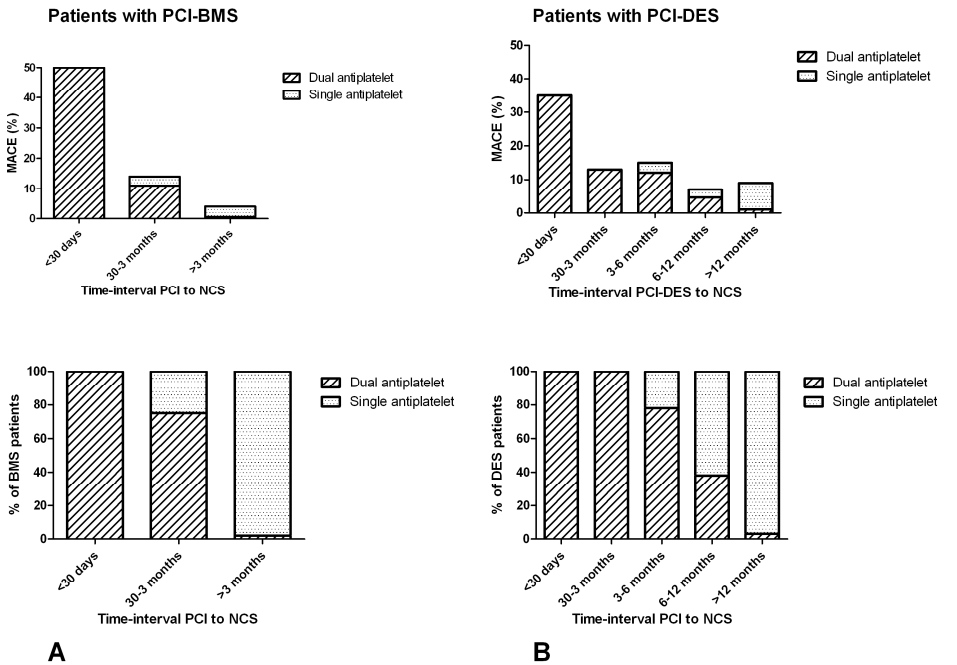
Table 3 **30-day MACEs**

PCI to NCS interval	**N**	***p*-value**
BMS (N=174)		
0 – 30 d (N=8)	4 (50%)	<0.001
31– 90 d (N=7)	1 (14%)	
> 91 d (N=159)	6 (4%)	
< 30 d (N=8)	4 (50%)	<0.001
≥ 30 d (N=166)	7 (4%)	
< 3 mo (N=15)	5 (33%)	<0.001
≥ 3 mo (N=159)	6 (4%)	
DES (N=376)		
< 30 d (N=46)	16 (35%)	<0.001
30 d – 3 mo (N=24)	3 (13%)	
3 – 6 mo (N=27)	4 (15%)	
6 – 12 mo (N=47)	3 (6%)	
> 12 mo (N=232)	22 (9%)	
< 1yr (N=144)	26 (18%)	0.015
≥ 1yr (N=232)	22 (9%)	

Thirty-day major adverse cardiovascular events (MACEs), stratified by interval between percutaneous coronary intervention (PCI) and noncardiac surgery (NCS)

On multivariate analysis, patients undergoing NCS within one year after PCI-DES, had an increased risk of perioperative MACEs (hazard ratio 2.0, 95% confidence interval 1.1 to 3.5) compared to patients undergoing NCS >1 year after PCI-DES.

Figure 1. *(A) Perioperative MACE and antiplatelet regimen in PCI-BMS. (B) Perioperative MACE and antiplatelet regimen in PCI-DES. Risk of perioperative MACEs during prespecified intervals between PCI and NCS. Antiplatelet regimens (single or dual antiplatelet therapy) subdivided according to occurrence of perioperative MACEs*

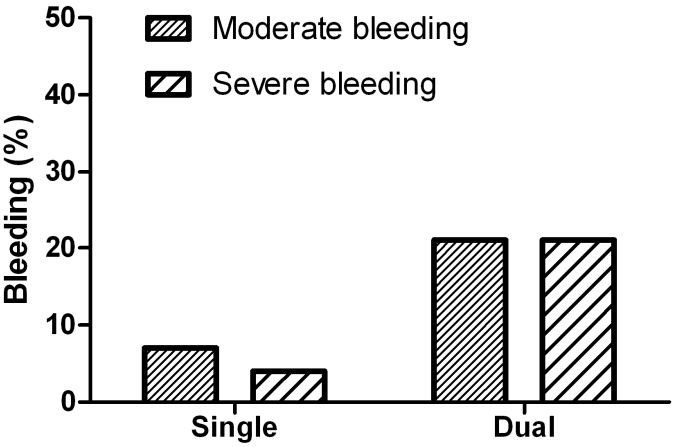


Dual antiplatelet therapy was used in 100 and 80% of the patients during the first 3 and 6 months after PCI-DES, respectively. Overall, dual antiplatelet therapy was continued until NCS in 112 (30%) patients, and 264 (70%) patients received single antiplatelet therapy. Of the patients who experienced a perioperative MACE, 56 and 44% had received dual or single antiplatelet therapy, respectively (p = 0.72). Because all patients were receiving dual antiplatelet therapy during the first 3 to 6 months after PCI-DES, the risk of perioperative MACE was only related to the interval to NCS after PCI. No relation was found between the concomitant use of clopidogrel and proton pump inhibitors and the risk of perioperative MACEs (28 vs 21% p = 0.38), compared to patients without proton pump inhibitor use. Patients in the PCI-DES group more often had a small stent-vessel diameter, but an increased lesion length, compared to those in the PCI-BMS group (84 vs 16% and 78 vs 22%, p < 0.001), respectively. No association was found between the

stent/vessel diameter or lesion length and the risk of perioperative MACEs (12 vs 15%, $p = 0.4$, and 11 vs 15%, $p = 0.2$), respectively.

Moderate and severe bleeding after surgery occurred in 56 (10%) and 42 (8%) patients, respectively. A strong association was found between the use of single or dual antiplatelet therapy at NCS and the risk of moderate, severe or any bleeding ($p < 0.001$; *Figure 2*). The risk of severe bleeding in patients receiving single or dual therapy at NCS was 4 and 21%, respectively ($p < 0.001$). Additionally, the risk of bleeding was associated with interval from PCI to NCS.

Figure 2. *Bleeding risk according to antiplatelet regimen (single or dual antiplatelet therapy)*



DISCUSSION

The results of the present study revealed an inverse relation between the interval from PCI to NCS and the occurrence of MACEs within 30 days after NCS in patients with PCI-BMS or PCI-DES. Irrespective of dual antiplatelet therapy continuation until NCS, early surgery after stenting was associated with an increased risk of MACEs. In addition, dual antiplatelet therapy at NCS increased the bleeding risk. Therefore, elective NCS should preferably be postponed for 90 days after PCI-BMS; however, if more urgent surgery is needed, a minimum interval of 30 days should be recommended. After PCI-DES, NCS should be delayed for ≥1 year.

In response to several small studies that reported cases of late stent thrombosis,[10,11] the first European Society of Cardiology guidelines recommended dual antiplatelet therapy for a minimum of three to four weeks after PCI-BMS. The most recent scientific advisory of the ACC/AHA on the discontinuation of dual antiplatelet therapy for patients with coronary stents proposed an interval of 6

weeks after PCI-BMS.[2,3] In the present study, the strongest decrease in the risk of perioperative MACEs in patients undergoing NCS after PCI-BMS was reached when NCS was postponed for a minimum of 30 days from PCI. In contrast, only a small additional effect was realized if NCS was postponed until six weeks after PCI compared to 30 days. Previous studies of patients undergoing NCS after PCI-BMS reported high rates of MACEs when NCS was performed within two weeks after PCI,[12,13] and others have recommended a delay of ≥6 weeks.[14,15] Recent studies have shown the greatest risk of ischaemic events when NCS was performed within 30 days of PCI, and the lowest after 90 days.[9] In line with these studies, our study found the same high risk of perioperative MACE with NCS within 30 days of PCI-BMS. However, the number of events in the present study was greater (10.7 vs 5.4%), possibly because of the intensive and close follow-up of our patient population. As mentioned by Nutall *et al.*[9] they used no protocol for the detection of perioperative MACE.

The occurrence of stent thrombosis is a multifactorial process that includes device-related factors (e.g. surface coating, stent diameter, stent length) and patient- or lesion-specific factors (e.g. interval from PCI to NCS, stent/vessel diameter, antiplatelet therapy, proton pump inhibitor use and left ventricular ejection fraction).[16] In the present study, only the interval from PCI to NCS was independently associated with an increased risk of perioperative MACEs after NCS. The continuation of dual antiplatelet therapy until NCS in PCI-BMS patients was not associated with lower rates of MACEs in the perioperative phase but was, however, associated with an increased risk of bleeding complications. Nuttall *et al.*[9] found no association between the different intervals after PCI-BMS and the frequency of bleeding events. After an interval of ≥30 days, they found a bleeding event rate of 4.6%, in line with our rate of 4%.

A significant association between the interval from PCI-DES to NCS and the risk of perioperative MACEs was detected, confirming the ACC/AHA advisory to postpone elective NCS for ≥1 year after PCI.[3] Although stabilization for the occurrence of MACEs was detected at a 6-month interval between PCI and NCS, other studies have shown catastrophic effects of early discontinuation.[17] The value of at least a 1-year continuation of dual antiplatelet therapy after DES placement was also shown.[18] In addition, more recent studies have shown that even if clopidogrel is stopped after the previous recommended three to six months, those who continue dual antiplatelet therapy have better survival and less late in-stent thrombosis than those with single or no antiplatelet therapy.[18,19] Rabbits *et al.*[4] performed the largest trial in patients with PCI-DES before NCS, and observed a nonsignificant trend-wise decrease in the rate of MACEs with an increasing interval

after PCI.[4] From these cited studies, prolonged dual antiplatelet therapy for ≥1 year is supported for patients with PCI-DES. Although our study demonstrated stabilization for the risk of MACEs after an interval of six months after PCI, an overall reduction in the incidence of MACEs was seen when NCS was performed ≥1 year after PCI-DES.

The continuation of dual antiplatelet therapy until surgery was not associated with a reduced risk of perioperative MACEs, compared to the discontinuation of dual antiplatelet therapy. In patients who underwent NCS within three months after PCI-DES, continuation of dual antiplatelet therapy was not sufficiently protective to prevent perioperative MACEs. Although this finding surprised us, Rabbitts *et al.*[4] detected the same association. They even found that use of thienopyridine <7 days from NCS was associated with an increased rate of MACEs, compared to the use of single antiplatelet therapy. In contrast, other studies showed the adverse effects of stopping dual antiplatelet too early.[12,19,20] In our study, all patients who developed a MACE during dual antiplatelet therapy had undergone surgery within three months after PCI. A possible explanation for the occurrence of MACEs in this specific subset of patients is minimal early re-endothelization of the coronary arteries at the stent-location. The combination of aspirin and thienopyridines during the hypercoagulable state during NCS seemed insufficient to reduce the risk of in-stent thrombosis during this vulnerable period.

Although the overall bleeding risk was in line with that reported by previous studies[4], an increased rate of severe bleeding episodes occurred in the PCI-DES patients that was related to (1) the use of dual antiplatelet therapy at NCS, (2) high-risk NCS, and (3) NCS within 30 days after PCI. Harder *et al.*[21] concluded that monotherapy with aspirin or clopidogrel usually does not need to be discontinued during surgery, which was confirmed in a meta-analysis by Burger *et al.*[21] However, an increased risk of severe bleeding was shown by the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial for patients receiving dual antiplatelet therapy.[22] Although the use of dual antiplatelet therapy has the disadvantage of an increased bleeding risk, the long-term survival effects of thienopyridines seem to outweigh these short-term negative effects.

The potential limitations of the present study merit consideration. First, a referral bias was possible, because we did not include patients who underwent NCS elsewhere. Second, although the present sample size represented a very small part of both databases, a minor susceptibility to chance remained. Third, a selection bias for the occurrence of MACEs during dual antiplatelet therapy was possible, because these patients were more prone to undergo nonelective NCS early after

PCI. Although no independent events' committee adjudicated clinical events, this was performed by 2 of us. Finally, we were unable to determine whether PCI was performed specifically for the subsequent surgery; however, almost 80% of PCI procedures were performed in a stable cardiac setting.

In conclusion, after PCI-BMS, NCS should preferably be postponed 90 days; however, if more urgent surgery is needed, a minimum interval of 30 days should be recommended. In patients with PCI-DES, elective NCS should be postponed for ≥1 year after PCI.

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Chapter 21

Timing of preoperative β-blocker treatment in vascular surgery patients: influence on postoperative outcome

Willem-Jan Flu
Jan-Peter van Kuijk
Michel Chonchol
Tamara A. Winkel
Hence J.M. Verhagen
Jeroen J. Bax
Don Poldermans

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Chapter 22

Screening for abdominal aortic aneurysms using a dedicated portable ultrasound system: early results

Willem-Jan Flu
Jan-Peter van Kuijk
Egon J.W. Merks
Ruud J. Kuiper
Hence J.M. Verhagen
Jeroen G. Bosch
Nicolaas Bom
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Background and Aims: Abdominal aortic aneurysms (AAA) are often diagnosed at time of (impending) rupture leading to a dramatic increase of morbidity and mortality. A simple screening device might be the key solution for widespread AAA screening. This study evaluated the diagnostic accuracy of a new portable ultrasound scanner (Aortascan BVI 9600) developed for automatic AAA detection.

Methods: A total of 150 patients with presumed aneurysmatic peripheral atherosclerotic disease were included in the study. Patients were first scanned with conventional ultrasound (US), serving as reference technique. An infra-renal abdominal aorta diameter of ≥30 mm was defined as an AAA. Hereafter, the aorta was scanned using the Aortascan BVI 9600. Statistical analyses were performed using SPSS version 15.0 statistical software.

Results: Abdominal aortic aneurysms were detected with conventional US in 78 (52%) patients, compared with 74 (49%) AAAs detected with Aortascan BVI 9600. The Aortascan BVI 9600 demonstrated a sensitivity, specificity, positive and negative predictive value of 90, 94, 95 and 89%, respectively, in the detection of AAA's.

Conclusions: The Aortascan BVI 9600 automatically detects the aortic diameter with a 90% sensitivity without the need for a trained operator. Because of these unique capabilities, it can be used for AAA screening outside the hospital.

INTRODUCTION

The prevalence of abdominal aortic aneurysm (AAA), in patients aged above 55 years, ranges from 4.1 to 14.2% in men and 0.35 to 6.2% in women.[1] The incidence of AAA is known to increase, due to an increased life expectancy.[2] Effective screening programs for detecting AAA are currently not available. Therefore AAA's are often diagnosed at time of (impending) rupture which leads to a dramatic increase of morbidity and mortality.[3] Abdominal ultrasound (US) and computerized tomography (CT) are the most frequently used non-invasive imaging tests to detect or exclude the presence of an AAA. These imaging techniques are expensive and require trained staff. In case of CT, the patient is exposed to a fair amount of radiation. Hence these techniques are not ideal for screening purposes. A simple screening device, which is less expensive and offers the possibility for use outside the hospital, might be the key solution for widespread AAA screening. In 2006, a pilot study conducted by Vidakovic *et al.*[4] demonstrated the diagnostic potential of an automatic bladder volume scanner (BVI 6400, Verathon Medical, Bothell, USA) to detect AAA. The current study evaluated the diagnostic accuracy of a new portable ultrasound scanner [Aortascan BVI 9600 (BVI 9600), Verathon Medical] developed for automatic AAA detection.

METHODS

Study population

The study population consisted of 150 consecutive patients referred to the outpatient clinic of the Department of Vascular Surgery of the Erasmus Medical Center (Rotterdam, The Netherlands) for presumed aneurysmatic peripheral atherosclerotic disease. Patient enrolment was performed from January until December 2008, after approval of the hospital's Ethics Committee. All patients gave informed consent at time of inclusion. Patients with abdominal aortic stents or a previous open aortic reconstruction were excluded from the study.

Baseline characteristics

A detailed history was obtained from every patient and the following characteristics were recorded; age, gender, body mass index, heart failure (defined as the presence of heart failure symptoms according the New York Heart Association classification or previous hospital admission for decompensated heart failure), ischemic heart disease (defined as history of angina pectoris, coronary revascularization or myocardial infarction), cerebrovascular disease (defined as a history of ischemic or hemorrhagic stroke), lower extremity arterial disease (defined as ankle brachial

index <0.9), renal dysfunction (defined as creatinin clearance >2.0 mg/dL), diabetes mellitus (fasting blood glucose ≥7.0 mmol/L or requirement for insulin and/or anti-diabetic medication), hypertension (blood pressure was measured during preoperative evaluation at the outpatient clinic and hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg in non-diabetics, systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg in diabetics or the use of antihypertensive medication), hypercholesterolemia (low-density lipoprotein cholesterol >3.5 mmol/L and the requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification) and smoking status.

Measurement of the abdominal aortic diameter

All patients were first scanned with conventional US and measurements obtained with conventional US served as the reference value. An infra-renal abdominal aorta diameter (either anterior-posterior or transverse) of ≥30 mm was defined as an AAA.[5] Hereafter, the aorta was scanned using the Aortascan BVI 9600 (*Figure 1 and 2).* The examinations were performed and reviewed by 2 physicians, both skilled and experienced in abdominal US. The interobserver variability between the two echocardiographists was up to 95% for the measured aortic diameter.

Conventional abdominal ultrasound

A handheld US device (SonoSite Titan, SonoSite Inc., Bothell, Washington) with a C11/8-5MHz broadband slightly curved array transducer was used for US evaluation of the abdominal aorta. Both anterior-posterior and transverse diameters at the largest portion of the abdominal aorta were measured. The aortic diameters were obtained using on-screen callipers from the outer edge to edge of the aortic wall, including intraluminal thrombus if present. The maximal obtained diameter, measured in the xiphoid to umbilical traject, was used for analysis.

Figure 1. *The Aortascan BVI 9600*

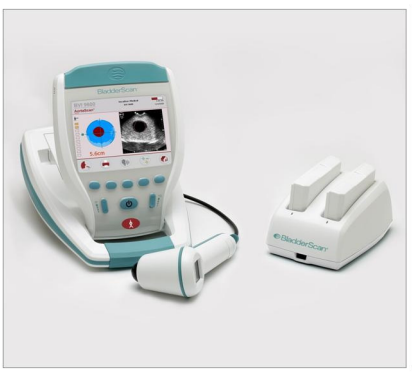
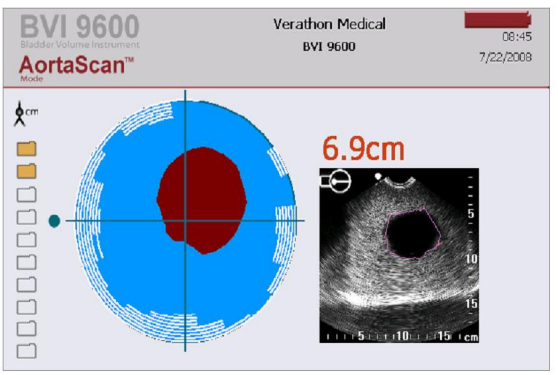
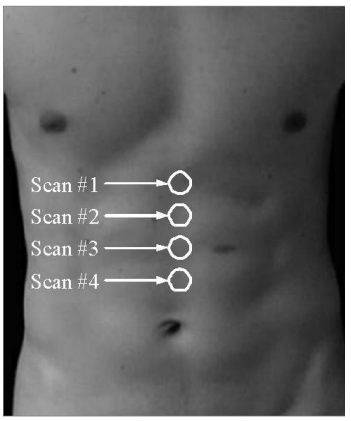


Figure 2. *Screenplay Aortascan BVI 9600*



The 3D dimensional scan is obtained as a set of 12 mechanically rotated two dimensional scans, 15 degrees apart. Each planar scan is obtained by mechanically sweeping a single element transducer through a 120° arc. The transducer is used for transmission and reception of ultrasonic waves at 3.7 MHz. Echoes originating from a depth up to 20 cm were included for analysis. Dedicated detection software uses the data obtained from the 3D scan to create a 3D geometry of the abdominal aorta. From this 3D geometry, the maximum diameter is deduced and displayed as result for the user. The user is also provided with a B-mode image representing the cross-sectional scan plane. Electronic callipers are provided to manually redefine the maximum diameter when necessary. Each Aortascan BVI 9600 assessment consisted of four consecutive scans, located at the midline of the abdomen, starting ~2.5 cm below the xiphoid. Scanning locations are shown in *Figure 3*. Abdominal aortic diameter measurements <30 mm were displayed solely as being <3.0 cm. An estimated diameter in mm was provided by the Aortascan, when the abdominal aorta diameter was assumed to be ≥30 mm. The maximal abdominal aorta diameter was used for the hypothesis on the presence of AAA.

Figure 3. *Scanning locations of the Aortascan BVI 9600*



Statistics

Dichotomous data are described as numbers and percentages. The continuous variables age and BMI are described as mean ± standard deviation (SD). Differences in baseline characteristics between patients with abdominal aorta diameter <30 or ≥30 mm, detected with conventional US, were evaluated using x^2 tests for categorical data. Continuous data were compared using one-way ANOVA. For all tests, a *p*-value less than 0.05 (two sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

A total of 150 patients with presumed aneurysmatic peripheral atherosclerotic disease were included in the study. Abdominal aortic aneurysms were detected with conventional US in 78 (52%) patients, compared with 74 (49%) presumed AAA's detected with Aortascan BVI 9600. Mean abdominal aortic size was 39 mm, measured with conventional US. Patients with aneurysmatic disease were older (70 vs. 65 years), more likely to be male (89 vs 59%, $p < 0.01$) and more often a BMI >25 compared with patients with normal abdominal aortic size. Other factors associated with an AAA were heart failure, renal dysfunction, and smoking. Baseline characteristics are shown in *Table 1*.

Table 1 **Baseline characteristics of the study population**

	Conventional ultrasound		
	No AAA [N=72]	**AAA** [N=78]	***p*-value**
Demographics			
Age (± SD)	65 (10)	70 (10)	0.022
Male (%)	43 (59)	72 (89)	<0.01
Body mass index (± SD)	25 (3)	27 (4)	0.008
Medical history (%)			
Clinical heart failure	4 (6)	16 (20)	0.009
Ischemic heart disease	20 (27)	33 (41)	0.082
Cerebrovascular disease	27 (37)	19 (24)	<0.01
Lower extremity arterial disease	42 (58)	27 (33)	0.003
Renal dysfunction	4 (6)	18 (23)	0.003
Diabetes mellitus	20 (25)	13 (18)	0.300
Hypertension	44 (61)	53 (66)	0.510
Hypercholesterolemia	37 (51)	45 (56)	0.548
Chronic Obstructive Pulmonary Disease	11 (15)	13 (16)	0.870
Smoking, current	28 (39)	20 (25)	0.066

Abdominal aortic aneurysm (AAA), standard deviation (SD), ultrasound (US)

In total, 70 (90%) AAA patients measured with conventional US were detected with the Aortascan BVI 9600 as well. Furthermore, 68 (95%) patients with normal abdominal aorta observed with conventional US had a normal abdominal aorta, measured with the Aortascan BVI 9600 as well. False-positive measurements, i.e. a presumed AAA detected with the Aortascan BVI 9600, which was not present with conventional US was observed in four patients (5%). False-negative measurements, i.e. an AAA detected with conventional US and missed with the Aortascan BVI 9600 was present in eight (10%) patients. We have found sensitivity, specificity, positive-predictive value and negative-predictive values of 90, 94, 95 and 89%, respectively (*Table 2*).

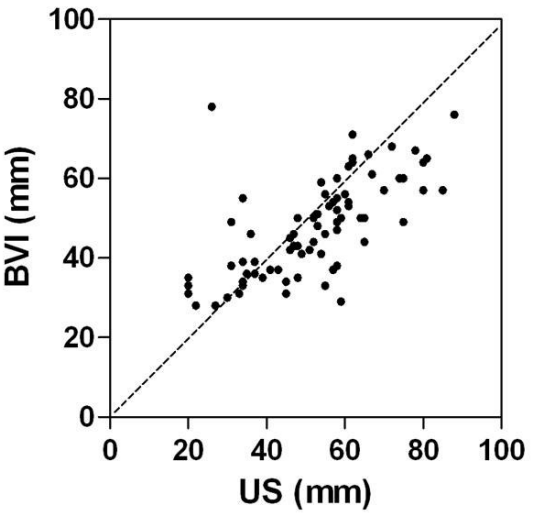
Table 2 **Conventional ultrasound vs. aortascan BVI 9600**

		Aortascan BVI 9600		
Conventional ultrasound	**AAA yes**	**AAA no**	***p*-value**	
AAA yes	70 (95)	8 (10)	<0.01	Sensitivity[a]: 90
AAA no	4 (5)	68 (90)	<0.01	Specificity[a]: 94

[a]*Aortascan BVI 9600. Abdominal aortic aneurysm (AAA)*

Furthermore, the correlation, in measured AAA diameter, between conventional US and the Aortascan BVI 9600 is demonstrated in *Figure 4*.

Figure 4. *Correlation between conventional ultrasound and Aortascan BVI 9600 (abdominal aorta size <30mm are not included because not measured with Aortascan BVI 9600), Ultrasound (US)*



DISCUSSION

The current study provides early results on the detection of AAA with the Aortascan BVI 9600, compared with conventional US. The main finding of this study was that the Aortascan BVI 9600 detects abdominal aortic aneurysms with a sensitivity and specificity of 90 and 94%, respectively. In addition to this, the positive- and negative- predictive values were 95 and 89%, respectively.

The development of aortic aneurysmatic disease is associated with alterations of connective tissue in the aortic wall, in which the process of atherosclerosis is regarded an important factor.[6] The formation of an AAA is initiated when vascular endothelium is injured and AAA progression is influenced

by factors such as (i) infection and complement activation, (ii) shear stress forces, (iii) increased oxidative stress and cytokine release leading to endothelial activation and dysfunction.[7,8] The prevalence and incidence of AAA has been widely investigated and a population-based study including 6.386 patients showed a prevalence of AAA in 263 (8.9%) men and 74 (2.2%) women.[9] Approximately 6% of men have an aortic diameter of more than 2.9 cm by the age of 65 years.[10] A meta-analysis performed by Cornuz *et al.* in 2004 included around 110.000 patients screened for AAA and concomitant risk factors.

The prevalence of AAA in Europe and America ranged from 4.1 to 14.2% in men and from 0.35 to 6.2% in women with all patients aged above 55 years.[1] In patients with symptomatic atherosclerotic disease, the prevalence of aneurysmatic disease is much higher, as data of our own population showed prevalence up to 25%. Therefore, the use of a quick and efficient AAA screening tool in this high-risk population, could add significantly to complete the patients risk profile. Patients with ruptured AAA have a worse prognosis, as up to 55% of the patients that reach the hospital alive will still die in the first 30 postoperative days.[11,12] Therefore, screening of patients at increased risk for developing AAA and subsequent elective surgical interventions may improve outcome. As noted by Hailey *et al.*,[13] the non-availability of an echo-system and/or operator at the point-of-care may lead to a delay in diagnosis and patient management. Although the first portable echo devices were developed in the 1970s,[14,15] portable echo has become commercially available since 1996.[16] In 2003, for instance, portable cardiac US (or echo-stethoscope) broadened the application of echocardiography to the patient's bedside.[17] The use of portable US for AAA detection was first described by Vidakovic *et al.*,[4] using the automatic BVI 6400 system.

Ultrasonography provides the possibility to diagnose or rule-out AAA rapidly and accurately.[18,19] However, finding the correct cross-sectional scan plane with the maximum aortic diameter remains the most difficult part in AAA screening. Small errors in the angle of cross-section causes direct errors in the found diameter and may lead to wrong diagnosis. Therefore, only well-trained echocardiographists should perform conventional US for the detection of AAA. Hence Vidakovic *et al.*[4] proposed to use the automatic BVI 6400 system for AAA screening because of (i) potential widespread availability, (ii) low costs (~10.000 €) compared with expensive conventional US equipment and (iii) steep learning curve compared with more intensive training required for conventional US. They concluded that the BVI 6400 is simpler for use, requires a less intensive training period and therefore can be used by a nurse or a technician. Furthermore, the BVI 6400 is roughly four times less expensive compared with conventional US. In the

pilot study conducted by Vidakovic *et al.*, volume measurements of the infrarenal abdominal aorta were performed with the BVI 6400 and compared with conventional US. On the basis of the technical characteristics of the BVI 6400, they estimated that a volume of 14 mL measured with the BVI 6400 corresponded with an abdominal aortic diameter of 30 mm, which is considered an AAA. Using the cut-off value of >14 mL for the presence of AAA, they demonstrated a sensitivity of 94% and specificity of 82% of the BVI 6400 in the detection of AAA. Furthermore, positive- and negative-predictive values for the BVI 6400 to detect AAAs were 88 and 92%, respectively. However, although these data look promising, the use of volume measurements, which have to be recalculated, remains questionable.

In our study, the Aortascan BVI 9600 directly measured the maximum abdominal aortic diameter and therefore, we did not have to estimate a volume cut-off value corresponding with the abdominal aortic diameter in mm. Consequently, results obtained from the Aortascan BVI 9600 can be directly compared with conventional US. With the use of these new types of measurements, we found a sensitivity of 90% and an increased specificity of 94% compared with the BVI 6400. Furthermore we found a negative-predictive value of 89% and an increased positive-predictive value of 95% compared with the BVI 6400. The Aortascan BVI 9600 provides a scan depth of 20 cm, which was sufficient for the patient population. Hence, no false negatives occurred due to a limited field of view. However, although the Aortascan BVI 9600 seems to detect AAA with a sufficient accuracy, the use of the system should not be extended as a replacement for conventional US. Patients with AAA detected by the Aortascan BVI 9600 should be referred to a radiologist to perform a conventional abdominal US.

Although we have used conventional US as the reference technique, we are aware that the sensitivity and specificity of conventional US is not 100%. This is mainly due to the difficulty of finding the right cross-sectional plane and location of the aorta, even for experienced operators. The 3D acquisition of the Aortascan BVI 9600 is likely to overcome the problems associated with two dimensional US. This was demonstrated in a patient with a curved aortic shape (including an AAA) not located at the midline of the abdomen. The measurement with conventional US initially produced a false-negative result, where the Aortascan BVI 9600 did detect an AAA. The presence of a true AAA was confirmed with a second conventional US measurement. This case underlines the need for future studies, evaluating the accuracy of the Aortascan BVI 9600, using angio-CT as the reference technique.

In conclusion, the Aortascan BVI 9600 automatically detects and calculates the aortic diameter with a 90% sensitivity without the need for a trained

operator. Because of these unique capabilities, it can be used for AAA screening outside the hospital and allows for AAA detection in patients who would not have been examined otherwise. However, final diagnosis and subsequent treatment requires additional medical examination.

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Chapter 23

Remote ischemic preconditioning in vascular surgery patients: the additional value to medical treatment

Jan-Peter van Kuijk
Willem-Jan Flu
Hence J.M. Verhagen
Jeroen J. Bax
Don Poldermans

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PERIOPERATIVE CARDIAC DAMAGE

Annually, more than 230 million major surgeries are performed worldwide, and this number continuous to grow.[1] Postoperative myocardial infarction and mortality are estimated to occur in 1% (2.300.000 patients) and 0.3% (690.000 patients), respectively.[1] The incidence of asymptomatic perioperative cardiac damage is estimated to be as high as 20% in patients undergoing high-risk surgery, such as vascular surgery.[2,3] Perioperative cardiac complications remain a significant problem, despite improved medical treatment and less invasive surgical techniques such as endovascular aneurysm repair (EVAR).

Since the early 1990s when EVAR was introduced to the worldwide vascular community, the use of the technique increased has increased steadily; in 2003, it accounted for over 40% of elective repairs of abdominal aortic aneurysms (AAA).[4] Several randomized trials have shown a perioperative survival benefit of EVAR compared to open repair, with fewer perioperative complications and a shorter recovery time.[5,6] In a recent population-based study, Schermerhorn and colleagues demonstrated that perioperative mortality rates were significantly lower in patients undergoing endovascular compared to open repair.[7]

However, renal and myocardial injuries still occur after elective EVAR in 5.5 and 7.0% of the patients, respectively.[7] These perioperative complications are the result of a multifactorial process in which hemodynamic instability with hypoperfusion plays a pivotal role. Vascular surgery patients are susceptible to ischemia-reperfusion injury, as this is an integral part of most vascular procedures. Renal injury may result from either (i) a low-flow state in the renal vasculature due to systemic hemodynamic instability, (ii) a no-flow state arising from direct interference with renal blood flow due to suprarenal or juxtarenal clamping, or (iii) to toxic metabolites that are released into the systemic circulation at the time of reperfusion of the lower limbs.[8] Perioperative cardiac events can be characterized by two distinct mechanisms, described as either type 1 and type 2 myocardial infarction.[9] Type 1 is defined as an acute coronary syndrome that occurs when a plaque ruptures, leading to thrombus formation and subsequent acute coronary thrombosis, ischemia and infarction. This type is elucidated by the perioperative stress response that includes a cathecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation and consequent hypercoagulability.[10] Type 2 arises from a low-flow state across a hemodynamically significant coronary artery stenosis, resulting in a sustained myocardial supply-demand imbalance.[10] Importantly, ischemia-reperfusion injury remains the final common pathway that leads to end-organ damage regardless of

the mechanism that led to ischemia in the first place.[11] Therefore, in addition to medical treatment, innovative strategies such as "ischemic preconditioning" (IPC) are increasingly investigated.

REMOTE ISCHEMIC PRECONDITIONING

Murry and colleagues were the first who used the term IPC in a study that demonstrated the ability to "condition" the heart to tolerate the effects of acute ischemia-reperfusion injury.[12] Several studies in human organs including the heart, kidney, liver and brain have demonstrated a powerful cardioprotective effect of IPC.[13,14] The mechanistic pathways underlying these endogeneous cardioprotective effects are complex in nature and have conventionally been divided into trigger factors, mediators and effectors, which include cell surface receptors (adenosine, bradykinin and opioids), signaling kinases and mitochondrial components.[15]

Intriguingly, some studies have reported that similar levels of cardioprotection can be achieved by applying brief episodes of non-lethal ischemia and reperfusion to an organ or tissue remote from the heart or kidneys, thereby obviating the need to "condition" the heart directly. This approach has been called remote ischemic preconditioning (RIPC) or ischemic preconditioning at a distance. In 1997, Birnbauam and colleagues presented the first animal study suggesting that transient ischemic limb ischemia could remotely pre-condition the ischemic heart.[16] Subsequent studies demonstrated that transient limb ischemia in humans protected against endothelial ischemic-reperfusion injury of an opposite limb and reduced ischemic myocardial damage during cardiac surgery.[17,18] Remote ischemic preconditioning in the setting of open AAA repair has been performed in one large clinical trial conducted by Ali and colleagues.[19] Postoperative myocardial injury (serum troponin ≥1.5 ng/mL) was significantly less frequent in patients who underwent RIPC prior to surgery. In addition, length of stay on the critical care unit was significantly shorter in the RIPC patients. Although the trial was relatively small, the results suggest that RIPC could have a role in strategies aimed at lowering the complication burden of major vascular surgery.

In this issue of *Journal of Endovascular Therapy*, Walsh and colleagues extend the concept of RIPC by reporting the results of a randomized clinical trial designed to determine the ability of RIPC in reducing renal and cardiac damage after EVAR. Forty AAA patients were randomized to preconditioning using sequential lower limb ischemia induction (N=18) or a control group (N=22). Primary

outcome was renal injury, measured by urinary levels of retinol binding protein (RBP) and urinary albumin:creatinin ratio (ACR). A significantly lower increase of RBP in the preconditioned group was detected. A secondary outcome was the occurrence of cardiac events; however, no difference was detected between the two groups in cardiac outcome. The results of this study performed in patients scheduled for elective EVAR seems promising with regard to the prevention of renal injury; however, several remarks can be made.

First, the study was designed and powered to assess the impact of RIPC on renal injury following EVAR. However, the only significant parameter for renal injury between the two groups was a significant increase of urinary RBP in the control group, while no differences in serum creatinin and estimated Glomerular Filtration Rate (eGFR) were observed between the two arms. Urinary RBP is a highly sensitive marker of renal tubular injury; however, in daily clinical practice, changes in serum creatinin are most often used. Notably, eGFR has been demonstrated to be a reliable marker for renal injury, and even minor temporary changes in eGFR after vascular surgery have been associated with adverse cardiovascular outcome.[20]

Second, no evidence of a cardioprotective effect of RIPC was detected, as there were no significant differences in either serum troponin elevations or major adverse cardiac events between the two arms of the trial. Troponin elevations after both open and endovascular repair of abdominal aortic aneurysm, have been associated with short- and long-term adverse cardiovascular outcome.[6,21]

Finally, preoperative statin use was significantly higher in patients who received RIPC. Statins are an important part of the medical treatment strategies for the prevention of renal injury and cardiac events after vascular surgery.[22] Therefore, patients with RIPC received more often optimal medical treatment in addition to RIPC, which could have influenced the occurrence of troponin elevations postoperatively.

MANAGEMENT OF PATIENTS WITH ASYMPTOMATIC CARDIAC DAMAGE

The need for cardiovascular prevention and treatment has emerged from the strong association between high-risk patients, perioperative ischemia characterized by troponin release, and its influence on short- and long-term outcome.[6,21] The unpredictable progression of an unstable coronary plaque during surgical stress is the most important target for systemic therapy. Medical treatment (including

perioperative β-blockade, statins and aspirin) has been established for perioperative as well as long-term risk reduction. The recent European Society of Cardiology (ESC) guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery provide a Class I recommendation for ß-blockade in patients with known ischemic heart disease or myocardial ischemia on pre-operative stress testing and in patients scheduled for high-risk surgery.[23] In our center, all patients scheduled for major vascular surgery are prescribed a low dose β-blocker (e.g. bisoprolol 2.5mg) initiated as early as possible, preferably 30 days prior to surgery. Furthermore, we promote the idea of prolonged treatment after surgery. As recommended, high-risk patients should receive statins in the perioperative period as well, ideally between 30 days and at least 1 week before surgery.[23,24]

Although these strategies have been demonstrated to improve outcome after surgery, each drug addresses a single etiologic mechanism. Therefore, other perioperative protective strategies such as RIPC, with the possible capability to protect multiple at-risk tissues simultaneously, could have an additional value. Although in patients undergoing major vascular surgery 2 randomized controlled trials have been performed, both had a relatively small sample size.

CONCLUSION

In conclusion, the occurrence of perioperative myocardial damage after vascular surgery is strongly associated with an increased risk for short- and long-term adverse cardiac outcome. Medical pre- and perioperative treatment strategies including ß-blockade, statins and aspirin have recently been recommended by the ESC, and remain the most important strategy for the prevention of postoperative cardiac complications.[23] Remote ischemic preconditioning has shown promising results in cardiac and vascular surgery patients; however, the clinical applicability should be further studied in large multi-centered randomized trials.

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Chapter 24

The efficacy and safety of clopidogrel in vascular surgery patients with immediate postoperative asymptomatic troponin T release for the prevention of late cardiac events: Rationale and design of the DECREASE-VII trial

Jan-Peter van Kuijk
Michiel T. Voûte
Willem-Jan Flu
Olaf Schouten
Michel Chonchol
Sanne E. Hoeks
Eric E. Boersma
Hence J.M.Verhagen
Jeroen J. Bax
Don Poldermans

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ABSTRACT

Background: Major vascular surgery patients are at high-risk for developing asymptomatic perioperative myocardial ischemia reflected by a postoperative troponin release without the presence of chest pain or electrocardiographic abnormalities. Long-term prognosis is severely compromised and characterized by an increased risk of long-term mortality and cardiovascular events. Current guidelines on perioperative care recommend single antiplatelet therapy with aspirin as prophylaxis for cardiovascular events. However, as perioperative surgical stress results in a prolonged hypercoagulable state, the postoperative addition of clopidogrel to aspirin within seven days after perioperative asymptomatic cardiac ischemia could provide improved effective prevention for cardiovascular events.

Study design: DECREASE-VII is a phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial designed to evaluate the efficacy and safety of early postoperative dual antiplatelet therapy (aspirin and clopidogrel) for the prevention of cardiovascular events after major vascular surgery. Eligible patients undergoing a major vascular surgery (abdominal aorta or lower extremity vascular surgery) who developed perioperative asymptomatic troponin release are randomized 1:1 to clopidogrel or placebo (300mg loading dose, followed by 75mg daily) in addition of standard medical treatment with aspirin. The primary efficacy endpoint is the composite of cardiovascular death, stroke, or severe ischemia of the coronary or peripheral arterial circulation leading to an intervention. The evaluation of long-term safety includes bleeding defined by TIMI criteria. Recruitment began early 2010. The trial will continue until 750 patients are included and followed for at least 12 months.

Summary: DECREASE-VII is evaluating whether early postoperative dual antiplatelet therapy for patients developing asymptomatic cardiac ischemia after vascular surgery reduces cardiovascular events with a favourable safety profile.

INTRODUCTION

The atherosclerotic process is often not limited to a single arterial location, giving it the character of a systemic and generalized disease. In 1984, Hertzer and colleagues demonstrated that only 6% of the patients undergoing vascular surgery for abdominal aortic aneurysms had a healthy coronary tree.[1] In the vast majority of the patients, the atherosclerotic process remains asymptomatic, until an accelerated progression is precipitated by a stressing factor such as a major surgical intervention. Worldwide more than 230 million surgeries are performed annually, and this number continues to grow.[2] The estimated post-operative myocardial infarction (MI) rate is 1% (approximately 2.300.000 patients).[3] According to the current guidelines, MI is characterized by the presence of 2 of the following 3 criteria: 1) presence of chest pain, 2) electrocardiographic (ECG) criteria, and 3) cardiac enzymes including creatine kinase (MB) and cardiac troponins.[4] However, in the perioperative period symptoms of cardiac complications might be masked by residual anaesthetic effects and postoperative pain. Consequently, as most cardiac events are asymptomatic or masked by other postoperative symptoms and ECG changes are often transient, cardiac ischemia might not be detected until it develops into an MI. It is estimated that up to 25% of patients undergoing high-risk surgery, such as vascular surgery, developed perioperative troponin release, of which more than 75% remain asymptomatic.[5,6] Importantly, the occurrence of asymptomatic troponin T release in vascular surgery patients has been associated with a more than 2-fold increased risk for short- and long-term mortality.[6,7]

The strong association between high-risk patients, perioperative ischemia characterized by asymptomatic troponin release, and its influence on short- and long-term outcome has emerged the need for prevention and treatment. The most recent guidelines on perioperative cardiac management in non-cardiac surgery patients, recommended medical therapy including beta-blockers, statins and aspirin.[8] Of note, perioperative stress results in a prolonged hypercoagulable state, which creates in combination with the presence of atherosclerotic plaques the perfect milieu for the development of perioperative cardiac ischemia. Although aspirin reduces the risk of plaque rupture and subsequent cardiovascular events, there remains a substantial risk for such events during the post-operative period and long term follow-up. The thienopyridine derivate clopidogrel is an antiplatelet agent that inhibits platelet aggregation induced by adenosine diphosphate. These distinct platelet-inhibiting mechanisms and separate target pathways for reducing platelet aggregation have made clopidogrel a more potent platelet-inhibiting agent when compared to aspirin. In the last decade, data from large randomized controlled trials of patients with acute coronary syndromes or those undergoing

percutaneous coronary intervention have demonstrated a significant reduction in cardiovascular endpoints with dual aspirin-thienopyridine therapy compared with aspirin alone.[9,10] More recent, a meta-analysis by Bowry et al. demonstrated the efficacy of combining clopidogrel and aspirin (dual antiplatelet therapy) compared to aspirin alone in patients with acute coronary syndromes, for the prevention of long-term cardiac complications.[11]

The most important complication of platelet inhibiting agents is the increased risk of bleeding. The combined use of aspirin and clopidogrel has been associated with an increased risk of minor bleeding. However, in large randomized controlled trials in patients with acute coronary syndromes, dual antiplatelet therapy was not associated with a significant increased risk of major bleeding compared with aspirin alone.[10,12] Most bleeding events are gastro-intestinal in origin as dual antiplatelet therapy has been associated with impaired healing of asymptomatic gastric ulcers.[13] To reduced these risks, recommendations from an expert consensus document supported the use of a gastroprotective agent, preferably proton pump inhibitors (PPIs), for the prophylaxis of dual antiplatelet-associated gastrointestinal injury.[13] However, several studies have demonstrated an increased risk of death in patients receiving both clopidogrel and PPIs.[14,15] Therefore the Food and Drug Administration has issued a warning on the co-administration of PPIs and clopidogrel, advising that the drugs should not be co-administered.

No prior studies investigated the use of dual antiplatelet therapy in high-risk patients developing asymptomatic cardiac ischemia immediately during the postoperative period. In the present study we aimed to assess the efficacy and safety of starting dual antiplatelet therapy within 7 days after vascular surgery, for the prevention of adverse long term cardiac events. Therefore, a large multicenter, prospective, randomized controlled trial has been set up: the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo-VII (DECREASE-VII) study.

METHODS

Sources of funding
JP van Kuijk, WJ Flu and SE Hoeks are supported by an unrestricted grant from the “lijf en leven” Foundation, Rotterdam the Netherlands. MT Voute is supported by an unrestricted grant from the Netherlands Heart Foundation (NHF #2009B020). All the authors of the manuscript are solely responsible for the design

and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Study objective

The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo-VII (DECREASE-VII) study (trial identifier NTR1436) is an investigator-initiated, national, multi-center, randomized, double-blind, placebo-controlled study. The primary objective is to assess the efficacy of clopidogrel in addition of standard medical treatment, compared to placebo, in preventing the primary endpoint. The secondary objective is to assess the safety of clopidogrel, compared to placebo, in addition of standard perioperative treatment with low molecular weight heparin and aspirin (100mg daily), on the occurrence of bleeding complications. The tertiary objective is to identify preoperative risk factors and novel biomarkers for the occurrence of the primary and secondary endpoint.

Table 1 Principal inclusion and exclusion criteria

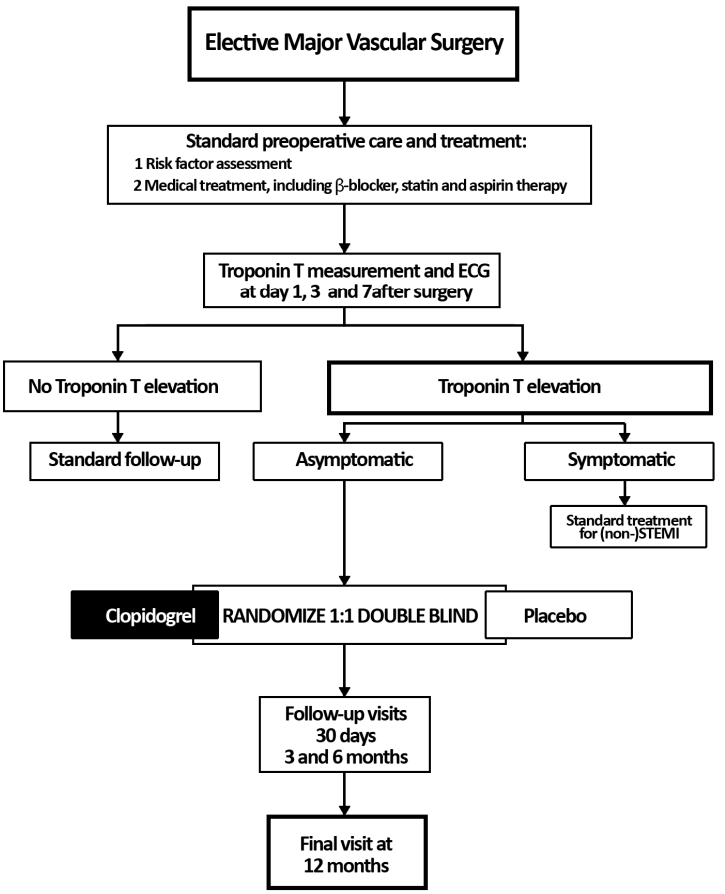
INCLUSION CRITERIA	
Major vascular surgery	Abdominal Aortic Aneurysm repair, Aortic stenosis repair, lower extremity vascular surgery
Age ≥ 18 years	
Asymptomatic Troponin T release	Elevated troponin T level at day 1, 3, or 7 after surgery, in the absence of chest pain complaints or electrocardiogram abnormalities
EXCLUSION CRITERIA	
Active bleeding	
Untreated left main disease	
Active cardiac conditions	Unstable angina pectoris, active chronic heart failure, serious cardiac arrhythmias, symptomatic valvular disease, in the recent <6 months
Preoperative elevated troponin T	
Inability to take clopidogrel orally	
Clear indication for long-term clopidogrel use	
Previous allergy or intolerance to clopidogrel	
Renal failure requiring dialysis	
Significant liver disease	ALAT, ASAT > 3 times Upper-Limit-of-Normal
Cancer	With an expected life expectancy <6 months
Anticipated non-adherence to clopidogrel	
Excessive alcohol abuse	
Pregnancy or planning to become pregnant	
Failure to provide informed consent	

Study population

The trial will enroll male and female patients who are 1) ≥18 years of age, 2) scheduled for elective major vascular surgery, and 3) develop asymptomatic postoperative troponin T release within 7 days after surgery. Major vascular

surgery is defined as 1) abdominal aortic aneurysm (AAA) repair, 2) abdominal aorta stenosis repair (Leriche syndrome), and 3) lower extremity vascular surgery. Asymptomatic troponin T release is an elevated troponin T measurement without the presence of ECG changes and/or presence of chest pain. Key exclusion criteria for this trial includes pre-operative active bleeding, untreated left main disease, active cardiac conditions, preoperative troponin T elevation, and inability to take oral medication. A complete listening of the entry criteria is provided in Table 1.

Figure 1. *Flow-chart of DECREASE-VII trial*



Study procedures

During a period of 4 years, all patients planned for elective surgery at the participating centers, will be screened for eligibility in the study. Those patients that fulfill all inclusion and exclusion criteria will be asked to participate in the study. Patients are pre-operatively asked for informed consent, with the knowledge

that definite inclusion into the study will only be accorded if they develop asymptomatic troponin T release during the perioperative period. Those patients that do not develop asymptomatic postoperative troponin T release will not be randomized and not be included in this study. However these patients will be followed according to the standard protocol after major vascular surgery, i.e. regular outpatient clinic controls. Data of these patients will be used for the tertiary objectives of this study. Prior to surgery, pre-operative work-up will be done in all patients, according the current ACC/AHA guidelines[16] which includes : 1) Age >70 years, 2) history of or current angina pectoris, 3) history of MI, 4) history of CVA/TIA, 5) history of or current congestive heart failure, 6) diabetes mellitus, insulin dependent or non-insulin dependent, 7) renal dysfunction (serum creatinine $\geq$ 160 mmol/l), 8) history of or current treatment for hypertension, and 9) chronic obstructive pulmonary disease. In addition, standard laboratory measurements (fasting glucose in non-diabetic patients, N-terminal-pro-Brain Natriuretic Peptide, troponin T, lipid spectrum and high-sensitive C-reactive protein) will be performed during routine outpatient clinic follow-up. Furthermore an electrocardiogram (ECG) will be performed in all patients. Additional stress testing, using stress-echocardiography or myocardial perfusion scintigraphy, will also be performed in patients with ≥3 cardiac risk factors (MI, stroke, angina pectoris, chronic heart failure, renal failure, age > 70 years). Preoperative stress test results will guide perioperative management. Patients with evidence of left main disease during additional stress testing will undergo coronary angiography and prophylactic coronary revascularization if needed. Prior to surgery all patients without contraindication will receive at least the following medication: 1) beta-blocker therapy (bisoprolol, with dose titration to a target heart rate of 60-70 beats per minute), 2) statin therapy (fluvastatin XL 80mg daily), 3) aspirin therapy (100mg daily), and 4) low molecular weight heparin (dose adjusted according manufacturers' recommendations and ESC guidelines[8]).

To assess the occurrence of troponin release, serial troponin T measurements and ECG recording will be performed on day 1, 3, 7 after surgery. Patients that do develop asymptomatic troponin T release at 1 or more time-points will be randomly assigned in a 1:1 ratio to double-blind treatment with either clopidogrel 75 mg once daily (with an initial dose of 300mg) plus aspirin (100mg daily) or placebo 75mg once daily (with an initial dose of 300mg) plus aspirin (100mg daily) during a treatment period of 12 months. Randomization of study treatment is performed via a central computerized telephone system. The presence of known cardiac risk modifiers for long-term outcome in vascular surgery patients with troponin T release (e.g. heart failure, renal dysfunction) will not be used for risk stratification before randomization. After randomization, all patients will be

treated according the current European Society of Cardiology guidelines on perioperative care, and must include at least a follow-up visit at 30 days, 3 months, 6 months and 12 months after surgery.[8] During these visits the occurrence of cardiovascular events are reported and verified with the treating specialist, in addition, standard laboratory measurement (fasting glucose, N-terminal-pro-Brain Natriuretic Peptide, troponin T, lipid spectrum and high-sensitive C-reactive protein) will be performed. In addition, after 18 and 24 months patients are followed by written or telephonic consultation.

Table 2 Definitions of study endpoints

EFFICACY ENDPOINTS	
Cardiovascular death	Any death with a cardiovascular cause, including those deaths following a cardiac procedure, cardiac arrest, myocardial infarction, pulmonary embolus, stroke, haemorrhage, or deaths due to unknown causes. Only deaths due to a documented non-cardiovascular cause will be classified as non-cardiovascular.
Non-fatal myocardial infarction	Requires 2 of the following: Characteristic ischemic symptoms (ie. Chest pain, shortness of breath, etc) lasting longer than 20 minutes; ECG changes including ST-elevation followed by appearance of Q-waves or loss of R-waves, or new left bundle branch block, or new persistent T-wave inversion for at least 24 hours, or new ST-segment depression which persists for at least 24 hours; A positive troponin, ie > 0.10 ng/ml, or peak CK-MB ≥ 8% of an elevated total CK with characteristic rise and fall
Stroke / Trainsient ischemic attack	Stroke: new focal neurological deficit thought to be vascular in origin lasting greater than 24 hours. Confirmation with CT-scan/MRI is recommended but not mandatory. Strokes will be further classified as ischemic, hemorrhagic or uncertain. TIA: new onset focal neurological deficit that resolves within 24 hours.
Severe coronary ischemia leading to intervention	Unstable angina with ECG changes requiring hospitalization which leads to coronary revascularization, using either percutaneous transluminal coronary angiography or coronary artery bypass grafting.
Severe limb ischemia leading to intervention	Severe ischemia of the lower extremity which is deemed to threaten the viability of the limb, and is associated with continuing ischemic pain, and neurological deficit, or inadequate skin capillary circulation, or inaudiable arterial flow signals by Doppler of the pedal arteries and which leads to hospitalization for an intervention such as thrombolytic therapy, angioplasty, bypass surgery, or amputation.
SAFETY ENDPOINTS	
Life-threatening bleeding	Fatal or intra-cranial bleeding requiring surgical intervention or transfusion of at least 4 units of blood or plasma expanders
Moderate bleeding	Bleeding which requires ≤ 3 units of blood or blood products
Minor bleeding	All other bleeding not requiring transfusion (leading to the temporary or permanent cessation of the study medication and/or aspirin).

Study endpoints

The primary efficacy objective is to determine the impact of clopidogrel on the incidence of long-term (12 months) cardiovascular death, myocardial infarction, stroke, or severe ischemia of the coronary or peripheral arterial circulation leading to an intervention. Detailed criteria for each type of primary end point event are described in Table 2. The major secondary safety objective is to determine the impact of clopidogrel on the occurrence of bleeding complications, defined as life-threatening bleeding, moderate and minor bleeding, according the Thrombolysis in Myocardial Infarction (TIMI) criteria.[17] Transfusions and the clinical site of bleeding will be recorded and reported. If a patient has to undergo an elective procedure with an increased bleeding risk due to the dual antiplatelet therapy, the continuation of dual or single antiplatelet therapy will be at the discretion of the treating physician or surgeon. If the treating physician decided to discontinue one or both antiplatelet drugs, it is recommended to stop aspirin at least 5-7 days and clopidogrel at least 7-9 days prior to the procedure or surgery.[8,18]

Statistical considerations

We anticipate an incidence of 30% of the primary outcome in the control group. These results are based on several reports in literature and our experience including approximately 2000 patients undergoing major vascular surgery.[7, 19-21] Clopidogrel treatment is expected to be associated with a 30% relative risk reduction. Based on these assumptions, we propose a sample size of at least 750 patients, with 375 patients in each group. The study will then have 80% power to detect the anticipated 30% risk reduction associated with clopidogrel therapy, with an $\alpha = 0.05$ (two-sided). The proposed study will be a multi-centre trial, including approximately 7 hospitals, to obtain the sample size of 750 patients within 3 years. They will be followed and analysed in the group to which they are allocated, regardless of whether or not they receive the assigned treatment or fulfil the eligibility criteria. Time-to-the-first occurrence of one of the components of the primary efficacy endpoint will be presented using the Kaplan-Meier curves. The rate of occurrence of the primary endpoint will be compared using the log-rank statistics. Employing the Cox proportional hazards model, the hazard ratio and its associated 95% confidence interval will derive treatment effect. Univariate and multivariate analyses will be conducted.

Safety outcomes will be compared using the log-rank statistic. An independent Data and Safety Monitoring Board (DSMB) will be established to monitor the progress of all aspects of the study and to ensure that the study meets the highest standards of ethics and patient safety. Stopping rules for futility endpoints are based on the estimate employed to reach the appropriate sample

size. One formal interim analysis is planned after the first 375 patients have been followed for 12 months. For efficacy, the combined endpoint of CV death, MI or stroke will be monitored. A modified Haybittle-Peto rule of 4 standard deviations in the first half of the study (before 50% of patients' 1-year data are available) will be used. The boundary will have to be exceeded at the 12-months time point. Safety data will be monitored every 6 months or more frequently if requested by the DSMB. Given the extensive previous experience with clopidogrel the main potential for adverse events is related to life-threatening bleeding. Data on bleeding risk in patients with dual antiplatelet therapy can be generated from large randomized trials comparing dual versus single antiplatelet therapy in patients with ACS or undergoing PCI. Bowry et al. performed a meta-analyses and demonstrated that long-term (>1 month) dual antiplatelet therapy had a 1.8 times increased risk of major bleeding (HR 1.80, 95% CI 1.41 to 2.30).[11] Based on these data we generated safety boundaries for the DSMB. A 2 standard deviation excess of life-threatening bleeding with the active agent (clopidogrel) constitutes ground for the DSMB to recommend study termination. The recommendation of the DSMB to stop the trial would be based on the pattern of the treatment effect of clopidogrel across all endpoints, and include an assessment of the overall benefit/risk ratio.

DISCUSSION

The DECREASE-VII trial was designed to test the hypothesis that early postoperative dual antiplatelet therapy for vascular surgery patients with asymptomatic perioperative troponin release will have a reduced incidence of cardiovascular events during long-term follow-up. This issue is of significant importance since asymptomatic troponin release after vascular surgery has a high incidence and is invariably associated with a poor prognosis during long-term follow-up. Currently medical treatment strategies for patients undergoing vascular surgery, with preoperative stress-inducible myocardial ischemia and to treat angina, symptomatic arrhythmias, heart failure and hypertension, include continuation of beta-blockade in patients already on beta-blocker therapy and initiation with up-titration of beta-blockers in beta-blocker naïve patients.[8] In addition, high-risk patients should also receive statins and aspirin in the perioperative period. Although aspirin has been demonstrated to effectively reduce the risk of plaque rupture and subsequent cardiovascular events in high-risk patients, there is a remaining substantial risk for such cardiac events during follow-up.[21] Extended antiplatelet therapy to reduce the adverse effects of the prolonged hypercoagulable perioperative state could effectively reduce this remaining risk.

Prophylactic coronary revascularization in cardiac stable patients with extensive stress-induced ischemia during preoperative testing is a subject of considerable debate. Both the Coronary Artery Revascularization Prophylaxis (CARP) trial and the DECREASE-V-pilot study showed no benefit of prophylactic coronary revascularization compared with optimal medical therapy, with the possible exception of left main disease.[22,23] Therefore the current recommendations for preoperative revascularization for patients undergoing surgery is similar to the general non-surgical population.[8]

Currently, asymptomatic cardiac ischemia detected by troponin measurements without ECG changes and/or presence of chest pain is not treated, although long-term outcome hereafter is severely compromised. According the ESC guidelines on the management of acute coronary syndromes in symptomatic patients presenting without persistent ST-segment elevation (NSTEMI), intermediate to high-risk patients have an increased risk for rapid progression to MI or death after non-ST-elevation myocardial infarction.[24] Therefore, early (<72hr) coronary angiography followed by revascularization (PCI or CABG) in these patients is recommended (Class I-A).[24] Prior to these intervention, antiplatelet and anticoagulant therapy should be initiated and include: aspirin, clopidogrel and unfractionated heparin, respectively. If a PCI has to be performed, additional treatment with glycoprotein IIb/IIIa should be initiated.

Surgery patients, and especially those after major vascular surgery, are at increased risk for bleeding complications immediately after surgery. In addition, if bleeding complications occur, local hemostasis is difficult to obtain, due to the site of surgery. Early postoperative revascularization, including medical treatment with dual antiplatelet therapy and heparin, for patients developing symptomatic troponin release is associated with an increased bleeding risk. However, based on several large randomized controlled trials it is recommended to use dual antiplatelet therapy in patients with ACS, even before the coronary anatomy is defined. Although the bleeding risk is increased, the risk:benefit ratio favors this strategy, mainly because only a minority of the patients (5-12%) with ACS will undergo cardiac surgery. Previous studies have demonstrated that of the patients with postoperative troponin T release, up to 25% had angina pectoris and/or ECG changes as well.[25] Of these patients, the majority (85%) had NSTEMI, while the remaining 15% had a STEMI and were referred for cardiac catheterization. Of the patients with a NSTEMI, only 15% was finally referred for cardiac catheterization. The addition of clopidogrel in addition of aspirin therapy in asymptomatic patients could effectively reduce the risk of early and long-term cardiac complications. The

addition of clopidogrel to aspirin (dual antiplatelet therapy) has a proven efficacy for the prevention of cardiac complications in symptomatic patients with acute coronary syndromes.[11] Although dual antiplatelet therapy is associated with an increased risk of bleeding complications, in patients with acute coronary syndromes there was a net benefit of dual antiplatelet therapy. Recent studies have reported the efficacy and safety of direct thrombin inhibitors. These drugs were demonstrated to have consistent positive outcomes in symptomatic patients with (un)stable angina, NSTEMI and STEMI.[26,27] Either with or without the addition of a glycoprotein IIb/IIIa inhibitor, direct thrombin inhibitors prevented ischemic complications with an associated lower risk of bleeding. However, in the present study with high-risk subjects we decided to use clopidogrel as this agent has a proven efficacy in a diversity of other populations with an acceptable safety profile.

Therefore, early detection of asymptomatic perioperative ischemia with subsequent extended antiplatelet therapy to prevent cardiovascular complications may have a major beneficial effect on long-term cardiovascular events. It is estimated that the additional costs of clopdiogrel will outweigh the costs associated with cardiac complications requiring hospitalization. Initial recruitment of patients at the Erasmus Medical Center and the participating hospitals began in (please add month) 2010. The end of patient recruitment and the results of this trial are expected in the summer of 2014. Further information on the DECREASE-VII trial can be obtained by www.erasmusmc.nl or by calling +31 10 7034613.

Summary

DECREASE-VII is a phase III, randomized, double-blind, placebo-controlled, multicenter, clinical trial designed to study the efficacy and safety of early postoperative clopidogrel treatment for the prevention of long-term cardiovascular events in patients who develop asymptomatic troponin T release after major vascular surgery. The trial will provide valuable information regarding the effects of this new indication of clopidogrel that has been proven to reduce ischemic complications in patients with acute coronary syndromes.

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Chapter 25

Summary and conclusions
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SUMMARY AND CONCLUSIONS

The process of atherosclerosis is a multifactorial syndrome which is very often not limited to a single arterial location. These aspects give it the character of a systemic and generalized disease. This thesis demonstrated a high prevalence of symptomatic and asymptomatic atherosclerotic disease in patients scheduled for vascular surgery. The presence of multiple affected vascular territories, called polyvascular disease, was invariably associated with a severely compromised long-term prognosis after surgery.

In the second and third part of this thesis two other important manifestations of atherosclerotic disease, namely insulin resistance and chronic kidney disease (CKD), are discussed. The prevalence and prognostic implications of these common co-morbidities in vascular surgery patients are reported.

In the last part the early results of a new screening tool for early detection of abdominal aortic aneurysm and a sophisticated treatment modality are presented. Finally, a randomized controlled trial for the treatment of asymptomatic perioperative troponin T release after vascular surgery was developed and is described in this thesis.

Part I: Prevalence and prognosis

Abdominal aortic aneurysms (AAA) and coronary artery disease (CAD) have traditionally been regarded as two separate vessel disorders with the atherosclerotic process as the common background. In **Chapter 2**, a detailed description of the pathophysiological processes, risk factors and prevalence of CAD in patients with AAA is given. Risk factor analysis identified age and gender as the most influencing factors for AAA development. Prognosis is strongly influenced by modifiable risk factors such as (a)symptomatic atherosclerosis in other arterial beds. Therefore early life style intervention and medical treatment is recommended to reduce the risk of cardiovascular complications.

Chapters 3 and 4 focus on the presence of asymptomatic vascular disease in symptomatic patients scheduled for vascular surgery. In chapter 3 a high prevalence of asymptomatic PAD, measured by a reduced ankle-brachial index, was demonstrated in subjects free of cardiovascular disease. The presence of an asymptomatic reduced ankle-brachial index had an additional value for long-term cardiac risk estimation. In chapter 4 the same association was observed for an increased common carotid intima-media thickness in patients free of cerebrovascular disease. The presence of an intima-media thickness ≥1.25 mm was

independently associated with 30-day cardiovascular events and long-term cardiovascular mortality.

Long-term prognosis of patients with atherosclerotic disease is diminished due to the occurrence of cardiovascular complications. In **Chapter 5** we studied a cohort of almost 3000 patients having elective vascular surgery for the presence of polyvascular disease. The prevalence and number of affected vascular beds before surgery were evaluated, and the prognostic implications of polyvascular disease on short –and long-term mortality were determined. Polyvascular disease was present in 54% of the patients, and the number of affected vascular beds correlated with the risk of cardiac complications during short –and long term follow-up. Patients with 3 affected vascular beds had the worst prognosis, as during a follow-up period of 10 years only 25% of the patients survived. In **Chapter 6**, the association between the obesity paradox and polyvascular disease was evaluated in the same cohort of patients. We demonstrated that patients with underweight had a reduced survival compared to patients with normal weight. In contrast, overweight patients had an increased survival. However, no direct interaction was observed between the obesity paradox and polyvascular disease.

During the period between 2002 and 2008, 1.005 patients scheduled for vascular surgery were preoperatively evaluated using echocardiography, as described in **Chapter 7**. Left ventricular dysfunction was observed in 506 (50%) patients, of which 80% had no clinical symptoms of heart failure. In patients undergoing open vascular surgery, asymptomatic left ventricular dysfunction was predictive for 30-day and long-term cardiovascular outcome. These results suggest the use of routine screening for asymptomatic left ventricular dysfunction in patients scheduled for open vascular surgery.

Myocardial ischemia during the perioperative period is an important predictor of morbidity and mortality after vascular surgery. **Chapters 8 and 9** emphasize the need of routine troponin T measurements for the detection of perioperative myocardial ischemia. Up to 20% of the patients undergoing vascular surgery will develop troponin T release, of which 90% remain asymptomatic. Importantly, even these asymptomatic troponin T releases are invariably associated with a risk of early or late myocardial complications. In chapter 8 we discussed the results of a randomized controlled trial comparing open versus endovascular AAA repair. We hypothesized that the lack of a survival benefit after 2 years of follow-up could be due to perioperative asymptomatic cardiac ischemia.

Part II: Diabetes mellitus

Patients with peripheral arterial disease (PAD) have a high prevalence of insulin resistance disorders due to generalized atherosclerotic disease. The majority of these patients are in a pre-diabetic phase, characterized by elevated glucose levels without the presence of symptoms. Importantly, elevated glucose levels are usually present for 7 to 10 years before the diagnosis of diabetes mellitus (DM) is made. In **Chapter 11** the results of a screening study for glucose regulation disorders in 404 consecutive patients without known DM are described. Impaired glucose tolerance and DM were detected using fasting plasma glucose in 26 (25%) and 12(28%) patients, compared to 78 (75%) and 31(72%) by using oral glucose tolerance testing. Importantly, patients with newly detected glucose regulation disorders had an increased risk of developing cardiovascular events and mortality during follow-up. Treatment of glucose regulation disorders during the perioperative phase has extensively been studied in intensive care unit patients. In **Chapter 10** these results are systematically reviewed and translated to the vascular surgery population. We recommended a moderate tight glucose control regimen as the most safest and efficient approach for vascular surgery patients.

Metabolic syndrome was primarily developed as a multiplex risk factor for the development of cardiovascular disease in patients free of cardiac history. In **Chapter 12** we compared the prevalence and prognostic implications of metabolic syndrome in high-risk vascular surgery patients with either occlusive or aneurysmatic disease. We observed a high prevalence of metabolic syndrome in both groups. In addition, the syndrome was an independent predictor of long-term cardiovascular events. Importantly, we demonstrated that if only the single components of metabolic syndrome were used as predictors of cardiac complications, the risk of future events would be under-estimated.

Diabetes mellitus and left ventricular dysfunction are often co-existent and invariably associated with increased mortality. However, as data on long-term prognosis of “isolated” diastolic left ventricular dysfunction are lacking, we evaluated the prognostic implications in vascular surgery patients with or without DM. In **Chapter 13** it was demonstrated that diabetic patients with PAD have an increased prevalence of isolated and combined left ventricular dysfunction. The presence or absence of DM did not influence the prognostic implications of left ventricular dysfunction on long-term outcome.

Part III: Renal disease

As a result of the systemic character of atherosclerotic disease, the process involves the renal vasculature as well. Importantly, polyvascular disease and chronic kidney disease have both separately been associated with an adverse cardiovascular outcome. In **Chapter 14** we assessed the prevalence of polyvascular disease in vascular patients with preoperative established CKD and observed that one-vessel disease was present in 54% of the patients with normal kidney function, while 62% of the patients with CKD (GFR<60() had polyvascular disease. Importantly, CKD patients with polyvascular disease had an increased risk for all-cause and cardiovascular mortality compared to patient without polyvascular disease.

The presence of subclinical atherosclerosis in the renal vasculature is reflected by the increased risk of acute kidney injury (AKI) after major vascular surgery. Although several studies investigated the predictive value of AKI for long-term cardiovascular disease and mortality, data regarding the relationship between temporary decline in renal function during the perioperative period with incident CKD are lacking. In **Chapter 15** we describe our results of a study that assessed the prognostic value of temporary renal function decline on the development of long-term CKD. We observed that vascular surgery patients have a high incidence of temporary (22%) or persistent (21%) renal function declines, both of which were independent predictors for development of long-term CKD. In addition, in **Chapter 16** we evaluated the influence of preoperative left ventricular dysfunction and the risk of AKI. We observed that patients with left ventricular dysfunction have an increased risk of developing AKI after surgery, and that the occurrence of AKI in these patients has an incremental predictive value towards cardiovascular mortality during long-term follow-up.

Serum phosphorus levels are a marker of renal function and have been associated with adverse long-term outcome in several populations. In **Chapter 17** we were the first to demonstrate the role of serum phosphorus levels as an independent predictor of all-cause and cardiovascular mortality during the first 30 days after vascular surgery. This study supported the use of routine phosphorus measurements before vascular surgery, thereby providing a simple and effective way of additional risk factor analyses in patients at high-risk for perioperative events.

Part IV: Risk reduction strategies and future perspectives

The management of polyvascular atherosclerotic disease consists of several treatment strategies, including life-style interventions, medical therapy and invasive procedures. According the European Society of Cardiology guidelines for

preoperative cardiac risk assessment, medical therapy in patients with PAD scheduled for vascular surgery included statins, ß-blockers and aspirin. In **Chapter 18** the role of statins in the treatment of patients with AAA is described. A systematic review of the current available literature demonstrated that statins reveal important pleiotropic effects. These non-lipid lowering effects could reduce aneurysm expansion; however, randomized controlled trials are needed. Another important medical agent used in patients with PAD are ß-blockers, which have important cardioprotective characteristics. Factors that may influence the effect of ß-blocker therapy include (i) type, (ii) dose, and (iii) timing of ß-blocker initiation before surgery. In **Chapter 21** we evaluated three different timing regimens of ß-blocker initiation. Our results indicated that ß-blocker treatment initiated >1 week before surgery is associated with lower preoperative heart rate and improved outcome, compared with treatment initiated <1 week preoperatively.

In patients with extensive atherosclerosis in the coronary arteries, preoperative coronary angiography is recommended in patients with high-risk noninvasive test results. However, in two randomized controlled trials, prophylactic preoperative coronary revascularization was not associated with improved immediate postoperative outcome. **Chapter 19** describes the long-term outcome data of one of these randomized trials, the DECREASE-V pilot study. This study demonstrated that preoperative coronary revascularization in high-risk patients undergoing major vascular surgery was not associated with an improved postoperative or long-term outcome compared with the best medical treatment. The lack of an (immediate) postoperative benefit might be explained by the fact that early surgery after coronary stent placement leads to an increase in adverse cardiac events caused by in-stent thrombosis or bleeding complications. **Chapter 20** demonstrates the results of our study to define the optimal timing interval between coronary artery stenting and noncardiac surgery. We found an inverse relationship between the interval from coronary artery stenting to noncardiac surgery and perioperative major adverse cardiovascular events. Continuation of dual antiplatelet therapy did not provide complete protection against cardiac complications. Based on these results, elective noncardiac surgery should be preferably postponed 90 days after placement of a bare metal stent and at least 1 year after placement of a drug eluting stent.

Abdominal aortic aneurysm has an increasing prevalence with age. Currently, no effective screening programs for early detection of AAA in subjects at risk are available. In **Chapter 22** the early results of a new screening tool for AAA are discussed. We observed a 90% sensitivity for the Aortascan BVI 9600 which automatically detects AAA. Based on these early results we recommended studies

for further validation of the screening tool in the primary care. In addition to new screening methods, **Chapter 23** is an editorial comment on the use of a potential treatment method for improvement of postoperative outcome. Remote ischemic preconditioning is a technique in which brief episodes of non-lethal ischemia and reperfusion are applied to an organ remote from the heart, thereby obviating the need to "condition" the heart directly. Early results of this technique in addition has demonstrated promising results; however, the clinical applicability should be further studied in large randomized trials.

In conclusion, patients with atherosclerotic disease have a high prevalence of polyvascular disease. In this thesis it was demonstrated that patients with symptomatic atherosclerotic disease, have two or more affected other vascular territories in 54% of the patients. The presence of extended atherosclerotic disease increases the risk of insulin resistance, acute kidney injury, chronic kidney disease and perioperative ischemia. The latter is reflected by troponin T release during the early postoperative period. The majority of these troponin T releases remain asymptomatic until it progresses to myocardial infarction. Nowadays, no treatment options are recommended for patients with perioperative ischemia, although late outcome hereafter is severely compromised. Therefore, we developed the DECREASE-VII trial (**Chapter 24**) which will evaluate in a randomized controlled design the efficacy and safety of immediate postoperative dual antiplatelet therapy (asprin and clopidogrel) for the prevention of late cardiac events after asymptomatic troponin T release.

SAMENVATTING EN CONCLUSIES

Atherosclerose is een multifactorieel syndroom hetgeen gekenmerkt wordt door een uitbreiding van de ziekte naar meerdere vaatgebieden. Deze aspecten geven atherosclerotisch vaatlijden het karakter van een systemische en gegeneraliseerde ziekte. In dit proefschrift wordt aangetoond dat patiënten die een vaatchirurgische ingreep ondergaan een hoge prevalentie van symptomatisch en asymptomatisch atherosclerotisch vaatlijden hebben. De aanwezigheid van meerdere aangedane vaatbedden, ofwel polyvasculair vaatlijden, is direct geassocieerd met een tweemaal verhoogd sterfterisico gedurende de lange termijn follow-up na de vaatoperatie.

In het tweede en derde deel van dit proefschrift worden twee belangrijke manifestaties van atherosclerose besproken, namelijk insuline-resistentie / diabetes mellitus (DM) en chronische nierinsufficiëntie. Het proefschrift toont een hoge prevalentie aan van deze comorbiditeiten in vaatchirurgische patiënten. Daarnaast wordt de belangrijke rol van deze ziekten met betrekking tot de korte en lange termijn prognose na een vaatoperatie beschreven.

In het vierde deel van het proefschrift worden de eerste resultaten van een nieuw screeningsmethode voor vroegtijdige opsporing van aneurysmata van de abdominale aorta gepresenteerd. Daarnaast worden diverse medicamenteuze en meer invasieve behandelingsmethoden van atherosclerotisch vaatlijden besproken. Als laatste wordt een nieuw geïnitieerde studie beschreven die zich richt op de behandeling van asymptomatische hartschade, hetgeen vaak voorkomt bij patienten die een vaatchirurgische ingreep ondergaan.

Deel I: Prevalentie en prognose

Aneurysmata van de abdominal aorta (AAA) en coronaire hartziekten worden van oudsher beschouwd als twee afzonderlijke aandoeningen met als gemeenschappelijke achtergrond het atherosclerotisch proces. In **Hoofdstuk 2** wordt een gedetailleerde beschrijving van de pathofysiologische processen, de risicofactoren en de prevalentie van coronaire hartziekten bij patiënten met een AAA gegeven. Op basis van een risicoanalyse blijken de leeftijd en het geslacht de meest belangrijke risicofactoren te zijn voor het ontwikkelen van een AAA. Daarnaast wordt de prognose sterk beïnvloed door de aanwezigheid van (a)symptomatische atherosclerose in andere arteriële vaatbedden. Het wordt aanbevolen om vroegtijdig te starten met life-style interventies en medicamenteuze behandeling, om het risico op cardiale complicaties te verminderen.

De hoofdstukken 3 en 4 richten zich specifiek op de aanwezigheid van asymptomatische atherosclerose in patiënten met symptomatisch vaatlijden in een ander vaatbed. In **Hoofdstuk 3** wordt een hoge prevalentie van asymptomatisch vaatlijden in de benen geobjectiveerd, middels meting van de enkel-arm-index, bij patiënten zonder aanwijzingen voor symptomatisch vaatlijden. Deze bevinding heeft een toegevoegde waarde voor de risico inschatting op cardiale complicaties. In **Hoofdstuk 4** wordt dezelfde bevinding gedaan in patiënten met een verdikte intima-media breedte in de wand van de halsslagader. De aanwezigheid van een intima-media breedte ≥1,25mm is een onafhankelijke voorspeller voor het ontstaan van cardiovasculaire complicaties binnen 30 dagen na de operatie en tevens gedurende de lange termijn follow-up.

Bij patiënten met atherosclerose is de lange termijn prognose verminderd door het optreden van cardiovasculaire complicaties. In **Hoofdstuk 5** wordt een cohort van bijna 3000 patiënten bestudeerd naar het voorkomen van polyvasculair vaatlijden in deze groep. De prevalentie en het precieze aantal aangedane vaatbedden werden geobjectiveerd, waarna de prognostische gevolgen van de ziekte op korte en lange termijn overleving werden bepaald. Het blijkt dat polyvasculair vaatlijden aanwezig is in 54% van de patiënten, en dat het aantal aangedane vaatbedden direct gecorreleerd is aan het risico op cardiale complicaties gedurende de korte en lange termijn follow-up na een vaatoperatie. Patiënten met 3 aangedane vaatbedden hebben de slechtste prognose, aangezien na een follow-up periode van 10 jaar nog slechts 25% van de patiënten in leven is. In **Hoofstuk 6** wordt de invloed van de zogenoemde “obesitas paradox” op de aanwezigheid van polyvasculair vaatlijden beschreven. Het blijkt dat patiënten met ondergewicht een slechtere prognose hebben in vergelijking met patiënten met een normaal gewicht. Patiënten met overgewicht blijken echter een verbeterde prognose te hebben. De aanwezigheid van polyvascular vaatlijden in deze patiëntengroepen blijkt niet van invloed te zijn op de paradoxale overlevingsverschillen.

Gedurende de periode van 2002 tot en met 2008 werden 1005 patiënten preoperatief onderzocht middels echocardiografie, zoals beschreven wordt in **Hoofdstuk 7**. Een linker ventrikel dysfunctie wordt waargenomen in 506 (50%) patiënten, waarvan 80% geen klinische symptomen van hartfalen heeft. Bij patiënten die een open vaatoperatie ondergaan, blijkt de aanwezigheid van asymptomatische linker ventrikel dysfunctie een voorspeller te zijn van de uitkomst kort na en gedurende lange termijn na de operatie. Op basis van deze resultaten kan het routinematig gebruik van echocardiografie, bij patiënten die een open vaatoperatie ondergaan, worden aanbevolen.

Ischemie van het hart tijdens de perioperatieve periode is een belangrijke voorspeller van morbiditeit en mortaliteit na een vaatoperatie. De **Hoofdstukken 8 en 9** wijzen op de noodzaak van routinematige metingen van het troponine T voor de detectie van perioperatieve ischemie. Het blijkt dat 20% van de patiënten die een vaatoperatie ondergaat een troponine T stijging zal ontwikkelen, hetgeen in 90% asymptomatisch blijft. Belangrijk hierbij is dat zelfs asymptomatische troponine T stijgingen direct geassocieerd zijn met een verhoogd risico op cardiale complicaties. In hoofdstuk 8 worden de resultaten van een gerandomiseerde studie van commentaar voorzien. Deze studie toont aan dat er 2 jaar na behandeling van een AAA middels open of endovasculaire chirurgie geen verschil in overleving is. Een mogelijke verklaring hiervoor zou de hoge prevalentie van perioperatieve myocardiale schade tijdens beide behandelingen kunnen zijn.

Deel II: Diabetes mellitus

Patiënten met perifeer arterieel vaatlijden (PAD) hebben een hoge prevalentie van insuline resistentie als gevolg van gegeneraliseerde atherosclerose. De meerderheid van patiënten met PAD bevindt zich in een pre-diabetische fase, gekenmerkt door verhoogde glucosespiegels zonder de aanwezigheid van symptomen. Opvallend is dat verhoogde glucosespiegels aanwezig zijn gedurende 7 to 10 jaar voordat de diagnose DM wordt gesteld.

In **Hoofdstuk 11** worden de resultaten van twee screeningsmethodes voor het opsporen van glucose regulatie stoornissen besproken, in een cohort van 404 opeenvolgende patiënten zonder bekende DM. Een gestoorde glucose tolerantie en DM wordt gedetecteerd op basis van nuchter plasma glucose bepaling in 25 en 28% van de patiënten. Bij gebruik van de orale glucose tolerantie test, wordt een gestoorde glucose tolerantie en DM gevonden in 75 en 72% van de patiënten. Belangrijk is dat patiënten met een nieuw ontdekte glucose regulatie stoornis of DM een verhoogd risico blijken te hebben op het ontwikkelen van cardiovasculaire complicaties. De behandeling van glucose regulatie stoornissen tijdens de perioperatieve fase is uitvoerig onderzocht bij intensive care patiënten. In **Hoofdstuk 10** worden deze resultaten systematisch beoordeeld en toegepast op de vaatchirugische populatie. Op basis hiervan wordt een matig strenge glucose controle als de meest veilige en efficiënte strategie aanbevolen voor vaatpatiënten tijdens perioperatieve periode.

Het metabool syndroom, ofwel insuline resistentie syndroom, werd in de eerste plaats ontwikkeld als een risicofactor voor de ontwikkeling van hart- en vaatziekten in de algemene populatie. In **Hoofdstuk 12** vergelijken wij de prevalentie en prognostische implicatie van het metabool syndroom in hoog-risico

patiënten met occlusief of aneurysmatisch vaatlijden. In beide groepen wordt een hoge prevalentie van het metabool syndroom gevonden. Bovendien blijkt het metabool syndroom een voorspeller van cardiovasculaire complicaties in vaatchirurgische patiënten te zijn. De belangrijkste bevinding is dat indien alleen de afzonderlijke componenten van het syndroom worden beschouwd als voorspeller van cardiale complicaties, er een onderschatting van het risico plaats vindt.

Diabetes mellitus en linker ventrikel dysfunctie komen vaak samen voor en beïnvloeden de prognose negatief. Aangezien gegevens met betrekking tot de lange termijn prognose van geïsoleerde diastolische linker ventrikel dysfunctie ontbraken, hebben wij de prognostische gevolgen hiervan bestudeerd in patiënten met of zonder DM. In **Hoofdstuk 13** wordt aangetoond dat patiënten met PAD en DM een verhoogde prevalentie van geïsoleerde en gecombineerde linker ventrikel dysfunctie hebben. Het al dan niet aanwezig zijn van DM heeft geen toegevoegd risico op de prognostische implicaties van linker ventrikel dysfunctie.

Deel III: Nierziekten

Als gevolg van het systemische karakter van atherosclerose, zijn de nieren ook betrokken binnen het ziekteproces. Uit de literatuur blijkt dat polyvasculair vaatlijden en chronische nierinsufficiëntie beide afzonderlijk in verband zijn gebracht met een ongunstige prognose. In **Hoofdstuk 14** wordt aangetoond dat 46% van de patiënten zonder nierinsufficiëntie polyvasculair vaatlijden heeft. Patiënten met nierinsufficiëntie (eGFR <60) blijken echter in 62% van de gevallen polyvascular vaatlijden te hebben. De aanwezigheid van polyvascular vaatlijden in patiënten met nierinsufficiëntie is geassocieerd met een verhoogd sterfte risico.

De aanwezigheid van subklinische atherosclerose in het renale vaatbed wordt weerspiegeld door het verhoogde risico op acute nierinsufficiëntie na een grote chirurgische ingreep. Hoewel diverse studies hebben aangetoond dat acute nierinsufficiëntie geassocieerd is met lange termijn sterfte aan cardiale oorzaken, ontbreken er studies betreffende het risico op lange termijn chronische nierinsufficiëntie. In **Hoofstuk 15** worden de resultaten van onze studie beschreven waarin de prognostische waarde van tijdelijke nierfunctie verslechtering ten opzichte van het ontstaan van chronische nierinsufficiëntie wordt bepaald. Een tijdelijke of continue verslechtering wordt gevonden in respectievelijk 22 and 21% van de patiënten. Het blijkt dat zelfs een kortdurende tijdelijke verslechtering van de nierfunctie een verhoogd risico geeft op het ontstaan van chronische nierinsufficiëntie. Daarnaast blijkt uit **Hoofdstuk 16** dat patiënten met een verminderde linker ventrikel functie een verhoogde kans hebben op acute nierinsufficiëntie. Wij hebben aangetoond dat het ontstaan van acute

nierinsufficiëntie in deze patiënten een additionele waarde heeft voor de risico-inschatting op lange termijn complicaties.

Serum fosfaat is een marker van de nierfunctie en wordt in diverse populaties gebruikt als een voorspeller voor lange termijn complicaties. In **hoofdstuk 17** beschrijven wij als eerste de rol van serum fosfaat als onafhankelijke voorspeller van cardiovasculaire mortaliteit gedurende de eerste 30 dagen na vaatchirurgie. De studie ondersteunt het gebruik van routinematig fosfaat bepalingen tijdens de preoperatieve evaluatie voorafgaande aan vaatchirurgie.

Deel IV: Risicoreductie strategieën en toekomstperspectieven

De behandeling van polyvasculair vaatlijden bestaat uit diverse aspecten, waaronder life-style interventies, medicamenteuze therapie en invasieve procedures. De Europose Vereniging voor de Cardiologie beveelt in haar richtlijnen betreffende preoperatieve cardiale risico-evaluatie, het gebruik van medicamenteuze therapie middels statines, ß-blokkers en aspirine aan. In **hoofdstuk 18** wordt de rol van statines bij de behandeling van patiënten met een AAA beschreven. Een systematische beoordeling van de literatuur laat zien dat statines belangrijke zogenoemde "pleiotrope" effecten hebben. Deze niet-lipiden verlagende effecten kunnen de groei van AAAs verminderen, echter dit dient uitgebreider onderzocht te worden in gerandomiseerde klinische studies. Een andere belangrijke groep medicijnen in de behandeling van atherosclerotisch vaatlijden zijn ß-blokkers. Deze groep medicamenten heeft belangrijke cardioprotectieve effecten tijdens en na vaatchirurgische ingrepen. De effectiviteit wordt echter sterk beïnvloed door (i) type, (ii) dosering, en (iii) het tijdsinterval tussen therapie initiatie en de operatie. In **hoofdstuk 21** worden drie verschillende tijdsintervallen bestudeerd. Het blijkt dat als ß-blokker therapie meer dan 1 week voor de operatie wordt gestart, er een belangrijke verlaging van de hartsslag optreedt en er een lagere kans op complicaties rond de operatie is. Bij patiënten met ß-blokker therapie korter dan 1 week voor de operatie worden deze effecten niet gevonden.

Invasieve procedures middels coronair angiografie voor de behandeling van atherosclerose, wordt aanbevolen bij patiënten met uitgebreide atherosclerose van de kransslagaders. Echter, uit twee gerandomiseerde studies is gebleken dat profylactische coronair revascularisatie niet is geassocieerd met een verbeterde uitkomst direct na de operatie in deze patiënten. In **hoofdstuk 19** worden de lange termijn resultaten na deze behandeling beschreven van één van deze studies, de DECREASE-V pilot studie. Deze studie toont aan dat preoperatieve coronair revascularisatie, bij patiënten met een hoog risico op cardiale complicaties, niet

geassocieerd is met een verbeterde lange termijn prognose, in vergelijking met optimale medicamenteuze behandeling. Het ontbreken van een (direct) postoperatief voordeel kan worden verklaard door het feit dat een snelle operatie na een coronair revascularisatie leidt tot een toename van cardiale complicaties ten gevolge van in-stent trombose of bloedingcomplicaties. **Hoofdstuk 20** toont de resultaten van onze studie betreffende het optimale tijdsinterval tussen coronair stenting en niet-cardiale chirurgie. Wij vonden een omgekeerde relatie tussen het interval van stenting tot chirurgie met betrekking tot het ontwikkelen van belangrijke cardiovasculaire complicaties. Continueren van "dual antiplatelet" therapie gaf in onze studie geen volledige bescherming tegen cardiale complicaties tijdens chirurgie na coronair stenting. Gebaseerd op deze resultaten, dient niet-cardiale chirurgie bij voorkeur 90 dagen uitgesteld te worden na gebruik van een "bare-metal stent" en tenminste 1 jaar na plaatsing van een "drug-eluting" stent.

De prevalentie van AAA is geassocieerd met toenemende leeftijd. Momenteel zijn er geen effectieve screenings methoden voor vroegtijdige opsporing van AAA. In **hoofdstuk 22** worden de eerste resultaten beschreven van een nieuw screenings apparaat voor de detectie van aneurysmata. De Aortascan BVI 9600 met automatische AAA detectie, heeft een sensitiviteit van 90% in deze eerste klinische studie. Uitgebreide validatie studies, bij voorkeur in de huisartsenpraktijk, zijn nodig voordat het apparaat daadwerkelijk toegepast kan worden als screeningsmethode. Naast nieuwe screenings methoden worden er ook nieuwe behandelmethoden voor patiënten met vaatlijden ontwikkeld. **Hoofdstuk 23** is een commentaar op een studie waarin het gebruik van "remote ischemic preconditioning" als nieuwe therapie voor de preventie van cardiovasculaire complicaties wordt beschreven. Deze techniek betreft het veroorzaken van kortdurende periodes van niet-schadelijke ischemie en reperfusie aan lichaamsdelen op enige afstand van het hart, zoals de armen of benen. Hierdoor wordt het hart als het ware getraind op het doormaken van kortdurende episodes van ischemie tijdens een vaatoperatie.

Concluderend kan worden vastgesteld dat patiënten met atherosclerose een hoge prevalentie van polyvasculair vaatlijden hebben. In dit proefschrift wordt aangetoond dat bij patiënten met symptomatisch atherosclerotisch vaatlijden, in 54% van de patiënten tevens sprake is van vaatlijden in twee of meer andere vaatbedden. De aanwezigheid van gegeneraliseerde atherosclerose verhoogt het risico op insulineresistentie, acute nierinsufficiëntie, chronische nierinsufficiëntie en perioperatieve ischemie. Dit laatste komt voornamelijk tot uiting door een stijging van het troponine T tijdens de vroege postoperatieve periode. De meerderheid van deze troponine T stijgingen verlopen asymptomatisch totdat het

zich ontwikkelt tot een volledig myocard infarct. Momenteel wordt er geen behandeling van deze perioperatieve ischemie aanbevolen door internationale richtlijnen, ondanks dat de korte en lange termijn prognose hierdoor sterk negatief beïnvloed wordt. In **hoofdstuk 24** wordt een nieuwe studie beschreven die wij hebben ontwikkeld voor de behandeling van deze patiëntengroep. Patiënten met postoperatieve troponine T stijging zullen dubbelblind gerandomiseerd worden voor een behandeling met clopidogrel of placebo om de effectiviteit en veiligheid van deze behandeling te testen met betrekking tot het voorkomen van cardiale complicaties na een vaatoperatie.

PUBLICATIONS AND PRESENTATIONS

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6. **Van Kuijk JP**, Flu WJ, Poldermans D. Comparing endovascular and open repair of abdominal aortic aneurysm. *Jama. 2010;Feb 303(6):513-514*
7. **Van Kuijk JP**, Flu WJ, Chonchol M, Welten GM, Verhagen HJ, Bax JJ, Poldermans D. The prevalence and prognostic implications of polyvascular atherosclerotic disease in patients with chronic kidney disease. *Nephrol Dial Transplant. 2010;25(6):1882-1888.*
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PRESENTATIONS AT NATIONAL AND INTERNATIONAL CONGRESSES

Oral presentations

1. Timing of non-cardiac surgery after coronary stenting with bare-metal or drug-eluting stents. *European Society of Cardiology, Barcelona, 2009*

2. Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery. *European Society of Cardiology, Barcelona, 2009*

Poster presentations

3. Preoperative oral glucose tolerance testing in vascular surgery patients; long-term cardiovascular outcome. *European Society of Cardiology, Barcelona, 2009*

4. Metabolic syndrome is an independent predictor of cardiovascular events in high-risk patients with occlusive and aneurysmatic peripheral arterial disease. *European Society of Cardiology, Barcelona, 2009*

5. Influence of left ventricular dysfunction (systolic versus diastolic) on long-term prognosis in patients with versus without diabetes mellitus having elective peripheral arterial surgery. *Voorjaarscongres Nederlandse vereniging voor Cardiologie, Arnhem, 2010 en European Society of Cardiology, Stockholm, 2010*

6. Repeated N-terminal pro B-type natriuretic peptide measurements as incremental predictor for long-term cardiovascular outcome after vascular surgery. *European Society of Cardiology, Stockholm, 2010*

7. Preoperative left ventricular dysfunction and postoperative acute kidney injury are associated with adverse long-term outcome after vascular surgery. *European Society of Cardiology, Stockholm, 2010*

8. Temporary worsening of renal function after vascular surgery is an independent predictor for chronic kidney disease. *European Society of Cardiology, Stockholm, 2010*

9. The influence of polyvascular disease on the obesity paradox in vascular surgery patients. *European Society of Cardiology, Stockholm, 2010*

PhD PORTFOLIO

Name PhD student: Jan-Peter van Kuijk Erasmus MC Department: Anesthesiology Research School: COEUR	PhD Period: **2008-2010** Promotor: Prof. Dr. D Poldermans	
1. PhD training		
	Year	**ECTS**
General courses and academic skills		
- Cardiac CT and MRI, Albert Schweitzer hospital, Rotterdam	2009	0.3
- Reviewer for The Open Cardiovascular Imaging Journal	2008-10	1.5
Specific courses (e.g. research school, medical training)		
- NIHES, Biostatistics for clinicians	2009	1.5
- COEUR PhD courses (Heart failure research and vascular medicine)	2008-10	3.0
- Basiscursus Regelgeving en Organisatie van Klinische trials	2009	1.0
Seminars and workshops		
- Journal club, Rotterdam (weekly)	2008-10	1.2
- Research meeting, Rotterdam (weekly)	2008-10	1.2
- Vascular clinical meeting, Rotterdam (weekly)	2008-10	1.2
- Ultrasound clinical meeting, Rotterdam (weekly)	2008-10	0.6
- COEUR, Research seminars	2008-10	1.2
Presentations		
- 2x oral presentation ESC congress 2009	2009	1.0
- 3x poster presentation ESC congress 2009	2009	1.5
- 6x poster presentation ESC congress 2010	2010	3.0
- COEUR research seminar presenter (vascular clinical epidemiology)	2010	0.5
(Inter)national conferences		
- European Society of Cardiology Congress, annual	2008-10	4.5
- NVVC, najaarscongres, Amsterdam	2009	1.0
- NVVC, voorjaarscongres, Arnhem	2010	1.0
2. Teaching		
	Year	**ECTS**
Lecturing		
- Clinical applications of the Aortascan BVI 9600, Dresden, Germany	2010	1.2
- Accuracy of the Aortascan BVI 9600, IJselstijn	2009	0.6
- Early results of screening for abdominal aortic aneurysm, Rotterdam	2009	0.6
- Anatomic variations of the abdominal aorta, IJsselstein	2010	0.6
Supervising		
- MsC students (O. Witteveen, C. Klein Nulent)	2008-10	3.0

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CURRICULUM VITAE

Jan-Peter van Kuijk is geboren op 30 augustus 1982 in Tholen. In 2001 slaagde hij voor het eindexamen Voorbereidend Wetenschappelijk Onderwijs aan het Driestar College in Gouda. In hetzelfde jaar starte hij met de studie Geneeskunde aan de Universiteit Leiden. Gedurende zijn 3e en 4e studiejaar was hij werkzaam als student-onderzoeker op de afdeling cardiologie in het Leids Universitair Medisch Centrum (begeleider: Dr. N.M.S. de Groot). Nadat in 2007 het artsexamen was behaald, heeft hij gedurende een jaar gewerkt als arts niet in opleiding tot specialist op de afdeling Interne Geneeskunde en de afdeling Cardiologie van het Groene Hart Ziekenhuis te Gouda. In juni 2008 startte hij als arts-onderzoeker in het Erasmus Medisch Centrum in Rotterdam aan zijn promotie-traject onder supervisie van prof.dr. Don Poldermans. Op 1 oktober 2010 zal hij starten op de afdeling cardiologie van het St. Antonius Ziekenhuis te Nieuwegein (opleider: Dr. W. Jaarsma).

Jan-Peter van Kuijk was born on August 30th 1982 in Tholen, the Netherlands. In 2001 he graduated at the Driestar College in Gouda after attending secondary school. Hereafter he started Medical School in 2001 at the University of Leiden. During his 3rd and 4th study year he worked as a student-researcher at the department of Cardiology at the Leiden University Medical Center (supervisor: Dr. N.M.S. de Groot). After obtaining his medical degree in 2007, he worked as a junior house officer at the department of Internal Medicine and the department of Cardiology of the Groene Hart Ziekenhuis in Gouda. In June 2008, he started a PhD-project at the Erasmus Medical Center in Rotterdam under supervision of prof.dr. Don Poldermans. October the 1st 2010, he will start at the department of cardiology at the St. Antonius Ziekenhuis in Nieuwegein (supervisor: Dr. W Jaarsma).